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Ronald F. Pfeiffer
Ivan Bodis-Wollner *Editors*

Parkinson's Disease and Nonmotor Dysfunction

Second Edition

Humana Press

CURRENT CLINICAL NEUROLOGY

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Second Edition

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We dedicate this book to our wives, Brenda and Olie, without whose patience and understanding this work could not have been undertaken and completed. They are amazing women with many insights into the daily problems we and our patients face. We thank them for their general and specific contributions to our patients' lives and to this book.

Ronald F. Pfeiffer
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Series Editor's Introduction

At the time of its appearance in 2005 the first edition of *Parkinson's Disease and Nonmotor Dysfunction* filled a major gap in the body of knowledge concerning Parkinson's disease. Drs. Pfeiffer and Bodis-Wollner correctly perceived that nonmotor features of Parkinson's disease were being given relatively little attention in the literature and were often being neglected by clinicians seeing these patients. Since that time there has been an explosion of new information concerning nonmotor aspects of the disease and several patient questionnaires have emerged to assay for nonmotor symptoms. It is worth emphasizing that nonmotor symptoms are particularly important because several of these such as constipation, depression, and sleep disorders may precede motor manifestations by as much as several years.

It is now well established that Parkinson's disease involves many brain regions outside of the dopamine-mediated nigrostriatal system. These include other brainstem structures such as dorsal motor nucleus of the vagus, locus ceruleus, raphe nuclei, and pedunculopontine nucleus; the olfactory bulb and its connections; structures related to cognitive function and behavior such as the nucleus basalis of Meynert and cerebral cortex; and certain regions of the hypothalamus. Specific regions of the peripheral nervous system are also involved including especially the sympathetic ganglia and submucosal parasympathetic ganglia of the gastrointestinal system. Recently, alpha synuclein and Lewy neurites have been identified in biopsies of salivary glands, submucosal layers of the esophagus, stomach and colon, and in the skin of living patients. These exciting discoveries highlight the widespread neuropathology of Parkinson's disease and, if confirmed, may also provide opportunities to study and follow alpha synuclein as a useful disease biomarker in living patients.

This new edition of *Parkinson's Disease and Nonmotor Dysfunction* once again highlights the fact that the evaluation and management of Parkinson's disease requires a careful multidisciplinary approach. Chapters concerning behavioral, autonomic, sleep, sensory, and other nonmotor manifestations have been updated and several new authors have been recruited. In addition, new chapters about topics as far afield as apathy, skin disorders, vestibular dysfunction, and maxillofacial disorders have been added. This volume will keep clinicians aware of the myriad nonmotor manifestations of Parkinson's disease and highlight the importance of

inquiring about nonmotor symptoms many of which do not emerge at the initial patient encounter. A particularly useful place for this book is close at hand in the clinic where either common or uncommon nonmotor symptoms that are reported can be easily looked up and discussed with our patients.

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Preface

The idea that Parkinson's disease (PD) is characterized only by motor features such as tremor, rigidity, bradykinesia, and postural instability has been deeply embedded not only in the minds of patients and their family members, but also in the training and practice of many physicians. However, even a quick perusal of the amazingly perceptive clinical description that James Parkinson put to paper in 1817 reveals that from the beginning, various features not reflective of motor dysfunction already were recognized and described as part of PD. It has only been relatively recently that attention has been refocused on these nonmotor features, and the realization has grown that nonmotor features are frequently present in PD, can be the source of considerable discomfort and disability for affected individuals, and at times may even play a dominant role in the clinical picture.

The first edition of *Parkinson's Disease and Nonmotor Dysfunction* was published in 2005 to provide a source of detailed information that could be readily accessed by the practicing physician, which described and explained these nonmotor features that had at that point received insufficient attention both in the medical and in the lay literature. Awareness and knowledge of the nonmotor features of PD have dramatically expanded in the 7 years since publication of that first edition, rendering an update of *Parkinson's Disease and Nonmotor Dysfunction* more than due. Thus, many of the same talented group of experienced researchers and clinicians who were the driving force behind the first edition have been reassembled to provide this updated, in-depth review of nonmotor dysfunction in PD. However, it also became evident that some additional aspects of nonmotor dysfunction in PD, such as dermatological, vestibular, and dental dysfunction, merited attention and thus have been included in this second edition, which remains subdivided into five diverse domains.

Behavioral abnormalities are perhaps the most feared nonmotor problems encountered in the management of PD, particularly, though not exclusively, in individuals with more advanced disease. They are both distressingly frequent and frequently distressing. Behavioral abnormalities may be intrinsic components of the disease process itself (depression and dementia), treatment-induced complications (psychosis and postsurgical behavioral changes), or a combination of both (anxiety and obsessionality). Apathy is yet another behavioral abnormality of PD, presumably intrinsic to the disease process itself, that has received increasing attention in recent years and can be a

source of great frustration to family members of PD patients; it is now addressed in this second edition. Whatever their derivation, behavioral abnormalities can seriously impact and impair quality of life for both patients and family members.

Autonomic dysfunction is often mistakenly considered to be a feature of multiple system atrophy and not PD. In reality, individuals with PD can, and frequently do, display various features indicative of autonomic dysfunction. Gastrointestinal, urogenital, cardiorespiratory, and thermoregulatory function all may become impaired in PD, not simply as consequences of medication-induced derangements, but as part of the disease process itself. These autonomic features often develop in the later stages of the illness but also may appear early, occasionally even before the classic motor components become evident. Gastrointestinal dysfunction in the form of constipation actually may become evident decades before the development of PD motor features. Dermatological abnormalities have been included in this section because seborrheic dermatitis often has been considered to be autonomic in origin. Although this assumption may not be correct and other dermatological abnormalities discussed in the chapter, such as melanoma, certainly are not autonomic, the chapter is positioned here.

Sleep-related dysfunction can be a source of considerable consternation, not only to patients but also to their family members, who often suffer the indirect, and sometimes the direct—at least in the setting of rapid eye movement (REM) sleep behavior disorder—consequences of the patient's sleep disturbance. As with behavioral and autonomic dysfunction, sleep-related disturbances can be either disease-related or medication-induced and may occur both early and later in the course of PD. REM sleep behavior disorder actually may precede the development of motor features by years.

Sensory dysfunction is perhaps the least well known or recognized and also the most purely nonmotor facet of nonmotor dysfunction in PD. Abnormalities of primary sensory function (vision and olfaction) occur, as do more complex sensory phenomena, as exemplified by the visuo-cognitive deficits and the various pain syndromes and disorders of sensation that may plague the patient with PD. Impairment of olfaction is yet another nonmotor feature of PD that may become evident years before the classic motor features emerge. In recent years, the possibility that vestibular dysfunction may also occur in the setting of PD has been raised and this issue is now addressed in this edition.

Finally, a section of this volume is devoted to several problems (oculomotor dysfunction, fatigue) that tread on, or perhaps cross over, the line between motor and nonmotor dysfunction in PD. However, they are included here because they often are not covered extensively in the more traditional discussions of the motor features of PD. Maxillofacial and dental abnormalities also are important, but often neglected, problems that may plague individuals with PD, and are now addressed in this volume.

It is our hope that this revised and expanded collection of contributions by an even larger contingent of superbly knowledgeable and erudite authors will serve to further increase awareness of the manifold contributions that nonmotor features may make to the collective clinical picture experienced by the patient with PD. Early recognition of these features will lead, we hope, to more prompt and effective treatment of them, a goal that can be firmly shared and appreciated by both patients and physicians alike.

Memphis, TN, USA — Ronald F. Pfeiffer
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Part I

Behavioral Dysfunction in Parkinson's Disease

Depression in Parkinson's Disease: An Update

1

Jeana L. Benton, Steven P. Wengel, and William J. Burke

Abstract

Depression is the most common psychological disturbance that affects people with Parkinson's disease (PD). Despite an increasing amount of research devoted to this topic, uncertainty still exists concerning many aspects of depression in PD. Significant questions remain regarding some very basic issues, including how best to diagnose depression in PD, how frequently depression complicates PD, the risk factors for developing depression, and how best to treat depression. This chapter provides a current perspective on what is known about depression in PD, reviewing its epidemiology, etiology, and treatment. Rather than providing a comprehensive overview, the focus here is on updating the major themes of research in this field.

Keywords

Parkinson's disease • Depression • Dysthymia • Mania • Mesocorticolimbic pathway • Selective serotonin reuptake inhibitor • Tricyclic anti-depressant • Pramipexole • Nortriptyline • Paroxetine • Electroconvulsive therapy • Subthalamic nucleus deep brain stimulation

Introduction

The most common psychological problem that affects those with Parkinson's disease (PD) is depression. Depression in PD patients is associated with worsening of motor symptoms, cognitive impairment, reduced quality of life, increased disability, increased psychiatric and medical comorbidity, and greater health-care utilization [1–4]. Despite the impact of depression in PD and growing research pertaining to this topic, many questions remain unanswered regarding basic issues such as prevalence, diagnosis, risk factors, and potential treatments. This chapter reviews the present knowledge about depression in PD, describing its epidemiology, etiology, and treatment.

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Prevalence

Even simple questions, such as how frequently depression occurs in persons with PD, can be difficult to answer. Reported rates of depression have varied enormously, ranging from 2.7% to greater than 90% [5, 6]. Possible explanations for this disparity include variations in study population, diagnostic tools, and types of depressive disorder included in the study. An overall depression rate of 43% is one of the most commonly cited figures [7]. This figure includes patients with major depressive disorder (MDD) as well as those with minor depression or dysthymia. Studies that have reported high rates have generally used specialty populations, in contrast to community-based samples in which lower rates have been found.

A recent large-scale chart review of the Veterans Affairs database examined the frequency of depression diagnoses in all PD patients age 55 or older receiving general clinical care. In this study, a depression diagnosis was recorded in 18.5% of PD patients. MDD accounted for 21.3% of depression diagnoses; the remainder were minor depression or dysthymia [8]. These results are consistent with other studies demonstrating that minor forms of depression may be more common in PD patients [9, 10].

A recent systematic review and meta-analysis examined the average prevalence of depressive disorders in the PD population, taking into consideration different settings and diagnostic approaches. Overall prevalence of MDD was reported to be 17%, minor depression 22%, and dysthymia 13% [5]. Diagnostic method was found to be an important variable affecting the reported prevalence of major depression. Studies using semi-structured interviews reported the prevalence of MDD to be 19%; those employing DSM criteria without a structured interview reported only 7%. Study setting also greatly influenced the reported prevalence of MDD. Prevalence was significantly lower in population studies than in outpatient or inpatient samples [5].

Veazy et al. [11] noted the effect of varied assessment techniques on reported prevalence of depression in PD. These authors reported that when classification of depression was based on self-report questionnaires, estimates of prevalence of MDD tended to be higher than those based on structured clinical interviews. This observation is consistent with results from a study that used structured clinical interviews to analyze all cognitively intact patients with PD in the community who reported positive symptoms on the General Health Questionnaire (GHQ) [12, 13]. Although depressive symptoms in the GHQ occurred in 34.2% of patients with PD, only 2.7% met criteria for MDD.

A study by Tandberg et al. [9] showed that the rate of major depression can also be strongly impacted by cognitive impairment, as defined by the Mini-Mental State Exam (MMSE) score [14]. The rate of MDD was 3.6% in patients with an MMSE score greater than 20 but increased to 25.6% in patients whose MMSE score was below 20. Rates were also higher in those with possible PD (18.8%) versus those with probable PD (4.6%). The authors attribute these figures to a higher rate of dementia in those with possible PD and suggest that the higher rates in the cognitively impaired indicate more widespread cerebral involvement [9].

A bimodal distribution has been suggested for the onset of depression in PD [15–17]. One peak seems to follow diagnosis and may be related to left hemisphere dysfunction; the second peak occurs late in the course of PD and may be associated with impaired activities of daily living [15]. Some evidence also suggests that depression in PD is more common in younger patients [18], females [19, 20], and in those with more bradykinesia and rigidity (as opposed to tremor dominance) [21–23].

Diagnostic Challenges

An issue that contributes to the diverse findings in the frequency and severity of depression is the process of diagnosis. Diagnostic and Statistical Manual of Psychiatric Disorders, 4th Edition (DSM IV) criteria [24] can be difficult to apply to patients with PD because only symptoms that are

not a result of a general medical condition or a direct physiological effect of a substance (e.g., medication) are counted. In PD, this presents obvious problems, particularly when deciding about the DSM IV "somatic" symptoms, such as sleep, appetite/weight, and energy disturbance and psychomotor change. If the "exclusive" directions of DSM IV are followed, many patients will end up without a mood disorder diagnosis despite appearing to meet criteria for MDD.

The difficulty inherent in assigning causality has led to alternative approaches, such as counting symptoms as present or absent (regardless of presumed causality—an "inclusive approach"), focusing only on the more "psychological" symptoms of depression (the "exclusive approach"), or including additional non-somatic symptoms to supplement the mood assessment. Clearly, the approach used for symptoms attribution affects the sensitivity and specificity of diagnosis and may influence which patients are included in clinical studies and treated in clinical practice.

Leentjens et al. [25] addressed this subject by viewing the sensitivity of individual depressive symptoms and their relative contribution to the diagnosis of depression in patients with PD. They examined the individual items of the Hamilton depression rating scale (Ham-D) [26] and Montgomery–Asberg depression rating scale [27] (MADRS) in a discriminate analysis. Not surprisingly, non-somatic symptoms were the most discriminating but somatic symptoms also had meaningful contributions. Specifically, reduced appetite and early-morning awakening were relatively low-prevalence symptoms that proved useful in supporting a diagnosis of depression, whereas other somatic symptoms were not. Perception and interpretation of symptoms also complicates diagnosis in PD. Self-report of symptoms may be limited by apathy or attribution of any mood symptoms to the underlying neurological disorder even when motor symptoms have been relatively stable and mood changes are relatively acute [28].

It is also important to consider the impact of dementia on the diagnosis of depression, because rates of depression may be higher in the cognitively impaired patient with PD. Dementia can complicate the evaluation process in several ways. First, several symptoms of dementia can overlap with depression. DSM symptoms that lose specificity in the context of mild cognitive impairment include loss of interest, decreased energy, psychomotor changes, and decreased concentration [29]. Also, as cognitive impairment progresses, it becomes increasingly challenging to recognize a depressive disorder because of the difficulty in accessing the individual's internal affective state.

Because depression in PD is common and significantly impacts motor disability [1, 2] and quality of life [3], accurate diagnosis is critical. A recent NIH-sponsored work group, convened to address the inherent difficulties in diagnosing depression in PD, recommended (1) adopting an "inclusive" approach to symptom assessment, (2) modifying the anhedonia/loss of interest criterion to distinguish depression from apathy or dementia, and (3) including information from caregivers when assessing depression in the cognitively impaired [28].

Relationship Between Depression and PD

Depression itself may be a preliminary symptom of PD and some data suggest that the onset of depression may predate the PD diagnosis by several years. Gonera et al. [30] compared the number of visits to a general practitioner between persons who developed PD and controls. In the 2 years preceding diagnosis, there were substantially more visits in the developing PD group and many of these visits were for mood disorders [30]. In another study, Schuurman et al. [31] found a strong positive association between depression and subsequent incidence of PD (Hazard Ratio 3.13 for depressed versus non-depressed subjects). Leentjens et al. [32] conducted a retrospective cohort study of general practice registry data in the Netherlands to compare the incidence of depression in patients later diagnosed with PD with age-matched controls and found a significantly higher incidence of depression in patients later diagnosed with PD

(odds ratio 2.4). Ishihara and Brayne [33] also concluded that premorbid depression was significantly more common in PD patients, based on a systematic review of the literature. The results have led to the hypothesis that a biological risk factor for depression is present in patients who later develop PD.

With the preponderance of clinical studies showing elevated rates of depression in patients with PD, a critical question arises: are these rates higher in patients with PD in comparison with those with other chronic illnesses? If depression is more common in patients with PD, a pathophysiological link between these conditions is implied.

Several medical illnesses have been associated with depression, yet often the nature of the relationship is unclear. Krishnan et al. [34] described the difficulty in establishing a causal relationship in comorbid illnesses, since the lifetime prevalence of all conditions is steady or increases with age. As such, there is a tendency to find a correlation between virtually all conditions. This "pseudo-correlation" is particularly observed in disorders where frequency increases with age, e.g., PD, Alzheimer's disease, and cardiovascular disease. Consequently, many of these associations may be only statistical artifact and not clinically relevant [34].

A study using the Danish Psychiatric Central Register and Danish Hospital Register attempted to answer the question of whether patients with PD are at increased risk of developing depression when compared with those with other medical illness [35]. These authors determined the rates of initial admissions for depression in patients with PD, diabetes, and osteoarthritis. They found an increased incidence of depression in those with PD versus those with the other conditions who had comparable degrees of disability. The risk of receiving a diagnosis of depression was highest in the 6 months of follow-up after the diagnosis of PD but remained elevated 1 year later, although to a lesser extent. The authors conclude that these findings support the theory that depression is not simply a psychological reaction to PD but that a common pathophysiology underlies these conditions [35].

Risk Factors

Many attempts have been made to identify risk factors for the development of depression in PD. Some studies have suggested that earlier age of onset, more severe disability, presence of "on/off" fluctuations, higher levodopa dose, and family history of PD may increase risk of depression in PD patients [6]. However, these efforts generally have failed to consider factors known to predispose people to depression in general. Accordingly, Leentjens et al. [36] first considered general risk factors for depression (e.g., age, sex, prior history of depression, family history of depression, and somatic comorbidity) in a PD population and found that these five risk factors predicted 75% of depression in their sample using a multivariate model. When disease-specific markers were then included in the model, only the right-sided onset of PD symptoms improved the model. Thus, established risk factors for depression may also be markers of depression in PD.

Etiology

Efforts have been made to attribute depression to either psychological or biological sources. This is a hollow effort, if only because biology of necessity underlies psychology. However, Brown and Jahanshahi [17] provided a summary of the role of psychosocial factors that may contribute to depression in PD. They concluded that certain patients are more vulnerable to depression including: (a) those who have an early age of onset; (b) patients in the earliest stages of disease; (c) those with more advanced disease; and (d) those with more rapidly progressive deterioration. Although only a weak association has generally been reported between depression in PD and severity of illness, a crucial factor is the rate at which disability progresses [17]. Those patients whose disability progresses slowly enough for them to adapt may show slight depression or recover from a prior depression. Those with more rapid progression may fail to adapt as easily and are then at higher risk of developing depression.

These authors also raise the question of why patients with apparently similar levels of physical illness and disability may have distinctly different affective states. Factors that seem to explain some of this variability are the availability and quantity of social support, as well as the strategies that individuals use to cope with stress. Patients who have good social support, who are satisfied with that support, and who have good self-esteem and active coping mechanisms appear to be at lower risk for depression [17, 37].

Pathology

The contribution of biology to depression in PD is likely on the basis of several known neuropathological changes that include the degeneration of serotonergic, dopaminergic, noradrenergic, and cholinergic nuclei in the brainstem [38]. Mayeux et al. [39, 40] formulated the "serotonergic hypothesis" after finding lowered 5-hydroxyindolacetic acid in cerebrospinal fluid (CSF) and degeneration of serotonergic nerve cells in post-mortem studies of PD patients. Because serotonin has an inhibitory effect on dopamine release in the striatum, the reduction in serotonin activity may be a compensatory mechanism for reduced dopamine availability. Lowered serotonin activity is also correlated with the development of depression and this common pathophysiology may explain the high prevalence of depression in PD patients [6].

The "dopaminergic hypothesis" [41] relates the development of depression to degeneration of the mesolimbic and mesocortical dopamine projections. The mesocortical limbic pathway arises in the ventromedial tegmental area and projects to areas critical for affect such as the cingulate, entorhinal, and orbitofrontal cortices, as well as the subcortical portions of the limbic forebrain [42, 43]. This pathway has been shown to be disrupted in patients with depression and PD. Additionally, positron emission tomography (PET) studies have demonstrated hypometabolism in the cingulate and frontal cortex in depressed PD patients, compared with controls [44].

Norepinephrine neurotransmission is also disrupted in PD and neuronal loss in the locus ceruleus may be even more severe than in the substantia nigra [45]. A recent study using [^{11}C] RTI-32 PET as an in vivo marker of dopamine and norepinephrine transporter binding investigated differences in catecholaminergic transmission in depressed versus non-depressed PD patients [46]. Significantly, lower binding was seen in the locus ceruleus of depressed PD patients and there was an inverse relationship between binding and severity of mood and anxiety symptoms. Binding was also reduced in other areas traditionally believed to be involved in affect regulation and emotional processing, including the amygdala, mediodorsal thalamus, anterior cingulate cortex, and the ventral striatum.

The emergence of subthalamic nucleus deep brain stimulation (STN-DBS) as treatment of refractory PD symptoms has also provided insight into potential mechanisms of depression in PD. One fascinating case involves a 65-year-old woman with a 30-year history of PD who developed acute depression during DBS [47]. This woman went from a euthymic state to one of acute depression when her left basal ganglia was stimulated 2 mm below the site where stimulation relieved the signs of PD. The authors suggest that stimulation may have affected the activity of nigral γ-aminobutyric acid (GABA) neurons innervating the ventral nuclei of the thalamus with projections to the prefrontal and orbitofrontal cortices. This is an interesting region because disruption of connections between the basal ganglia and frontal cortex has been reported to have a role in stroke-related depression, and disruption of these pathways by vascular disease has been proposed as an etiology for late-life depression [48].

Although the above data provide some insight into potential pathophysiological explanations for depression in PD, much is left to learn. Many individuals do not develop depression in spite of similar pathophysiological abnormalities. Thus, the etiology of depression in PD is likely multifactorial with contributions from biology as well

as psychosocial factors including personality, individual coping strategies, and availability of social supports [6].

Interplay of Mood and Cognition in Parkinson's Disease

Cognitive impairments in PD are common and vary in severity. The most frequently affected areas are free recall of previously learned information, visuospatial skills, and executive functions, such as problem solving, planning, and flexibility [44]. The overlap in the effects of depression and PD on cognitive function is substantial. Consequently, the ability of the clinician to pinpoint the independent impact can be challenging.

The depressed patient often presents in a hesitant manner and may appear to give up easily while undergoing cognitive testing [49, 50]. However, when encouraged to try answering the question, the depressed patient will often provide a correct response. Moreover, depressed patients are often inconsistent in their responses. Rosenstein [51] offered these general guidelines regarding the cognitive functioning of the depressed patient: (a) memory and attention, although slightly below expectation, are usually not in the impaired range; (b) language functioning is nearly always normal, as are intellectual functioning and visuospatial functioning; (c) psychomotor functions are often within normal limits, but below expectation; (d) and finally, the efficacy of executive functions appears to be reduced.

The relationship between depression and PD and its influence on cognition is not well understood. Nevertheless, depression and PD do appear to have individual as well as overlapping influences on cognitive functioning. In the case of the non-demented patient with PD who becomes depressed, the additive effect of depression on executive functioning alone, much less memory, may lead one to suspect the patient has developed dementia. However, it is more likely that the cognitive dysfunction associated with PD alone is exacerbated by depression. A patient with mildly impaired cognitive flexibility prior to the onset of depression may now appear moderately impaired. Additionally, memory functioning may be significantly worse because of encoding and consolidation problems; consequently, the ability to even recognize previously learned information is reduced. Thus, timely treatment of depression in the patient with PD may help to reduce the risk of developing excess disability, thereby helping to maintain a better quality of life.

Mood Effects of Parkinson Disease Treatment

Antiparkinsonian Drug Treatments

Conflicting reports exist regarding the effects of antiparkinsonian drug treatment on mood symptoms. Some studies have shown improvement in depressive symptoms after treatment with levodopa [52, 53] but others have found no improvement [7, 11] or worsening of depressive symptoms [11, 53]. One explanation for this is that most studies of these agents have been designed to monitor effects of drugs on motor symptoms rather than mood. Additionally, mood swings often accompany the "on–off" motor fluctuations associated with levodopa treatment, with some patients fulfilling clinical criteria for major depression during "off" periods [11]. Thus, the effect of levodopa on mood may be more related to changes in motor symptoms than to a true antidepressant effect [53].

Other antiparkinson agents have also been reported to have beneficial effects on mood symptoms in small studies. Pramipexole treatment has been linked to reduction in scores on the Ham-D [54] and the MADRS [55] as well as improvement in motor symptoms. In a recent meta-analysis, Leentjens [56] concluded that pramipexole had a beneficial effect on mood and motivational symptoms in PD patients without major depression but that the effect of pramipexole in PD patients with major depression is less clear. Limited data also suggest an improvement in depressive symptoms following treatment with

bromocriptine [57], pergolide [55], and selegiline [11, 58, 59].

Manic symptoms such as extreme optimism, spending sprees, and euphoria have also been linked to dopaminergic agents. Originally reported to occur in 1.5% of levodopa-treated patients [53], manic symptoms also have been reported with other dopaminergic agents such as bromocriptine and selegiline [53]. Unlike depressive symptoms, manic symptoms do not seem to occur in untreated PD patients but appear to be a consequence of treatment of PD symptoms.

Subthalamic Deep Brain Stimulation

In recent years, STN-DBS has become a well-established surgical treatment for motor symptoms in advanced PD. Studies of STN-DBS have shown significant improvements in activities of daily living [60–63] and quality of life measures [60, 63–65]. Some studies have also reported beneficial effects on depressive symptoms [63, 66]. However, significant post-operative psychiatric and behavioral symptoms have been reported, including depression [60–62, 67–72], mania [64, 69, 73, 74], emotional reactivity [69], and diminished executive functioning [64, 75].

Although most psychiatric side effects have been described as transient in nature, studies have reported a greater than expected rate of suicide in patients undergoing STN-DBS [67, 68, 70]. Burkhard et al. [70] reported a suicide rate of 4.3% in a cohort of 140 patients undergoing DBS for a wide variety of movement disorders. Voon et al. [67] and Soulas et al. [68] have reported suicide rates of 0.45–1% in patients undergoing STN-DBS for advanced PD. Despite high rates of depression, suicide risk in PD is low and has been estimated to be about ten times less than that observed in the general population [76]. Thus, the observed rates of suicide following STN-DBS are substantially elevated and suicide is postulated to be one of the most important preventable risks of mortality following STN-DBS for advanced PD [77].

Factors most highly associated with suicide following STN-DBS have been post-operative depression and impaired impulse regulation [67, 68]. Other factors less strongly associated were younger age, younger age at PD onset, and history of prior suicide attempts [67, 77]. Most notable was the fact that suicide can occur despite clear evidence of motor improvement [68–70]. Depression and quality of life measures may not change or worsen following DBS treatment in many patients despite reduction in motor disability [78, 79]. Mechanisms by which STN-DBS increases the frequency of suicide are unknown but difficulty adjusting to psychosocial changes following surgery, a reduction in dopaminergic medications, and direct effects of STN-DBS on mood and impulse control by spread of current to nonmotor associative or limbic areas have all been postulated to contribute [68].

In one study, the premorbid depression rate in patients presenting for assessment prior to STN-DBS was 60% despite prescreening for disabling psychiatric symptoms [80]. Patients with premorbid depression have been found to have an elevated risk of developing significant depression in the post-operative period [67, 69]. These data along with the elevated risk of suicide observed following STN-DBS highlight the need for thorough psychiatric assessment prior to STN-DBS and close follow-up with aggressive treatment of symptoms in the post-operative period.

Treatment of Depression in PD

Maximize Antiparkinsonian Therapy

Many patients with PD report that their mood symptoms fluctuate in concert with their motor symptoms. That is, when "off" motorically, they may experience fairly abrupt dysphoric episodes. Poor control of motor symptoms can also lead to reduction in quality of life and exacerbation of depressive symptoms. The most appropriate treatment in these patients is to optimize PD therapy first rather than to add an antidepressant [11, 81, 82]. In fact, one author suggested "optimized dopaminergic therapy is a prerequisite for successful management of depression—particularly in patients with fluctuating PD" [83].

Use of Antidepressant Drugs

SSRIs and TCAs

Despite the extensive literature describing prevalence, characteristics, and impact of depression in PD, there are few well-designed treatment studies. Most studies of anti-depressant medications have been open-label, underpowered, or have contained significant methodological flaws [84–86]. The use of open-label studies is particularly problematic in PD patients since a placebo response rate up to 80% has been reported in this population [6, 87]. Thus, although uncontrolled studies have suggested that depression in PD patients may be responsive to therapy with antidepressant medications, they cannot provide convincing evidence for anti-depressant efficacy [88–94].

Since the locus ceruleus and the raphe nuclei are affected by PD, levels of norepinephrine and serotonin may decrease as the illness progresses. Therefore, use of agents to ameliorate deficiency states of these neurotransmitters seems reasonable. However, placebo-controlled trials examining the efficacy of antidepressants for treating depression in PD are scarce and not entirely consistent. A 2003 study by Leentjens et al. [87] compared sertraline (maximum dose 100 mg) with placebo and found no difference between the two groups in MADRS score after 10-weeks follow-up. Similar results were obtained when citalopram was compared with placebo in a 1998 study by Wermuth et al. [95]. Two older studies comparing the tricyclic antidepressants (TCAs) nortriptyline [96] and desipramine [97] with placebo for the treatment of depression in PD patients found both TCAs to be superior to placebo, but these studies contained significant methodological flaws and did not use validated assessment measures [11, 84].

Results of the above trials have led to speculation that dual-action reuptake inhibitors may be superior to selective serotonin reuptake inhibitors (SSRIs) in the PD population [86]. Two studies comparing TCAs, SSRIs, and placebo yielded contradictory results. Menza et al. [86] examined change on the Ham-D in depressed PD patients treated with paroxetine CR, nortriptyline, or placebo. Nortriptyline dosage was initiated at 25 mg and could be increased up to 75 mg based on efficacy and tolerability. Paroxetine CR dose was initiated at 12.5 mg and could be increased to 37.5 mg. Monitoring parameters included Q–T_c interval, vital signs, and nortriptyline levels, which averaged 74.88 ng/ml. In this study, nortriptyline was significantly better than placebo for overall change in the Ham-D score, percent responders, and secondary outcomes of sleep, anxiety, and social functioning; paroxetine CR did not differ from placebo [86].

These results are in contrast to those of Devos et al. [98]. In this study, anti-depressant dosage was fixed throughout the trial—citalopram was dosed at 20 mg; desipramine was started at 50 mg and increased to 75 mg by day 2. Both desipramine and citalopram produced significant improvements in MADRS score at day 30 compared with placebo. However, the remission rate was significantly higher in the desipramine group.

Although the above results seem to more strongly support the efficacy of TCAs over SSRIs, these data must be interpreted with caution. The total number of participants in all the above studies combined was only 222. Small sample size and a large placebo response may have limited the ability to detect improvements that might be demonstrated in larger trials. Despite this limited evidence, antidepressant medications are frequently prescribed to depressed PD patients. A recent Veterans Affairs database study [8] indicated that over 75% of PD patients with depression filled a prescription for an antidepressant in the 12-month period following diagnosis. Almost two-thirds of these prescriptions were for SSRIs; TCAs comprised only 7.4% of the total. The overwhelming preference for SSRIs in this patient population despite the paucity of evidence supporting their efficacy is likely influenced by their favorable side effect profile and ease of use.

As a class, SSRIs have numerous attractive features. Dosing is straightforward, with once-daily administration usually being adequate. Additionally, titration is often unnecessary because the starting dose may be therapeutic for many patients. SSRIs virtually never cause

orthostatic hypotension and rarely produce anticholinergic adverse effects, with the exception of paroxetine. However, they may have an antagonistic effect on dopamine [81]. Case reports have been published of patients with PD who experienced worsening of motor symptoms when an SSRI was added to their regimen; nevertheless, this is a relatively uncommon phenomenon. Ceravolo [90] and Devos [98] each describe one patient treated with an SSRI who experienced worsening of motor symptoms with drug treatment, but three randomized, placebo-controlled trials have shown no difference in overall motor score between SSRI and placebo groups [86, 87, 98].

A second concern about SSRIs in PD patients is the possibility of inducing serotonin syndrome if an SSRI is prescribed to a patient already taking a monoamine oxidase inhibitor such as selegiline or rasagiline [99]. Symptoms of the serotonin syndrome include myoclonus, delirium, tremors, fever, hyperreflexia, and diaphoresis [83]. This concern has been somewhat alleviated by a large survey of clinicians in which a very low frequency of both possible (0.24%) and definitive (0.04%) serotonin syndrome was described with this combination of medications [100].

At one time the mainstay of treatment for depression, TCA use has declined with the advent of newer anti-depressants. The anticholinergic properties of TCAs may have a beneficial effect on tremor in PD but can also cause impairment of cognition, urinary retention, impaired gastric mobility, and even delirium [11]. Orthostatic hypotension is also a potential adverse effect. PD patients are more susceptible to this as a consequence of both the disease itself and dopaminergic therapy. Any PD patient on a TCA should be counseled to consume adequate fluids and exercise special care when rising from a chair or bed. TCAs have also been associated with cardiac arrhythmias due to lengthening of the P–R interval, QRS duration, and Q–T_c interval. These potential adverse effects must be taken into consideration, but no differences in cognitive measures, cardiac conduction parameters, or vital signs have been reported between placebo and TCA treatment groups in recent randomized, controlled trials of desipramine [98] and nortriptyline [86]. Desipramine and nortriptyline are the least anti-cholinergic and the least sedating of the TCAs and thus may be the best tolerated in PD patients.

Other Antidepressant Drugs

No other antidepressant medications have data from controlled trials for treatment of depression in PD patients. Venlafaxine and duloxetine are two non-TCA dual-reuptake inhibitors that do not have significant cardiac effects beyond occasional reports of increased blood pressure. Both venlafaxine and duloxetine appear to be well tolerated in PD patients and a recent study showed that duloxetine was associated with a reduction in pain scores in PD treatment [101].

Mirtazapine is a non-SSRI anti-depressant that is an antagonist of a-2 noradrenergic autoreceptors and serotonin-2 and -3 receptors and appears to be well tolerated in patients with PD. However, a case series reported four patients with PD who developed sleep-related behavioral problems, including nocturnal confusion, talking during sleep, and hallucinations while taking mirtazapine [102]. Symptoms resolved when mirtazapine was discontinued.

Bupropion is a novel anti-depressant that inhibits both norepinephrine and dopamine reuptake. It is usually well tolerated in patients with PD and does not produce orthostatic hypotension. It tends to be more "activating" than many other anti-depressants and may therefore ameliorate fatigue. Its putative effect on dopamine transmission has led to speculation that it may be particularly effective in PD; however, no controlled clinical trials have been conducted.

Electroconvulsive Therapy

Electroconvulsive therapy (ECT) is a treatment of choice for major depression refractory to medical treatment [103]. It has been reported to improve both mood and motor symptoms in

depressed PD patients [104, 105]. It also decreases "off" time in patients with PD who have severe "on–off" phenomena who are not depressed [105–107]. Initial motor improvements appear to be transient, lasting several weeks. However, long-term benefit has been reported with maintenance treatment [106, 108–110]. Case reports have suggested that ECT can possibly be safely used in patients with STN-DBS electrodes in place [111–113]. ECT may be particularly useful in this population, since depressive symptoms following DBS surgery are associated with an increased risk of suicide [67, 68].

Although ECT is effective for depressive symptoms, it may cause delirium in susceptible individuals. It may also contribute to an increase in dyskinesia or even psychotic symptoms in patients with PD, perhaps from an increase in the permeability of the blood–brain barrier. If either of these symptoms is seen during a course of ECT in a patient with PD, the dose of antiparkinson medication should be reduced [114].

Psychosocial Treatment

Although antidepressants are effective and often necessary for treating depression in patients with PD, psychosocial interventions should not be neglected. Psychotherapy can be very helpful for cognitively intact patients with PD, and may be the most helpful for those demonstrating depressive symptoms at the time of diagnosis [83]. Because PD is a chronic, progressive illness, helping patients develop coping strategies and providing support is beneficial. Involving the spouse in the treatment plan is recommended, as the spouse is often the key support person for the patient. Support groups should be strongly recommended, since they may provide an excellent form of encouragement for both the patient and family.

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Anxiety in Parkinson's Disease

2

Tanya Simuni and Hubert H. Fernandez

Abstract

Anxiety is a common neuropsychiatric manifestation of PD that has a significant impact on disease-related QOL. There is a remarkable paucity of organized data on the choice of pharmacological management of anxiety in PD. Well-designed studies are necessary. However, based on clinical experience, the agents that are effective in management of the primary anxiety disorders also appear to be efficacious in PD-related anxiety.

Keywords

Anxiety disorders • Agoraphobia • Anxiety disorders in PD • Beck anxiety inventory • Hospital anxiety and depression scale • Zung self-rating anxiety scale • Hamilton anxiety rating scale • Spielberger state trait anxiety inventory • Anxiety status inventory

Definition

According to the diagnostic and statistical manual of mental disorders (DSM) IV classification, anxiety disorders are classified into the following: panic disorder without agoraphobia, panic disorder with agoraphobia, agoraphobia without panic disorder, specific phobia, social phobia, obsessive–compulsive disorder (OCD), posttraumatic stress disorder, acute stress disorder, generalized anxiety disorder (GAD), anxiety disorder due to a general medical condition, substance-induced anxiety disorder, and anxiety disorder not otherwise specified [1].

A *panic attack* is a discrete period characterized by the sudden onset of intense apprehension, fearfulness, or terror, often associated with feelings of impending doom. During these attacks, symptoms such as shortness of breath, palpitations, chest pain, choking or smothering sensations, and fear of "going crazy" or losing control are present. In *panic disorder*, there is a persistent concern over recurrent unexpected panic attacks.

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Agoraphobia is anxiety about, or avoidance of, places or situations from which escape might be difficult (or embarrassing).

In *specific phobia*, the anxiety is provoked by exposure to a specific feared object or situation, often leading to avoidance behavior; *social phobia* is provoked by exposure to certain types of social or performance situations.

Obsessive compulsive behavior is characterized by obsessions (which cause marked anxiety or distress) and/or by compulsions (which serve to neutralize anxiety).

Post-traumatic stress disorder is characterized by the reexperiencing an extremely traumatic event, accompanied by increased arousal and avoidance of stimuli associated with the trauma. The symptoms are similar in *acute stress disorder*, except they occur immediately in the aftermath of an extremely traumatic event.

Generalized anxiety disorder is characterized by at least 6 months of persistent anxiety and worry.

Epidemiology

Most non-Parkinson's disease (PD) studies demonstrate that anxiety disorders are less common in the elderly than in younger adults. In the Epidemiologic Catchment Area Study, the overall prevalence of anxiety disorders was 5.5% in people over the age of 65 years, compared with 7.3% in subjects of all ages [2]. Bland et al. [3] found the 6-month prevalence rates of all anxiety disorders to be 3.5% in people over the age of 65 living independently, 5.5% in people ≥65 living in institutions, and 6.5% in subjects of all ages.

In contrast, anxiety disorders in PD exceed prevalence rates in the geriatric population and occur more frequently than in any other medical illness of comparable disability [4, 5]. The reported prevalence of anxiety in the PD population varies between 25 and 40% [5–12]. Variability is ascribed to the type of anxiety disorder studied, differences in methodology including ascertainment cohorts (tertiary referral centers versus general PD population), and criteria of the diagnosis of anxiety disorder. A recent cross-sectional prospective survey of 450 non-demented PD patients reported the prevalence of anxiety in a PD population to be 51%, compared with 29% in the group of patients with other medical conditions, based on the Hospital Anxiety and Depression Rating Scale (HADS) [4]. Another study that used DSM-IV structured interview reported 43% cross-sectional and 49% lifelong prevalence of anxiety disorders in PD [13]. Overall, the studies that use self-reported scales provide higher prevalence rates compared with the studies that utilize standardized clinical diagnostic interviews, but all report substantially higher prevalence of anxiety in PD compared with the general population. Anxiety disorders in psychiatric patients generally begin by young adulthood, compared with an older age of onset in PD. Anxiety along with depression may predate the onset of motor manifestations of PD by several years [14]. Thus, the observations that anxiety may be a pre-motor feature of PD and that its prevalence is higher in PD than in the geriatric population and other chronic illnesses are suggestive that anxiety may be etiologically related to the neurobiological changes that accompany PD and not simply a behavioral reaction to chronic disability.

Impact of Anxiety on PD-Related Quality of Life

Multiple studies demonstrate that mood dysfunction is the leading factor contributing to PD-related quality of life (QOL) impairment [15, 16]. Anxiety, along with depression, plays a significant role. A recent study explored the impact of non-motor symptoms on QOL in 1,072 consecutive patients with PD and reported that anxiety was the second most common complaint (56%), after fatigue (58%), reported by the patients; along with apathy, it was the major contributor to QOL impairment [17]. These data should strongly enforce the need for vigilance by physicians and other health professionals with regard to the diagnosis of anxiety and awareness of potential treatment approaches for anxiety in PD.

Diagnosis of Anxiety in PD

Anxiety remains under-diagnosed and under-recognized in PD. Physicians tend to focus on the motor disability in PD, frequently neglecting to address the nonmotor manifestations of the disease. Likewise, PD patients tend to attribute their symptoms to suboptimal motor control, which makes it difficult to recognize the neurobehavioral aspects of disability unless structured questionnaires are administered. Shulman et al. [10] demonstrated a significant discrepancy between the assessment of the presence of anxiety based on validated patient self-reported scales (39%) compared with the assessment of the physician (19%). The same discrepancy was present for depression and sleep disturbance.

One of the major limitations of epidemiological and interventional studies of anxiety in PD is the absence of a specific diagnostic scale that is accepted as a screening tool for this disorder in the PD population. A Movement Disorders Society Task Force has reviewed multiple scales and identified six anxiety rating scales that have been either partially validated or used in PD [18]: the Beck Anxiety Inventory (BAI) [19], the Hospital Anxiety and Depression Scale (HADS) [20], the Zung Self-Rating Anxiety Scale (SAS), and Anxiety Status Inventory (ASI) [21], the Spielberger State Trait Anxiety Inventory (STAI) [22], and the Hamilton Anxiety Rating Scale (HARS) [23]. Item 5 (anxiety) of the NPI was also included in the review [24]. The HADS has been used most frequently, though none of the scales possesses all the necessary validation and clinimetric properties to be considered a disease-appropriate screening tool. The committee recommended further validation of the existing scales [18]. In the interim, clinicians should use their judgment and familiarity with the particular scale they choose, with the understanding that the formal diagnosis of anxiety also requires a DSM-IV based clinical diagnostic interview.

Clinical Features

Types of Anxiety Disorders Found in PD

GAD, panic disorder, social phobia, phobic disorder, agoraphobia, and OCD all have been described in individuals with PD [7, 25–27]. The types of anxiety disorders in PD appear to be clustered in the panic, phobic, and GAD areas [13, 26, 27]. Vazquez et al. [11] described only panic disorder, whereas Schiffer et al. [9] reported the presence of panic and GAD. Lauterbach and Duvoisin [7] described anxiety disorders in familial parkinsonism and noted a lower rate of panic disorder (7.9%) and higher rates of social phobia (5.3%) and OCD (13.2%) in their cohort. A recent study in a cohort of 127 subjects with PD reported that anxiety disorder not otherwise specified (NOS), often associated with PD motor fluctuations, was the most common type of anxiety (30%) followed by specific phobia (19%), panic attacks (10%), and social phobia (9%) [13].

There also are OCD-like behaviors described in PD that have received a lot of attention recently; these are discussed in detail in Chap. 3.

Anxiety and Motor Performance

Older studies have observed anxiety symptoms to appear after the diagnosis of PD has been established, in contrast to depression, which may precede the onset of motor disability [11, 27]. However, more recent data point to the fact that anxiety also can be part of the pre-motor manifestations of PD [7, 14, 28, 29].

Although most studies have documented no significant differences in PD severity between those with and without anxiety [26, 27], the relationship between anxiety and motor fluctuations is intriguing. It has long been recognized that symptoms like panic, flushing, and sweating can be principal nonmotor manifestations during the "off" state [30]. Moreover, pervading anxiety

disorders are reported to occur more often among PD patients who experience "on–off" motor fluctuations and symptoms tend to worsen during the "off" state [5, 11, 27]. Some studies have noted that anxiety improved significantly from "off" to "on", and worsened again in the "on" state when dyskinesias appeared [31]; others have failed to consistently show a relationship between anxiety and motor state [32]. Thus, anxiety itself can be a manifestation of an "off" state, can be worsened by motor fluctuations, or can occur independently of, and even precede, motor manifestations.

Anxiety and Medications

There are conflicting reports on the relationship between anxiety and anti-PD medications. Some describe panic attacks as more common in levodopa-treated patients [11]; others find no relationship with levodopa therapy [26, 27]. Similar conflicting findings have been reported with pergolide [26, 33].

Depression, Dementia, and Anxiety

Depression occurs in up to 40% of PD patients. Although anxiety in PD can occur in the absence of depression, there appears to be a special relationship between the two psychiatric disorders in PD [4, 11, 34]. Menza et al. [26] found that 92% of PD patients with anxiety also had depression and 67% of depressed PD patients carried a diagnosis of anxiety. Similar data were reported recently in a large cohort of French PD patients: 55% of individuals with possible/probable anxiety had comorbid depression, compared with 24% in the group without anxiety; 70% of patients with depression had comorbid anxiety [4]. That study and others have reported that depression in combination with panic and/or anxiety occurred more frequently among PD patients than in subjects with other medical conditions or in healthy controls [5]. Depression in PD often has been described as "atypical," with greater anxiety and less self-punitive ideation [9, 35].

Information is limited on the relationship between anxiety and dementia in PD. Aarsland et al. [36] reported the prevalence of neuropsychiatric co-morbidity based on the 10-item Neuropsychiatric Inventory (NPI) in a cohort of 537 patients with PD dementia who were enrolled in a study of rivastigmine; 89% of patients had a least one symptom on the NPI with the most common being depression (58%), apathy (54%), anxiety (49%), and hallucinations (44%). NPI symptoms separated into clusters; patients with high scores on depression/anxiety (mood cluster) had lower scores on apathy scales and vice versa. Although the presence of mood dysfunction in PD dementia was similar to the profile seen in Alzheimer's disease, the prevalence of apathy and hallucinations was substantially higher, suggesting that a different pathological substrate is responsible for these symptoms in PD dementia. Similar results were reported in earlier smaller studies [11, 34, 37], although a few studies noted a low prevalence of anxiety in PD dementia patients [27, 38]. Additional data are necessary.

Neurobiology

The etiology of anxiety in PD is not well understood and, unfortunately, has not been systematically studied. The notion that the higher prevalence of anxiety in PD compared with the general population is based on the impact of chronic illness on the patient's psychological state is disputed by data demonstrating a higher frequency of GAD and panic attacks in PD compared with patients with multiple sclerosis or other debilitating medical conditions, such as osteoarthritis [26, 27]. As mentioned earlier, some recent studies have demonstrated that anxiety symptoms may precede the onset of motor features in PD [14]. There are also data demonstrating that premorbid anxiety can be a risk factor for PD. A cohort of 35,815 male health care professionals was followed prospectively for 12 years [39]. At the end of the follow up period, 189 subjects had developed PD. After adjustment for age, smoking, and caffeine intake, the relative risk of PD was 1.5-fold higher in the group with

the highest level of anxiety, compared with the group with lowest [39]. There also is intriguing data that first-degree relatives of patients with PD have a higher prevalence of anxiety disorders [40]. Thus, most of the available data support the hypothesis that anxiety in PD is caused by neurochemical and neuropathological changes of the disease itself rather than simply a psychological reaction to a chronic condition.

Neuroanatomy

The alterations in basal ganglia (BG) motor circuitry in PD have been well studied and delineated [41]. However, the pathophysiology of PD extends beyond the "motor" basal ganglia [42]. Early manifestations of anxiety and depression in the clinical course of the disease can be well explained by Braak's hypothesis of the staged progression of the neuropathological changes in PD, with α-synuclein staining of the locus ceruleus (noradrenergic) and raphe nuclei (serotoninergic) preceding the earliest changes seen in the substantia nigra [42]. Additional neuroanatomical circuits potentially linking anxiety and PD may involve the nucleus accumbens, which modulates the output of the striatal motor system based on ventral tegmental and temporal lobe limbic inputs [43]. The shell of the nucleus accumbens is closely linked or continuous with the anterior extension of the amygdala [44]. Thus, both structures provide circuitry linkage between the BG motor system and limbic structures, thereby possibly generating an anxiety-type response [45].

Neurochemistry

The neurochemical substrate of anxiety in PD is complex. Obviously, the main neurochemical dysfunction in PD is dopamine (DA) deficiency. Anxiety in PD may be directly related to dopaminergic deficit or may be the result of imbalance in other neurochemical pathways that are directly or indirectly affected by PD. The main neurotransmitters implicated in the pathogenesis of anxiety are norepinephrine (NE), serotonin, gamma-aminobutyric acid (GABA), as well as few neuropeptides [46].

Dopamine

Some evidence suggests that DA deficiency may be directly related to anxiety, specifically social phobias and panic disorder [47, 48]. In a study of levodopa infusion in patients with motor fluctuations, higher serum levodopa levels correlated with lower anxiety scores [49]. Anxiety scores were lowest during the "on" state and highest during the motor "off" state [49]. Although no escalation of anxiety with dyskinesia was evident in this study, other authors noted a negative impact of dyskinesia, at least on mood [31]. A recent study involving a cohort of PD patients who underwent DBS surgery strongly supports the role of mesolimbic DA in the control of anxiety [50]. A subset of patients, who postoperatively had a significant reduction of the dose of oral dopaminergic therapy as a result of successful DBS stimulation, developed anxiety along with depression and apathy. The presence of preoperative nonmotor fluctuations during a levodopa challenge test was a significant predictor of the development of postoperative mood changes. Nonetheless, it is unlikely that DA deficiency is the sole neurochemical reason for anxiety in PD, since the majority of studies have demonstrated no difference in the degree of motor disability between PD patients with and without anxiety [5, 26, 27].

Norepinephrine

One of the major neurotransmitters implicated in the development of anxiety is NE [44]. Loss of catecholaminergic cells in the locus ceruleus has been demonstrated in PD and is supported by Braak's data [42, 51, 52]. The noradrenergic pathways originating from the locus ceruleus are affected as well, specifically the dorsal ascending noradrenergic pathway that projects from the locus ceruleus to the cerebral cortex, amygdala, hippocampus, and septum. Recent functional imaging data support the role of monoamines in the development of mood dysfunction in PD. PD patients with and without depression and anxiety

were imaged with [11C]RTI-32 PET, an in vivo marker of both DA and NE transporter binding, to compare differences between the cohorts [53]. Severity of anxiety was inversely correlated with [11C]RTI-32 binding in the locus coeruleus and in several regions of the limbic system.

Another postulated mechanism of the development of primary anxiety disorder is inhibition of presynaptic alpha-2-adrenergic receptors [46]. In animal models, inhibition of these receptors presynaptically results in increased NE activity and anxiety behavior [46]. Yohimbine, an alpha-2-adrenergic receptor antagonist, has been shown to cause panic attacks in patients with panic disorder but not in healthy controls [54]. The number of alpha-2-adrenergic receptors is decreased in PD subjects both centrally and peripherally [26, 55]. Richard et al. [56] demonstrated that yohimbine challenge in PD subjects with a history of anxiety produced panic attacks at a rate comparable to psychiatric patients with primary panic disorder. All PD patients, irrespective of a history of anxiety, demonstrated sensitivity to yohimbine-induced somatic symptoms; none of the controls did [56]. These data support the role of impairment of NE pathways in PD-related anxiety disorders.

Serotonin

Another neurotransmitter implicated in the development of primary anxiety disorders is serotonin. There is strong evidence of degeneration of the serotoninergic system in PD. Studies demonstrate loss of neurons in the median and dorsal raphe nuclei [57]. A recent postmortem study demonstrated loss of all key serotonergic markers (neurotransmitter and metabolite, transporter protein, synthesizing enzyme protein) in the striatum in patients with PD compared with controls, with preferential loss in the caudate compared with putamen [58]. Braak's data also support early involvement of the raphe nucleus in the neurodegenerative process of PD [42]. PD is associated with reduced concentrations of serotonin in the basal ganglia nuclei and frontal cortex; reduced density of binding sites for serotonin-reuptake inhibitors is also evident in the putamen [59].

A functional polymorphism in the promotor region of the serotonin transporter gene has been linked to anxiety [44]. PD patients who carried the short allele of the serotonin transporter scored higher on the anxiety scales than non-carriers, pointing to potential common genetic mechanisms of primary anxiety and anxiety in PD [60].

Gamma-Aminobutyric Acid

The potential role of GABA in the development of anxiety is supported by the animal data. Animals exposed to prolonged stress had a reduction in GABAA receptor binding in frontal cortex, hippocampus, and hypothalamus [61]. More importantly, the efficacy of benzodiazepines, which are GABAA agonists, for the treatment of anxiety supports involvement of the GABAergic system in the development of anxiety disorders [62]. The exact role of GABA dysfunction in the development of anxiety in PD has not been established. Autopsy data from PD brains demonstrate conflicting evidence of increased concentration of GABA in the putamen and pallidum but reduced concentration in the cortex [63].

Glutamate

Glutamate could play a role in the development of PD-related anxiety [63]. PD is associated with disinhibition of glutamatergic output of the subthalamic nucleus, which results in excessive glutamatergic stimulation of the basal ganglia motor nuclei and potentially of mesolimbic structures as well [41]. Glutamate receptors mediate excitatory neurotransmission, which is activated by stress [63]. *N*-Methyl-D-aspartate receptor (NMDA) antagonists have an anxiolytic effect in animal models of anxiety [64]. However, studies of NMDA antagonists in human subjects have been halted because of the impact of those agents on memory and cognition.

Neuropeptides

A number of neuropeptides have also been implicated in the development of primary anxiety disorders. Cholecystokinin (CCK) and corticotropin releasing factor (CRF) seem to be anxiogenic; Neuropeptide-Y (NPY) and Substance-P are anx-

iolytic [46]. Pharmacological agents acting on those neuropeptides may prove to be more efficacious than the existing strategies for the treatment of anxiety, although their role in PD anxiety remains to be determined.

Treatment

The key to successful management of anxiety in PD is its early recognition. Once anxiety is identified, a "team approach" to treatment is most beneficial. Non-pharmacological management that includes education, counseling, and stress-reduction strategies should be an integral part of the management of any neurobehavioral disorder, but the majority of patients still will require pharmacological intervention.

The number of studies addressing the pharmacological management of anxiety in PD is insufficient [65, 66]. PD motor symptoms need to be adequately treated. Although most studies find no correlation between PD disability and incidence of anxiety, for the subset of patients with motor fluctuations, there is a clear correlation of anxiety with "off" states [13, 49, 67].

A number of animal studies have addressed the role of dopamine agonists in the treatment of anxiety. Ropinirole was demonstrated to have anxiolytic properties in rat, mouse, and marmoset models of anxiety, but these were not PD animal models [68]. An investigational D2-selective dopamine agonist, U-95666E, was shown to have both an antiparkinsonian and anxiolytic effect in the 6-OHDA rat model of PD [69]. Clinical trials of available dopamine agonists in PD have not looked at anxiety as an end-point; however, in some studies the incidence of treatment-induced anxiety was higher with dopamine agonists than with levodopa [70, 71]. Pramipexole has demonstrated an antidepressant effect in primary depression and PD depression, but its impact on anxiety was not studied [58, 59, 72–74]. A recently described dopamine agonist withdrawal syndrome is manifested by anxiety, panic attacks, agoraphobia along with other features, supporting a role of dopamine agonists in the control of anxiety in PD [75].

Benzodiazepines

Although there are no controlled data on the use of anxiolytic agents in the management of PD anxiety, their pharmacological properties and efficacy in other anxiety disorders support their use in PD population. The majority of PD patients with anxiety will require anxiolytic therapy in addition to dopaminergic medications. Benzodiazepines can be effective for management of GAD, panic disorders, and social phobias, but are not effective in OCD [76]. There is no adverse interaction between benzodiazepines and dopaminergic therapy but the potential additive sedative effect of both agents can lead to escalation of daytime somnolence, disruption of the sleep–wake cycle, and falling. Cognitively impaired patients may experience worsening of cognition and are at risk for hallucinations. These agents should be avoided in the elderly, and specifically PD patients on polypharmacy. Benzodiazepines should be limited to short-term use. Chronic use of this class of agents should be considered only when all alternative strategies to treat anxiety have failed.

Selective Serotonin Receptor Inhibitors

Selective serotonin receptor inhibitors (SSRIs) are becoming the preferred agents for the management of essentially any type of anxiety. SSRIs have a favorable adverse effect profile and limited drug–drug interactions. SSRIs are widely used in PD for the management of depression and associated anxiety. There are data on the efficacy of SSRIs in PD-related depression, although a practice parameter review on the subject concluded that the data are limited and more studies are necessary [66]. There are no studies addressing the efficacy of these agents in PD-related anxiety. Citalopram improved both anxiety and depressive symptoms in PD patients treated for depression in a small open label study [77]. Overall, SSRIs are safe to use in PD. However, there are a few issues of which physicians should be aware:

1. Concomitant use of SSRIs and monoamine oxidase inhibitors (MAOIs) can lead to the

development of the "serotonin syndrome" (SS). Non-selective MAOIs are contraindicated in patients taking levodopa due to the risk of hypertensive crisis. Selegiline and rasagiline are selective MAO-B inhibitors; neither have an MAO-A inhibitory effect in the prescribed doses. However, at higher doses both may become non-selective MAOIs [78]. The package insert of both drugs has a warning against the concomitant use of either tricyclic antidepressants (TCAs) or SSRIs due to their potential central nervous system toxicity, specifically SS, which presents with alteration of mental status, motor dysfunction, and autonomic dysfunction. Despite the theoretical concern for the increased risk of SS with concomitant use of these agents and antidepressants, it is a rare phenomenon, based both on the manufacturers' information and on a survey of a large group of movement disorders specialists [79, 80].

2. There are case reports of motor worsening or new-onset drug-induced parkinsonism in the setting of SSRI use, specifically fluoxetine [81, 82]. Whether this reflects unique properties of fluoxetine or is merely a reflection of falsely elevated incidence due to its wide use is unclear.
3. SSRIs can interact with agents metabolized by the cytochrome P450 system. Although some dopamine agonists can inhibit P450 enzymes, this interaction is of limited clinical significance. Among dopamine agonists, pramipexole does not inhibit P450 enzymes [83]. SSRIs vary in their degree of P450 inhibition: sertraline causes relatively less inhibition than fluoxetine and paroxetine [84].

Until formal clinical trials address the issue of the efficacy and safety of SSRIs in PD, the choice of a particular SSRI in the management of anxiety in PD should be based on the adverse effect profile of the particular agent, the patient's tolerance, and comorbidities.

Tricyclic Antidepressants

TCAs act by blocking NE and serotonin uptake; they also produce a long-term increase in receptor sensitivity [85]. There is a role for TCAs in the management of PD-related depression, pain, sleep dysfunction, as well as hypersalivation. There is essentially no information on the efficacy of TCAs in the management of anxiety in PD. A placebo-controlled study of nortriptyline and paroxetine CR designed to explore the efficacy of these agents for depression in PD included anxiety assessment as the secondary outcome measure [86]. Nortriptyline was superior to paroxetine CR and there was no difference in tolerability between the two agents. However, overall use of TCAs in PD is limited by the risk of anticholinergic adverse effects. TCAs carry a high risk of causing or worsening confusion. Amoxapine, a type of TCA, should not be used in PD because it is, in part, a dopamine receptor blocking agent and can worsen parkinsonism [87].

Bupropion and Buspirone

Bupropion is a monocyclic antidepressant with indirect dopamine agonist properties [85]. Bupropion improves depression in some PD patients [88], and may also have a positive effect on PD motor symptoms. The most problematic aspect of the drug is its potential to produce seizures, although this predominantly is limited to subjects with preexisting epilepsy. The effect of bupropion on PD anxiety has not been systematically evaluated, but its overall "stimulating" properties may limit its use.

Buspirone, which pharmacologically is related to bupropion, also has dopamine agonist properties. It can be effective for GAD, but is less likely to help panic or social phobia [89]. Based on its mechanism of action, buspirone has been studied in PD. The drug was well tolerated in doses up to 60 mg/day but did not produce either antiparkinsonian or anxiolytic effects [90]. At higher doses (100 mg/day), it caused worsening of motor function and worsening of anxiety [90]. Another study that looked primarily at the impact of buspirone on dyskinesia in PD did not demonstrate its anxiolytic effect at a dose of 20 mg/day [91].

Other Therapies

Mirtazapine is an antidepressant that acts via indirect enhancement of serotonin 5-HT1 receptors, as well as direct inhibition of alpha-2-presynaptic adrenergic receptors. It is effective in GAD [92]. It may potentially be a good treatment option for PD patients with anxiety and sleep dysfunction, due to its sedative effect at low doses.

Deep Brain Stimulation

Surgery has been established as an effective treatment option for patients with advanced PD. There is an extensive body of literature on the impact of surgical interventions on the cognitive and mood status in PD patients [93–95]. Information on its effect on anxiety is limited and mixed [96]. In order to interpret the literature, it is important to appreciate the high prevalence of anxiety in patients considered for surgical intervention, reported to be in the realm of 40%, on par with the general PD population [97]. Interpretation of most studies is limited by small cohorts of patients, the heterogeneous nature of the tools used for assessment of anxiety, and lack of a medical control arm. Studies report either improvement [95] or no change [98] in the level of anxiety postoperatively and occasional worsening, usually when it was not diagnosed preoperatively [99].

Witt et al. reported the neuropsychiatric outcomes of one of the few surgical studies that included a medical therapy control arm; in the study, 156 PD patients were randomized to the subthalamic nucleus (STN) DBS procedure versus best medical therapy [95]. Anxiety was reduced in the DBS group compared with the medication group (difference of changes in Beck anxiety inventory was 10.43 points); however, four patients in the DBS group developed postsurgical depression that remitted 6 months later. Ten patients in the DBS group and eight patients in the best medical treatment group had psychiatric adverse events. Smaller studies also have reported postoperative reduction of anxiety [100]. One study explored the role of DBS surgery in the earlier stages of PD and reported improvement of anxiety along with other measures of psychiatric morbidity in the surgical group, compared with the medically treated group, although the size of the cohort was small (20 subjects) [101]. In contrast, another study reported persistence and slight worsening of GAD after STN DBS [102]. A large proportion of patients with postoperative anxiety attributed their symptoms to the fear of failure of stimulators [102]. Recent reports have described increased risk of suicide in DBS patients; however, postoperative anxiety was not one of the risk factors, which included postoperative depression, impulse control disorders, and degree of postoperative reduction of dopaminergic therapy [103]. Impact of the target of stimulation, STN versus globus pallidus interna (GPi) on anxiety, has not been systematically studied.

Although the long-term impact of DBS on anxiety requires further investigation, the presence of uncontrolled anxiety is considered a relative contraindication for surgery until symptoms are adequately treated. In general, surgical protocols exclude patients with a high degree of anxiety, unless sufficiently treated, due to the concern that these patients will be unable to go through a lengthy and stressful surgical procedure performed while awake. Additional data in the form of prospective blinded studies addressing the efficacy of different surgical targets are necessary.

In conclusion, anxiety is a common neuropsychiatric manifestation of PD that has a significant impact on disease-related QOL. There is a remarkable paucity of organized data on the choice of pharmacological management of anxiety in PD and well-designed studies are necessary. However, based on clinical experience, the agents that are effective in the management of the primary anxiety disorders also appear to be efficacious in PD-related anxiety.

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Obsessionality

3

Marie-Andrée Bruneau

Abstract

This chapter examines the fascinating issue of obsessionality in Parkinson's disease (PD). The concept of obsessionality and current notions about the pathophysiology and neuropsychology of obsessive–compulsive disorder (OCD) are initially described. Particular features of obsessionality in neurological illnesses, and especially in PD, are provided. Both the parkinsonian personality and similarities that may link bradyphrenia and obsessional slowness are discussed and descriptive studies of obsessive–compulsive symptoms (OCS) in PD are reviewed. Repetitive-reward seeking behaviors in PD associated with dopaminergic treatment are described; similarities and differences between impulsive and compulsive disorders are outlined. OCS in neurological illnesses, including PD, may be clinically identical to idiopathic OCD, but descriptions usually reveal certain differences. OCS in neurological diseases are often associated with movement disorders and cognitive dysfunction, primarily of the dysexecutive type. Symptoms are mainly compulsive in nature, without the obsession or anxiety usually associated with idiopathic OCD. Questions remain about the distinctive pathophysiology and treatment response of OCS in PD.

Keywords

Parkinson's disease • Obsessionality • Obsessive–compulsive disorder • Reward-repetitive behavior • Impulse control disorders • Perseveration • Executive dysfunction • Basal ganglia • Cortico-subcortical circuits • Parkinsonian personality • Obsessional slowness • Hedonic dysregulation • Dopaminergic dysregulation syndrome • Behavioral addictions • Punding

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Introduction

Parkinson's disease (PD) is one of the most intriguing neuropsychiatric disorders. It offers a striking demonstration of the intricate intertwining of motor, cognitive, and behavioral functions within the brain. PD has been associated with many comorbid psychiatric disorders, such as depression, anxiety, and psychosis, which are discussed in other chapters of this book. However, one has to question whether psychiatric syndromes in neurological diseases are comparable to primary psychiatric illnesses and, if so, whether they share the same pathophysiology, clinical expression, and response to treatment. This question is especially relevant to obsessive–compulsive disorder (OCD). This chapter aims to clarify and update the reader's knowledge about obsessive–compulsive symptoms (OCS) in PD and also highlights some issues that should be investigated in future research.

The Concept of Obsessionality

OCD and OCPD

Obsessionality is usually associated with OCD or obsessive–compulsive personality disorder (OCPD). OCD is defined in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [1] as recurring obsessions and compulsions "severe enough to be time-consuming… or cause marked distress or significant impairment" while people recognize that their reactions are irrational or disproportionate and egodystonic (i.e., aspects of a personality that are viewed as disgusting, unacceptable, or incompatible with the rest of the personality). Obsessions are recurrent intrusive thoughts, impulses, or images that the patient attempts to ignore or suppress. Examples of topics are fear of contamination, aggressive or sexual thoughts, pathological doubt or concern about symmetry. Compulsions are repetitive behaviors or mental acts (e.g., washing, counting, or checking) that the patient feels driven to perform in order to reduce the anxiety associated with obsessions or according to rules that must be rigidly applied.

Since OCD is a clinically heterogeneous condition, with different phenotypic expressions, recent studies have tried to identify symptom dimensions in OCD [2]. A meta-analysis [3] of these studies demonstrated a robust four-factor symptom structure for OCS across the lifespan. The four OCD factors were: (1) symmetry and ordering, (2) forbidden thoughts (aggression, sexual, and religious), (3) contamination and cleaning, and (4) hoarding. Furthermore, these dimensions have been associated with distinct patterns of comorbidities, heritability, neural activity, and response to treatment [4]. Several other subtypes of OCD have received significant attention (OCD with early onset, with tics, with poor insight, with evidence of streptococcal infection).

OCPD is a pervasive pattern of preoccupation with orderliness, perfectionism, mental and interpersonal control at the expense of flexibility, openness, and efficiency [1]. Coincident aspects of OCD and OCPD are the need for order and symmetry, hoarding behaviors, and a maladaptive cognitive and behavioral inflexibility [5]. There is a debate whether OCPD is a true personality disorder or whether it represents a phenotypic variant of OCD; thus, it is often classified within the OCD spectrum disorders.

OCD Spectrum Disorders

Some DSM-IV Axis-I conditions share overlapping clinical features, genetic contributions, and possibly treatment response and have been proposed to belong within an obsessive–compulsive spectrum. Members of this putative spectrum so far include OCPD, body dysmorphic disorder, hypochondriasis, tic disorders, autistic disorders, and eating disorders. Some authors even include neurological illnesses such as PD and Huntington's disease as part of this spectrum [6]. Impulse-control disorders (ICD), in which repetitive behaviors are driven by pleasure rather than by relieving anxiety, are also part of the OCD spectrum. Such disorders encompass pathological gambling,

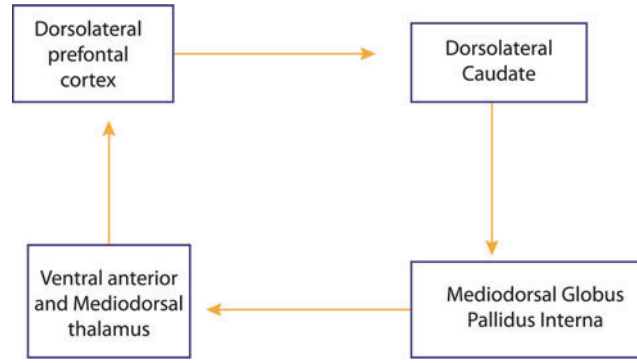


Fig. 3.1 Dorsolateral circuit

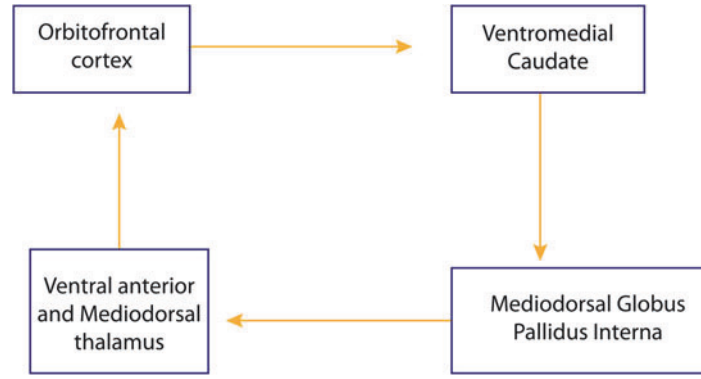


Fig. 3.2 Orbitofrontal circuit

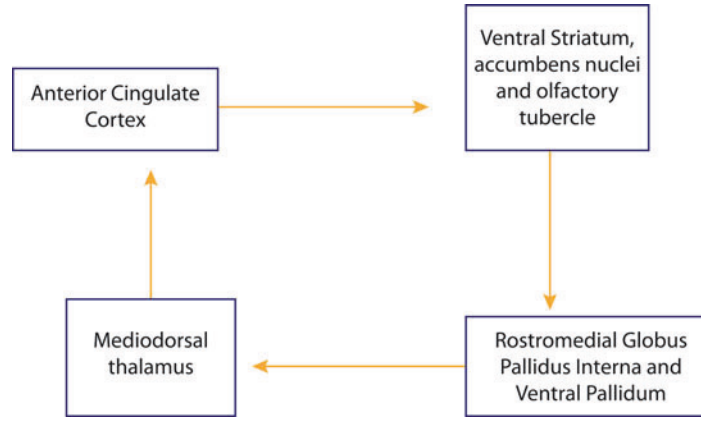
compulsive sex, compulsive shopping, trichotillomania, and compulsive skin picking. Impulsivity and compulsivity have been considered opposite poles of a continuous spectrum, but their relationship seems to be more complex. OCD often has features of impulsivity, especially in OCD associated with neurological illnesses (Tourette's, autism, frontal lesions, etc.). Furthermore, ICD are characterized by repetitive behaviors and impaired inhibition of these behaviors, suggesting a similarity to the frequently excessive, unnecessary, and unwanted rituals of OCD [7].

Pathophysiology of OCD

The pathophysiology of OCD has been studied in recent years by imaging, provocation, and treatment studies [8, 9]. Neurobiological theories of OCD suggest that specific frontal–subcortical circuits are involved in the symptoms and cognitive deficits associated with the disorder [10]. The dorsolateral loop (see Fig. 3.1) is involved in executive functions; the orbitofrontal circuit (see Fig. 3.2) is responsible for behavioral inhibition and selection of one response over others. The orbitofrontal cortex is also responsible for emotional reactions associated with environmental safety (e.g., reproduction, violence, hygiene, and order). Furthermore, the medial part of the orbitofrontal circuit has interactions with the cingulate ventral circuit (see Fig. 3.3) and thus plays a role in motivational evaluation of actions [11].

The striatum integrates complex neural networks related to motor, cognitive, and motivational functions. Thus, it is responsible for motor planning and integration, learning and reinforcement,

Fig. 3.3 Cingulate circuit



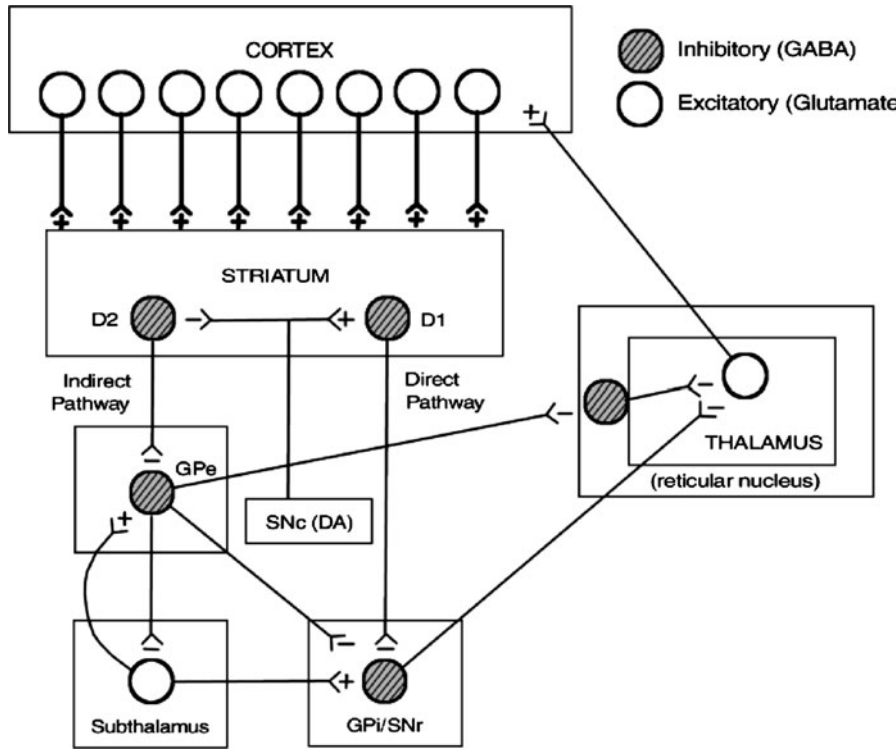


Fig. 3.4 Direct and indirect dopaminergeric pathways. *SN* substancia nigra, *GPi* globus pallidus internal, *GPe* globus pallidus external, *D2* dopaminergeric receptors type 2, *D1* dopaminergeric receptors type 1

and behavioral integration and selection. The striatum is also responsible for maintaining a balance between the excitatory and inhibitory influences on thalamocortical pathways via dopaminergic modulation of the direct and indirect loops (see Fig. 3.4) [10]. This balance allows initiation, reinforcement, maintenance (direct pathway), and suppression (indirect pathway) of complex motor programs, when appropriate. In a simplified way, the direct loop is operative until the desired action

is completed; the indirect path then suppresses the behavior, permitting a switch of behavioral sets. The direct loop is more strongly linked to the orbitofrontal and cingulate cortex and is activated by dopaminergic action on D1 receptors. The indirect loop is related to the dorsolateral cortex and inhibited by dopaminergic action on D2 receptors. The direct and indirect loops are also modulated by other neurotransmitters such as serotonin [2].

Functional imaging of OCD is characterized by hyperactivity, not only of the orbitofrontal cortex but also of the cingulate and caudate nuclei [8, 9]. Researchers have suggested that an imbalance between the direct and indirect pathways within frontal striatal circuits results in a hyperactivated ventral (orbitofrontal and cingulate) and inhibited dorsolateral system, explaining both the clinical and neuropsychological symptoms of OCD [12]. It is postulated that, in OCD, the striatal filter is dysfunctional and allows unselected impulses to spread to the orbitofrontal and cingulate cortex, maintaining danger avoidance responses. The orbitofrontal and cingulate hyperactivity reflects compensatory mechanisms that allow higher order restraints over striatally mediated dyscontrol [13]. The premise in OCD is that direct influences are prominent because the indirect loop is dysfunctional. If there is a loss of indirect influences, the patient becomes stuck in a "what if?" set. Treatment of OCD by serotonergic medications, cognitive-behavioral therapy, or psychosurgery changes the balance between direct and indirect pathways by reducing the global excitatory tonus of the system and consequently reducing excitatory thalamocortical projections [14, 15].

It remains unclear why this indirect loop becomes dysfunctional in OCD. One hypothesis is that some striatal neurons (striosomes) are very sensitive to hypoxic insults. If they are injured, the influence of the direct pathway becomes excessively prominent. The origin of such hypoxic insults could be varied [14, 15]. In idiopathic OCD, a prenatal hypoxic insult associated with a possible genetic predisposition has been postulated. About 10% of patients with OCD have family members with OCD, and this reaches 15–30% in OCS. Twin studies show a 60–90% monozygotic concordance, compared with 20–50% for dizygotic twins [16]. However, any kind of insult (ischemic, infectious, or traumatic) to these neurons could give rise to the same symptomatology and explain the pathophysiology of "neurological" OCD (i.e., OCD appearing after a neurological insult).

In short, conscious executive processing (frontal) and implicit-automatic processing (basal ganglia) function in parallel in a normal brain. If the basal ganglia filter is dysfunctional, the frontal cortex becomes overloaded with information that is usually treated automatically (or unconsciously). This kind of information then intrudes into conscious knowledge, which leads to obsessions. Behavioral selection is then confined to compulsive actions. As Valerie Voon elegantly put it: "OCD could be considered as the result of implicit processing deficits reflected in the aberrant processing of species-specific procedural strategies (related to social and territorial concerns focusing on themes of violence, hygiene and sex), presumably stored within the striatum" [17].

Neuropsychology of OCD

Perseveration is defined as the inappropriate continuation of an act or thought after its proper context has passed, or as the pathological repetition of the same response to different stimuli [18]. Cummings [19] declared that perseverations might represent OCS in neurological patients with cognitive dysfunction. Indeed, perseverations have a stereotypical and repetitive aspect similar to OCS. Perseveration involves self-regulation difficulty and mental inflexibility—aberrations usually associated with executive dysfunction. Executive functions include task planning, problem solving, mental flexibility, self-control, and inhibition. These functions are processed mainly by the dorsolateral cortico-subcortical pathway [10].

To complicate the issue, executive dysfunction has been described in some, although not all, neuropsychological studies in OCD [20–22]. Some studies demonstrate set-shifting and

response inhibition deficits in OCD [11]. In one study [23], OCD subjects made significantly more perseverative errors on the Wisconsin Card Sorting test (WCST), which is a set-shifting test, than normal controls and linear associations were found between the obsessive factor of the Yale-Brown Obsessive-Compulsive Scale (YBOCS) [24] and WCST errors [25]. However, since performance on the WCST seems to be mostly affected by lesions of the dorsolateral prefrontal cortex, the validity of using WCST in OCD has been questioned. Consequently, some authors used the Object Alternating Test (OAT) and Delayed Alternation task (DAT), which are set-shifting tasks sensitive to orbitofrontal damage, and found marked deficits in OCD patients [26]. These studies also reported linear associations between symptom severity and perseverative errors of commission on response [11].

Gu et al. [12] and Evans et al. [11] proposed that task-switching abilities are related to decreased responsiveness of the dorsal circuit for switching sets and increased responsiveness of the ventral (orbitofrontal and cingulate) areas repeating a previous task, in accordance with current neurobiological models of OCD. These deficits in cognitive flexibility might also be trait-like in nature, based on the findings of impaired set-shifting ability in unaffected first-degree relatives of OCD [27].

OCS in Neurological Illnesses

OCS have been described in many neurological illnesses. Frontal lobe lesions are associated with perseverative and stereotypic behaviors [28]. An example of early frontal lobe degeneration is frontotemporal dementia (FTD). A diagnosis of FTD supposes mental inflexibility, perseverative, and stereotypical behavior or speech as supportive features [29]. As many as 78% of patients with FTD display OCS, and these may be the symptoms leading to diagnosis [30]. Descriptions range from classical OCD (counting, checking, cleaning, and symmetry compulsions) to, more commonly, verbal and motor stereotypies. OCS in FTD are associated with coincident executive dysfunction. Lack of frontal lobe inhibition on existing striatal motor programs may explain these symptoms. Patients with FTD display less distress, resistance, and insight, and their compulsions are less likely to be associated with obsessions, compared to the typical patient with OCD [30].

Pathological processes that involve basal ganglia, particularly the caudate nucleus, are associated with OCD. An elegant serie of OCD associated with basal ganglia lesions of various etiologies (e.g., ischemic, infectious, and toxic) has been published by Laplane et al. [31, 32]. They described OCD linked with lesions frequently localized to the caudate, putamen, or pallidum. Descriptions ranged from classical OCD to motor or verbal stereotypies. For example, some patients could not stop stirring soup or turning lights on and off. Punding and sucking behaviors were also described. The absence of anxiety or distress with compulsions is striking in the majority of these descriptions. No evident obsessions could be found to account for the compulsive behavior. OCS were often associated with movement disorders and executive dysfunctions.

Sydenham's chorea, a poststreptococcal infection movement disorder involving antineuronal antibodies directed against basal ganglia, is associated with OCS in 60–80% of the cases [33]. OCD occurs only in relationship to the chorea, never with the poststreptococcal rheumatic arthritis alone, which supports the concept that central nervous system involvement is necessary for the expression of this symptomatology. Some descriptions of OCD in Huntington's disease [34], a neurodegenerative genetic disorder affecting the caudate nuclei, with predominant dysfunction of the indirect pathway, are also recorded in the literature.

Moreover, OCD is strongly linked with Tourette's syndrome (TS) to the extent that some authors view OCD as a differential expression of the putative TS gene [35]. The pathophysiology of TS may involve dopaminergic striatal hyperinnervation, which then gives rise to hyperactive cortico-subcortical pathways via thalamic disinhibition. Sensory-motor loop hyperactivity may be responsible for tics; hyperactivity in orbitofrontal and cingulate loops may produce OCD

[36]. However, the phenomenological distinction between complex tics and compulsions remains a difficult task. Tics are usually preceded by a sensory urge; compulsions may be driven by a cognitive urge (obsession?). Performance of tics and completion of compulsive behaviors both provide relief to the patients with TS.

A neurological illness associated with parkinsonism and OCD is Von Economo's encephalitis [37]. Von Economo's encephalitis, or encephalitis lethargica, was pandemic between 1917 and 1929, affecting up to five million people worldwide. Its etiology has never been determined, although an infectious pathogen was suspected. Its pathology entailed basal ganglia, substantia nigra, and mesencephalic inflammation. Patients first presented with flu-like symptoms and then developed neurological symptoms—most prominently lethargy or hypersomnolence. Movement disorders (parkinsonism, choreoathetosis, and myoclonus) also occurred in some patients, along with psychotic features (e.g., delusions, hallucinations, and catatonia). The postencephalitic syndrome, appearing months to years after the acute infection, was associated with parkinsonism in 30–60% of cases and with neuropsychiatric features in 50–100%. It was also associated with a subcortical type of dementia with prominent executive dysfunction. OCS appeared in conjunction with oculogyric crisis. Case reports depicted stereotyped compulsive movements without obsessions; counting, touching, or symmetry compulsions; sexual or aggressive obsessions; sensations of "forced thought"; and coprolalia and palilalia [38]. These crises could last from a few minutes to hours and sometimes were associated with tics and acute mood changes.

OCS in PD

Basal Ganglia Illnesses

OCD, Like PD involves basal ganglia dysfunction. Degeneration of the dopamine-containing neurons of the substantia nigra, with consequent loss of dopaminergic input to the basal ganglia, leads to the clinical presentation of PD [39]. Dopaminergic neuronal loss and its effect on the nigrostriatocortical circuit are illustrated clinically primarily by hypokinetic and cognitive syndromes. Cognitive dysfunction in PD was originally believed to be related to dorsolateral striatocortical circuit dysfunction [40], also the consequence of the loss of monoaminergic afferents, primarily dopaminergic but also noradrenergic, serotonergic, and cholinergic. Although PD can be associated with an Alzheimer's type of cognitive dysfunction (PD + Alz) and Lewy body dementia, the usual type of cognitive dysfunction related to PD is a subcortical type of dementia. Findings include bradyphrenia, visuospatial deficits, working memory difficulties, diminution of verbal fluency, and executive dysfunction, including mental rigidity and perseverations [41].

Parkinsonian Personality

A premorbid parkinsonian personality with obsessional features (perfectionism, preoccupation with control, and mental rigidity) has been described in PD, the so-called "parkinsonian personality" [42–44]. Analogies can be made between this description and Cloninger's hypodopaminergic personality with reduced novelty seeking [45, 46]. It can be questioned whether these characteristics represent early signs of central hypodopaminergism associated with executive dysfunction. Executive dysfunction may impede the adaptation to new settings because patients have difficulty changing strategies or cognitive sets. Such individuals may also be less likely to engage in novelty-seeking behavior because they may have problems dealing with new situations. To further complicate matters, the retrospective quality of such descriptions is subject to recollection bias, which itself might be influenced by the actual symptomatology.

Obsessional Slowness and Bradyphrenia

Some authors have compared the obsessional slowness encountered with severe forms of OCD to the parkinsonian bradyphrenia [47, 48]. They

suggest that obsessional slowness represents difficulty in initiating action and suppressing perseverative behaviors. Patients with this type of OCD are excessively meticulous and disintegrate their sequences of action until perfection is reached, resulting in slowness of execution. In bradykinesia, spontaneity of movement is lost, and movements disintegrate into multiple cautious and slowed action sequences. Bradyphrenia and obsessional slowness in thought processes may, therefore, share a common ground [49].

Prevalence Studies of OCS in PD

Despite the clinical wisdom that PD can be associated with OCS, only six studies measured the prevalence of OCS in PD from 1984 to 2010. Tomer et al. [50] studied OCS in 30 patients with PD using the Leyton Obsessional Inventory (LOI). The LOI is divided into "symptoms" questions (recurring thoughts, checking, dirt and contamination, order and routine, etc.) and "trait" questions (stubbornness, pedantry, hoarding, etc.). Of these 30 patients, 17 suffered from OCS and 19 had an "obsessional trait". A significant correlation was found between LOI results and the results on the Beck Depression Inventory. Müller et al. [51] reviewed OCS in 20 PD patients using the Maudsley Obsessive-Compulsive Inventory (MOCI) and the Hamburg Obsessive-Compulsive Inventory. Patients with PD scored higher than controls only on the "ordering" subscale. Maia et al. [52] measured OCS in 100 patients with PD using the Yale-Brown Obsessive-Compulsive Scale (YBOCS) and found OCS in 17 patients; only five patients met the criteria for OCD. No differences in OCS between PD and controls could be demonstrated. However, OCS, particularly for symmetry and ordering, were associated with left side motor symptom predominance. Alegret et al. [53] reported on 72 patients with PD, finding higher MOCI and LOI scores in patients with PD than in controls. However, these scores did not reach a pathological level. Alegret et al. found higher proportions of "checking," "doubting," and "cleaning" OCS in their subjects with PD. Patients' MOCI scores correlated with the severity and duration of their illness. Harbishettar et al. [54] assessed OCS and OCD in 69 non-demented PD patients and 69 matched medically ill controls, using the YBOCS, and found no difference between the two groups. Siri et al. [55] used the SCL-90 self-report questionnaire in 486 non-demented PD patients. One of the nine subscales of the SCL-90 measures OCS. Forty-eight percent of patients had mild OCS while 10% had severe OCS.

Taken as a whole, these six studies suggest the presence of OCS in PD. However, rarely do these symptoms reach values diagnostic for OCD. Furthermore, different screening instruments, small numbers of patients, and the absence of a control group in some studies make these results difficult to interpret. Based on this literature, there no is clear epidemiological picture of OCS in PD, Also unknown, whether OCS in PD might be related to adverse effects of medication or to affective or executive symptoms. Also unknown is whether OCD in basal ganglia "neurological" illnesses, such as PD, is truly similar to "idiopathic" OCD.

Punding in PD

Punding has been defined as a constellation of complex but purposeless stereotyped behaviors. Examples are repetitive manipulation of equipment; the continual handling, examining, and sorting of objects; excessive grooming; hoarding; incessant fidgeting at clothes or oneself; and repetitive verbalizations [56]. The possible phenomenological confusion with symmetry-ordering or hoarding OCS is easy to recognize. Punding was first described in amphetamine and cocaine addicts. The first description of punding associated with levodopa treatment goes back to 1994. The stereotyped behaviors in punding are likely homologous to the complex stereotyped behaviors in animals with amphetamine stereotypies. In prevalence studies, punding was present in 1.4–14% of PD patients and correlates with the total daily dose of dopaminergic drugs [57, 58]. It has a compulsive flavor; any interruption from an outside source leads to frustration and irritability,

but no intrusive fears or obsessions are associated with it. The behavior is irresistible but rarely considered pleasurable; rather it is associated with feelings of relief. Insight into the disruptive or senseless nature of the behavior is often absent. It is frequently related to the individual's previous interests [56]. Some investigators have conceptualized punding as motor intrusions or aberrant processing of learned procedural strategies from past experiences, presumably within the striatum [17]. Others view it as the inability to modulate automatic routines, likely due to impaired cognitive control, resulting from impaired frontal lobe functions [57]. Some classify punding within the dopamine dysregulation syndrome and as such, relate it to plastic changes in the ventral and dorsal striatal structures, including the nucleus accumbens [56]. Usually, reduction in dopamine agonist dosage improves the behavior.

Repetitive-Reward Seeking Behaviors in PD Associated with Dopaminergic Therapy

Recently, complex behaviors, linked by their reward or incentive-based and repetitive natures, have surged to clinical relevance as they occur during dopamine replacement treatment. Various names have been applied to these behaviors, including impulse control disorders (ICD), hedonic dysregulation, behavioral addiction, dopamine dysregulation syndrome, or repetitive-reward seeking behaviors in PD associated with dopaminergic therapy. These behaviors include pathological gambling, compulsive sexual behavior, compulsive buying, compulsive binge eating, compulsive medication use, and punding. They are the result of a failure to resist an impulse to perform an act that is potentially harmful to the person or others. They occur commonly without subjective distress and are frequently hidden, since they are experienced as being internally consistent with one's thought and behavioral repertoires [59]. The true prevalence of ICD in PD is unknown but preliminary estimates are approximately 2–6% for pathological gambling, 2–10% for compulsive sexual behavior, and 0.4–2% for compulsive buying [60]. ICD are more prevalent in PD than in the normal population (0.25–3%) and rise to 14–17% in PD patients on dopamine agonist therapy, in contrast to only 0.7% in PD patients on levodopa alone [61]. Dopamine agonists increase the risk of developing ICD by 2–3-fold [62]. This effect is class specific and presumably the result of their action on D3 ventral striatum receptors [60]. Eighty percent of ICD will appear during the first year of treatment [62]. Risk factors have been identified and include male gender, early-onset PD, novelty seeking and impulsivity personality traits, personal or immediate family history of alcoholism, comorbid depression, or family history of psychiatric illness [63].

Dopaminergic input within the mesolimbic (nucleus accumbens, ventral tegmental area, amygdale, and hippocampus) and mesocortical pathways (orbitofrontal and cingulate) is critical for the mediation of reward and reinforcement behaviors. D3 receptors are predominantly expressed in ventral areas of the striatum and their function is involved in reward, emotional, and cognitive processes. In untreated PD patients, there is some evidence of an abnormal reward response due to reduced dopamine availability in these mesolimbic and mesocortical pathways [62]. Impaired decision making in PD patients is also associated with an inability to learn from negative reinforcement. The dopaminergic overdose hypothesis postulates that in PD, dopaminergic stimulation of dopamine-deficient dorsal striatal receptors is associated with cognitive enhancement whereas dopaminergic (over)stimulation of the relatively intact ventral striatal receptors is associated with ICD [60]. Furthermore, the intermittent and chronic stimulation of the mesolimbic pathway, induced by pulsatile dopaminergic medication, may disrupt the physiological patterns of dopamine release (both phasic and tonic) and produce abnormalities of the mesocortical dopaminergic pathways, with plastic adaptative changes (sensitization) within the reward circuit [62].

The management of these behaviors should begin even before initiating dopamine agonist

treatment, by warning patients (especially those at high risk) and their family of the potential development of these behaviors; this may assure closer follow-up. If the impulse control behaviors then develop, decreasing or discontinuing agonist therapy may be effective. External control, cognitive-behavioral therapy, and pharmacotherapy can also be considered. There are very few studies of pharmacological management of ICD in PD; those published consist primarily of case reports in which atypical neuroleptics or selective serotonin reuptake inhibitors were utilized [62]. Chronic subthalamic nucleus deep brain stimulation (STN-DBS) for PD has been associated with improvement in ICD, perhaps as a result of significant reductions of dopamine replacement therapy; ICD also may begin or worsen transiently after STN-DBS [60]. There also are reports of OCD improvement in PD patients treated with STN-DBS [64].

OCS in PD: Perseverations?

With the hypothesis that OCS are present and significant in PD and may represent early manifestations of an emerging dysexecutive syndrome, we studied OCS in 35 patients with PD and 35 paired controls [65, 66]. Our primary outcome measure was the YBOCS score [24]; we used the WCST to measure perseverations [25]. Subjects were divided into two groups according to YBOCS scores (<8 = negligible OCS/>8 = presence of OCS). Mann–Whitney U tests were performed on reported variables. A Chi-square test was done to evaluate the possible relationship between OCS and levodopa treatment (comparing the presence/absence of OCS and levodopa treatment) in patients with PD. Patients with PD had statistically significantly higher scores on the YBOCS than controls. They showed higher level of anxiety (Beck-Anxiety Inventory) and depressive symptoms (Beck Depression Inventory) than controls. Mini-Mental State Exam (MMSE) scores and Trail-B tests were also lower in PD than controls. Based on the presence or absence of OCS, early perseverative errors in the WCST were more frequent in patients with PD and OCS when compared to those without. No differences were found between subjects who had PD with or without OCS in terms of anxiety, depression, motor symptoms, demographic variables, or MMSE scores [67]. The presence or absence of OCS could not be predicted by levodopa therapy. No variables discriminate between the two control groups based on the presence or absence of OCS.

Confirming our hypothesis that OCS are present to a significant extent in PD, our group of patients with PD showed higher YBOCS scores than controls. However, the mean YBOCS score did not qualify for an OCD diagnosis. We found that our patients with PD were more prone to OCS of the ordering, symmetry, or checking type, and that these symptoms were egosyntonic. Our findings also suggest a link between higher obsessionality and perseverative symptoms. The need for symmetry and sameness could be explained by a difficulty in changing strategies to adapt to a continually evolving environment (early executive dysfunction). Checking could compensate for memory difficulties.

Conclusion

In summary, OCS in neurological illnesses like PD may be clinically identical to idiopathic OCD. However, typical descriptions reflect certain differences. OCS in neurological illnesses are primarily associated with compulsions; obsessions are less well defined. Compulsions may range from pure motor stereotypies to more complex behaviors. Order and symmetry compulsions, and repetitive movements are often described. Anxiety is not overwhelming in a majority of cases, and patients consider these OCS to be egosyntonic. Therefore, they make less effort to resist these urges. OCS often correlate with movement disorders and cognitive dysfunction, mostly dysexecutive in character. Some overlap, or communication between different cortico-subcortical loops, could explain why motor dysfunction (motor pathway), cognitive difficulty (cingulate and dorsolateral pathways), and OCS (cingulate and orbitofrontal pathways) occur simultaneously [10].

The question remains whether the etiopathology of OCS in neurological illnesses is similar to idiopathic OCD. Whether the phenomenology varies depending on type and location (frontal vs. striatal) of the causal "lesion", or whether cognition is preserved or not, is also in question. This raises the possibility that measuring obsessions and compulsions separately may lead to a better definition of the concept. In this regard, the DSM-IV criteria used in defining obsessional illnesses are not helpful. Accurate definitions of OCS and perseveration should be proposed to distinguish both concepts. Both compulsion and perseveration involve inhibition difficulties. However, perseverations are devoid of emotion and motivation, which usually are present in compulsions (i.e., compulsions without obsessions?). If OCS and perseverations are considered to be part of the same pathophysiological spectrum, some contradiction remains in the fact that executive dysfunction (perseveration) is associated with dorsolateral hypofunction, whereas OCS are associated with orbitofrontal and cingulate hyperactivity. One hypothesis is that perseverations in neurological illnesses have been mistakenly labeled as OCS in some reports. An alternative hypothesis is that both disorders may occur simultaneously. Yet another possibility is that orbitofrontal hyperactivity may lead to relative dorsolateral hypofunction, in which the frontal cortex is unable to analyze stimuli other than the one that predominates. Carefully designed imaging studies may help to provide answers.

Randomized, placebo-controlled studies of treatment of OCS in neurological illnesses are needed. In this regard, OCS in PD might be more related to dopamine imbalance than serotonin's. It would be helpful to know if OCS in PD can be alleviated by pharmacotherapy or psychotherapy in the same manner as in idiopathic OCD. Very interesting questions remain to address regarding the neuropsychiatry of PD, and to do so, researchers and clinicians from both the neurology and psychiatry domains should unify and share a common language and understanding of these fascinating symptoms.

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Dementia

4

Patricia Kavanagh and Karen Marder

Abstract

With an estimated prevalence of about 24%, dementia is common in Parkinson's disease (PD) [Aarsland D, Zaccai J, Brayne C. Mov Disord 20(10):1255–1263, 2005]. Postmortem studies have not found distinct associations between PD, PD with dementia, dementia with Lewy bodies, and Alzheimer's disease (AD). The varying syndromes may represent a spectrum in which individuals exhibit differences in the type, sequence, or time-course of degeneration of dopaminergic and other neurochemical pathways. Dementia in PD is clinically associated most frequently with older age and more severe motor symptoms, which may have a combined effect.

Environmental and genetic risk factors have been proposed, but they have yet to be demonstrated consistently. Early features of dementia in PD are executive dysfunction, impaired verbal fluency, and visuospatial disturbances, making it clinically distinct from AD. Memory impairment can occur early or late, and diagnostic criteria that require memory impairment may lead to delayed diagnosis. Depression, medication-induced psychosis, and apathy are more common in cognitively impaired individuals and may herald dementia. Dementia in PD is an independent risk factor for morbidity and mortality, and treatment should begin with the reduction or

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elimination of anticholinergic medications and amantadine, followed by the reduction of dopaminergic medications. Cholinesterase inhibitors may help to preserve function in mild to moderate Parkinson's disease dementia (PDD). Effects of deep-brain stimulation (DBS) on cognitive decline appear to be modest in carefully selected patients.

Keywords
Parkinson's disease • Dementia • Cognitive impairment • Executive dysfunction • Cholinesterase inhibitors

Introduction

Cognitive impairment and dementia are frequently associated with Parkinson's disease (PD), although this relationship was not described originally. In his 1817 description of paralysis agitans, James Parkinson stated that "…the senses and intellect (are) uninjured" [1]. Later observers debated this point. In 1973, Martin et al. [2] proposed that intellectual impairment was recognized as a feature of PD, based on an observational study of 100 consecutive cases of PD. Parkinson's disease dementia (PDD) is linked most clearly with age and severity of motor symptoms [3–7]. Investigators have proposed criteria for PDD [8], and mild cognitive impairment [9, 10]. PDD can be clinically distinguished from Alzheimer's disease (AD) by more prominent impairment of executive function, verbal fluency, and visuospatial skills early in the disease [11, 12]. Memory impairment can be a primary encoding or primary retrieval deficit [13]. Dementia is associated with increased morbidity and mortality [14–16]. The presence of dementia, after adjustment for severity of extrapyramidal signs (EPS), had a twofold increased risk of mortality over a mean follow-up of 3.9 years [15]. No specific pathological substrate for PDD has been identified. The USA Food and Drug Administration (FDA) has approved rivastigmine for treatment of PDD [17, 18], and other cholinesterase inhibitors may be beneficial [19, 20]. Two randomized controlled trials of memantine in PDD failed to show benefit, although the sample sizes were small [21, 22].

Epidemiology

Prevalence

Prevalence estimates for dementia in PD range from less than 10% to more than 80% [23–25]. This wide range reflects varying diagnostic criteria for both PD and dementia, methods of evaluation, and use of both hospital- and community-based samples. A systematic review of 12 prevalence studies that met predefined inclusion and exclusion criteria for PD or dementia in PD had a combined prevalence of 24.5% (95% confidence interval [CI] = 17.4–31.5) [26]. In the four studies that met the prespecified criteria most closely, the combined prevalence was 31.1%. Among people with dementia, the estimated prevalence of PDD was 3.6% (95% CI = 3.1–4.1), and the estimated overall prevalence of PDD in all subjects aged 65 and older was 0.2%.

Incidence

Incidence rates in community- and hospital-based series range from 42.6 to 112.5 per 1,000 person–years of observation [3, 5, 7, 27–29]; the two highest rates were from community-based samples [5, 7].

The relative risk (RR) of incident dementia among patients with PD when compared with age-matched controls without PD in community-based samples ranges from 1.7 (95% CI = 1.1–2.7) to 5.9 (95% CI = 3.9–9.1). Although the

incidence of PDD was similar in the two studies, there was a higher incidence of dementia in the control population of the first study, which resulted in a lower RR [5]. The largest community-based study of incident dementia among 126 subjects newly diagnosed with PD, reported the lowest incidence to date: 30.0 (95% CI = 15.4–42.9 [30]. As there were patients with early disease, the incidence would be expected to be lower than in previous cross-sectional studies.

Incidence and Prevalence as a Measure of Dementia

Because dementia is associated with increased mortality [15, 16, 31], incidence may be more useful than prevalence as a measure of PDD frequency. Nursing home residents with a possible higher prevalence of dementia [4] have not been included in some studies [28] and may not be proportionally represented in others.

In a longitudinal study of 210 PD patients, there was a significant association between failure to follow-up and poorer performance on neuropsychological testing, suggesting that incidence studies may underestimate the true occurrence of PDD [32].

Other measures, such as cumulative incidence, may be more relevant to the clinician. In a longitudinal study of 136 community-living patients newly diagnosed with PD, 83% of 20-year survivors met criteria for dementia. Mean follow-up time to dementia was 10.9 years (standard deviation [SD] = 5.5) [33].

Prevalence and Incidence of Parkinson's Mild Cognitive Impairment

Estimates of the prevalence and incidence of Parkinson's mild cognitive impairment (PMCI) are even more problematic because of lack of consensus definitions. Various series have reported prevalence of 22–55% of non-demented PD patients [34, 35]. Differences in prevalence rates may reflect choice of neuropsychological tests as well as patient selection and characteristics of the control groups. Patients with early-stage PD are less likely to have confounding effects from medication, and will have less motor impairment affecting tests of processing speed Compounding the lack of consensus assessment tools is the variability of neuropsychological impairments, especially at onset of MCI. One series found an association of PMCI with older age at diagnosis of PD [36].

Pathology

The hallmarks of idiopathic PD are neuronal loss in the substantia nigra (SN) with Lewy bodies (LBs) in some of the surviving neurons [37]. Lewy body (LB) pathology has been proposed by Braak [38] to occur in a topographic distribution, with clinical correlation. In stages one and two, the LB pathology is confined to the medulla and pons, and the olfactory bulb. In stages 3 and 4, the SN and other nuclei of the basal mid- and forebrain are affected, during which stages the patient meets clinical criteria for PD. In stages 5–6, the neocortex is involved, with dementia correlating with cortical LBs [38, 39].

Cognitive impairment in PD has been associated with increased pathology in the medial SN [40]. Additional work has demonstrated pathological changes in other brain structures, including the ventral tegmental area and locus ceruleus (LC) [41], along with the basal forebrain [40, 42]. A study that examined the LC, SN, and nucleus basalis of 86 subjects with AD and 19 with PD (both demented and non-demented) found the greatest neuronal loss to be in the LC [43]. Another study reported that dementia in PD without concurrent AD was linked with significantly lower LC neuronal counts [41]. Taken together, these studies demonstrate that non-dopaminergic structures are impaired in PDD.

Studies of PDD have shown heterogeneous pathology, and recent work has focused on describing clinicopathological subtypes. In the Sydney Multicenter Study of Parkinson's Disease, three clinicopathological groups were identified. One group consisted of subjects with younger-onset,

long-duration disease, whose autopsy findings were consistent with Braak stages; these subjects did not have significant Alzheimer's-type pathology. A second group had older-onset PD (>70 years) with more rapid clinical progression and shorter survival after diagnosis. This group had both higher cortical LB burden and plaques. A third group presented with early dementia; at autopsy they had diffuse cortical LBs and Alzheimer-type changes consistent with dementia with Lewy bodies (DLB) [44].

In a series of prospectively assessed patients, investigators reported that in the group of 28 with PDD, longer duration of disease was associated with less severe cortical LB pathology and lower burden of plaque. [45]

A group of PDD patients with ($N=28$) and without ($N=23$) Alzheimer's-type pathology at autopsy were found to have had no significant differences in education, levodopa responsiveness, hallucinations, or Unified Parkinson's Disease Rating Scale (UPDRS) scores. However, the subjects with AD pathology were significantly older at age of PD onset and progressed to dementia more rapidly [46].

These findings imply that PDD may represent a stage in PD that shares pathological changes with AD.

Relationship of PDD to DLB

The consensus guidelines for DLB diagnosis require progressive cognitive decline observed within 12 months of the onset of motor symptoms [47]. The requirement for dementia to occur within the narrow time-frame may not be sensitive for DLB, because the duration from motor symptoms to dementia may be longer in some individuals ultimately found to have LB pathology. In one study, subjects with clinically diagnosed PD with onset of dementia at least 4 years after onset of motor symptoms, who had become unresponsive to levodopa, were compared with non-demented controls with PD. Of 13 individuals with dementia, 12 had findings of diffuse or transitional LBD as the primary pathological substrate for dementia (one had progressive supranuclear palsy). Mean and median LB counts were increased nearly tenfold in neocortex and limbic areas. Alzheimer pathology was modest, but there was a significant correlation with neocortical LBs and senile plaques, as well as neurofibrillary tangles [48]. Other pathologists have proposed that PDD with cortical LBs be considered as on a spectrum with DLB [45].

Because both LB and AD pathology are associated with PDD, the question of the dominant pathology was studied. In another series of 22 PD patients who were followed prospectively until death, 18 developed dementia. At autopsy, none met National Institute on Aging and Ronald and Nancy Reagan Institute (NIA-Reagan) criteria for AD. All had limbic or neocortical LB disease (LBD), although none fulfilled Braak stages 5 and 6 criteria. The authors conclude that LB pathology is the principal substrate for the development of PDD [49].

Risk Factors

PDD has been related to older age [3–5, 7]. In one community-based series, the prevalence of dementia in PD increased from 0 for those under age 50 to 787.1 per 100,000 for those over age 80 [50]. Severity of extrapyramidal motor symptoms (EPS), particularly bradykinesia, has been consistently associated with incident dementia [5, 7, 27, 29, 51, 52]. In one study, dementia was more frequent at baseline among patients who had masked facies and hypokinesia, compared with those who presented primarily with tremor or rigidity [53]. The postural instability-gait disorder (PIGD) subtype of PD consistently has been associated with increased risk of dementia, compared with the tremor-dominant subtype [36, 54–56]. Hallucinations before baseline and orthostatic hypotension have been identified as risk factors for dementia [57–61].

Older age and more severe EPS may have a combined effect. When patients were grouped by age and severity of motor impairment, the incidence of dementia increased with both age and motor impairment. By age 80, if the UPDRS score was less than 25, cumulative incidence was

0.07, but when the UPDRS score was greater than 25, the cumulative incidence was 0.12 [5]. In another study, the combination of older age (>72) and more severe EPS (UPDRS>25) increased the risk of incident dementia tenfold (RR 9.7, 95% CI=3.9–24.4). Older age combined with low EPS, or severe EPS combined with younger age, was not associated with a significant increase in dementia risk [6]. This suggests that the risk of incident dementia is the result of combined, rather than separate, effects of age and severity of EPS. In some studies with PDD [27, 28, 50], age at onset of PD is a factor, but not in others typo (7) [5, 27, 59].

A prospective study of PD patients in New York, Norway, and Denmark found a significant effect of age at baseline assessment on the time to develop dementia, but there was no effect of age at onset itself. Further, there was no increased relative effect of age on the time to develop dementia in PD cases compared with controls [62]. Men are at increased risk for PDD [29, 50, 63–65]. Analysis of the progression to cognitive impairment in the Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism (DATATOP) cohort found the hazard ratio (HR) for male sex to be 2.95 (95% CI=1.32–6.59) [66].

A longitudinal study of levodopa-responsiveness found no association between initial levodopa response and development of dementia, although the number of patients who survived to the final assessment at an average of 14.8 years was small ($N=17$). The investigators found that the patients with dementia had worse "on" and "off" motor scores at the last two assessments ($p<0.001$) and smaller magnitude of levodopa response at 14 years ($p=0.008$) [67].

Although the risk of PD is inversely correlated with smoking history [68, 69], smoking appears to increase the risk of cognitive impairment in PD. In a series from the Nurses' Health Study and Professional Follow-up Study comparing cognitive performance of PD patients who were current smokers at onset versus never-smokers, smokers had poorer scores on the Telephone Interview for Cognitive Status (difference=−0.82 (95% CI: −1.33, −0.30)). The difference in a global score (difference=−0.36 (95% CI: −0.72, 0.01)) between age-matched PD smokers vs. PD nonsmokers was equivalent to the difference in global score observed among healthy controls 10 years apart in age [70]. In a cohort of 180 non-demented patients with PD and controls, current smoking, but not smoking history, was found to be associated with incident dementia in PD (RR=4.5, 95% CI=1.2–16.4 [71]). The same study found no link between incident PDD and history of head injury, hypertension, or diabetes mellitus.

Pesticides, organophosphates, toluene, xylene, rural living, and well-water exposure have not been associated with increased risk of dementia in PD [63, 65]. An inverse relationship has been observed between postmenopausal hormone replacement therapy and PDD (odds ratio [OR] 0.22, 95% CI=0.05–1.0), but hormone replacement therapy was not shown to affect the risk of PD itself [72]. Another cross-sectional study of nursing home residents found that female PD patients on estrogen therapy had better cognitive status than those not receiving estrogen [73]. One investigator reported that patients taking amantadine had longer duration to dementia (9.1±5.7 years), compared with patients never exposed to amantadine [74].

Family history of dementia may increase the risk of dementia in PD. In a pilot case-control study, patients with PDD were six times more likely to have a first-degree relative with dementia, compared with non-demented patients with PD. In another study, siblings of patients with PDD were three times more likely (RR=3.2, 95% CI=1.1–9.4) than siblings of normal subjects to have AD. For siblings of patients with PDD older than 65, the RR of AD was 4.9 (95% CI=1.1–21.4) in comparison with siblings of normal subjects over 65 [75, 76]. One large case-control study found no increased risk of dementia in first-degree relatives of subjects with PD without dementia [49]. However, a prospective, community-based study followed 219 PD patients over 12 years with neuropsychological assessment. Over the observation period, the development of dementia was significantly associated with family history of PD ($p<0.05$) (but not with a family history of dementia) [77].

Another investigator found three baseline measures to be significant predictors of dementia risk: age >= 72 years, semantic fluency < 20 words over 90 s; and impaired pentagons copying. When all three features were present, patients had an odds ratio of 88 (95% CI = 8–962) for the development of dementia within 5 years of diagnosis [78].

Genetic Risk Factors

Several genetic risk factors for AD have been examined in demented patients with PD. APOE ε4 has not been found to be associated with PDD by most investigators [79–81]. However, one investigator found the APOE ε4 allele more than twice as frequently in PDD subjects as in normal controls. Non-demented patients with PD did not differ significantly from controls [82]. A meta-analysis of ten studies examining APOE as a risk factor for dementia in PD estimated an OR of 1.78 (95% CI = 1.22–2.60) for APOE ε4 [83]. One series suggests a correlation with APOE ε2 and the dementia of PD [84] although findings are not consistent [85].

In a few families in Southern Italy and Greece, PD has been associated with mutations in the gene for α-synuclein; some individuals were demented. A clinicopathological study of familial PD with dementia in two families found α-synuclein triplication [83]. A study of another kindred with autosomal dominant DLB demonstrated a novel mutation [86]. Intracellular aggregations of α-synuclein also have been found in a range of neurodegenerative diseases, but these have not been indicated to be related to genetic mutations in idiopathic PD or PDD [87].

There are case reports of cognitive impairment in patients with LRRK2 gene mutations [88]; however, in a population sample selected from a longitudinal aging study, 49 of 192 elderly Ashkenazi Jewish individuals (25.5%) were found to have dementia, but none had the LRRK2 G2019S mutation. Two non-demented individuals did have the mutation [89]. The overrepresentation of the H1 haplotype of tau has been reported in progressive supranuclear palsy [90], frontotemporal dementia [91], and idiopathic PD [92]. In a series that followed 109 incident PD cases for a mean of 3.5 years, 11 developed dementia (defined as MMSE < 24). The H1/H1 haplotype was found in all 11 cases, compared with a carrier frequency of 61% in non-demented individuals ($p = 0.015$); this suggests a role for tau in cognitive impairment [93].

Several studies have demonstrated an association of LB disorders with heterozygous mutations in the glucocerebrosidase (GBA) gene [94, 95]. A study of 187 subjects with primary neuropathological diagnoses of LB disorders, with or without AD changes, found GBA mutations in 28% of those with primary LB pathology, compared with 10% of those with AD findings and 3% of those without AD or LB pathological findings [96].

A clinicopathological study found the frequency of GBA mutations in 790 PD subjects to be 4.18% vs. 257 age- and ethnicity-matched controls ($p = 0.01$). Clinical features in 31 GBA mutation carriers included early onset of disease, hallucinations in 45% and cognitive impairment in 48%. Autopsy of 17 carriers revealed diffuse limbic, neocortical, and cortical LB pathology (Braak stage 5 and 6) in all subjects [97].

In the largest multicenter, multiethnic study conducted to date of GBA mutations in PD, the odds ratio for the two most common GBA mutations was 5.43 vs. controls. Clinical features of GBA mutation carriers included cognitive changes in 26% vs. 17% of noncarriers with PD ($p = 0.007$) [98].

Although one study suggested that the estrogen receptor gene is a susceptibility gene for PDD (but not PD [99]), the *Pvu*II polymorphism was not linked with PDD in a clinicopathological study [100]. Generally, toxin exposures have not been demonstrated as significant factors, but increased risk of PDD among patients with the CYP2D6 29B+ allele and pesticide exposure has been reported [101].

Psychiatric Comorbidity

Depression and medication-induced psychosis may be more common in demented individuals with PD. In a community-based study, 22% of

patients with PDD had major depression versus 2.3% of non-demented patients ($p < 0.001$ [102]). A Hamilton Depression Rating Scale (HDRS) [103] score greater than 10 was associated with incident dementia in PD (RR 3.55; 95% CI = 1.6–7.9) in another series [5]. In a longitudinal study, patients with major depression had greater cognitive decline than mildly or nondepressed patients ($r = -0.42$, $p < 0.01$) [104]. At follow-up, the mean HDRS of patients who had become demented had improved from 10.6 to 7.1. It is possible that major depression is associated with a more aggressive form of PD that includes progression to dementia and that preexisting depression may interact with PD to produce a more rapid evolution to dementia. The improved HDRS scores may alternatively reflect that depression is more difficult to assess independently in a demented patient.

Psychosis and confusional states may predict cognitive impairment. Although confusion or psychosis may be induced by levodopa, an inverse correlation between duration on levodopa therapy and organic mental syndrome was observed in 203 patients. Patients who developed confusion and psychosis had older onset, more severe EPS, and were treated with levodopa earlier in their course [105]. A prospective study of 30 PDD patients recruited from an outpatient setting found 5 (16.7%) who manifested delusional misidentification syndromes (DMS); these patients had levels of executive and visuospatial function similar to the patients without DMS but had more severe language and memory impairment [106]. In another study, incident dementia was associated with baseline depression (OR = 6.1, 95% CI = 1.4–26.9) and confusion or psychosis from levodopa (OR = 2.9, 95% CI = 1.5–6.0 [51]).

Apathy in PD may exist with or without depression, but it may be independently associated with dementia. As measured by tests, including the MMSE and Cambridge examination of cognition in the elderly (CAMCOG), patients suffering from PD with high apathy were more impaired, especially in executive function. Apathy was better correlated with cognitive impairment than with depression [107]

Neuropsychological Features of Cognitive Impairment and Dementia in PD

DSM-IV [108] requires memory impairment for the diagnosis of dementia. This requirement may lead to underdiagnosis, because in some patients with early PDD, memory impairment may be mild relative to other aspects of cognitive decline. When dementia presents before motor symptoms, other causes such as AD or DLB should be considered. Parkinsonism with dementia may also occur in progressive supranuclear palsy, olivopontocerebellar degeneration, or vascular dementia, yet cognitive impairment may be a late phenomenon.

Cognitive impairment in PD can present along a spectrum and may be unrecognized in its early stages because of more prominent motor impairment. Attention is impaired and may fluctuate [109]. Early PDD characteristically involves impaired executive function (i.e., planning, initiating, sequencing and monitoring tasks, and set shift). Visuomotor and visuospatial skills are relatively impaired. Verbal fluency is usually impaired, but other language functions are relatively unaffected, as is orientation. When compared with non-demented PD cases, patients with PDD demonstrate disturbed organization during memory encoding and retrieval, and deficits in verbal fluency, attention and vigilance [109].

Premorbid State

Baseline cognitive impairment may portend the development of dementia in PD. Only three longitudinal studies to date have examined the neuropsychological impairments associated with Table 4.1 incident dementia in non-demented PD patients [11, 12, 28]. In a non-demented cohort of 164 patients with PD followed for a mean of 3.7 years, impaired verbal memory and executive function were associated with the development of dementia [12]. When patients questionably demented at baseline were excluded, total

Table 4.1 Neuropsychological impairments associated with incident dementia in Parkinson's disease

Author	Year	Abnormal test	Relative risk
Williams-Gray[a] [30]	2007	Verbal fluency (global deficit)	9.4 (2.0–44.8)
		Pentagon copying	5.2 (1.9–14.1)
Levy[b,c] [12]	2002	Immediate recall	0.92 (0.87–0.97)
		Delayed recall	0.73 (0.59–0.91)
		Selective reminding	0.87 (0.77–0.99)
Aarsland[d] [7]	2001	Line orientation	$p<0.001$
		Visual retention	$p<0.001$
		Stroop test, time in seconds	$p<0.001$
		Stroop test, errors	$p=0.002$
Mahieux[(a)] [28]	1998	Picture completion	4.99 (1.0–24.1)
		Interference-Stroop	3.8 ($p=0.08$)
		Verbal fluency	2.7 (0.8–9.1)
Jacobs[(a, c)] [11]	1995	Letter fluency	3.3 (1.0–10.8)
		Category fluency	6.01 (1.25–28.84)

[a]Deficit is associated with increased relative risk of incident dementia
[b]Higher scores are associated with reduced risk of dementia
[c]These studies were conducted in essentially the same cohort of community dwellers in northern Manhattan. Jacobs followed the cohort for mean of 2.7 (±1.03) years, and Levy for a mean of 3.7 (±2.3) years
[d]Relative risk not provided; *p* value compares baseline performance of subjects who later became demented to those who did not

immediate recall and delayed recall were still associated with later dementia.

Table 4.1 summarizes key premorbid neuropsychological impairments and their RR of incident dementia.

Progression of Dementia

As dementia progresses, existing deficits worsen, but memory loss may become more prominent. In one study, subjects demonstrated poorer performance on visual confrontation naming (Boston Naming Test) and delayed recall memory [110]. It is not understood whether this represents progression of cognitive impairment specific to PD or the onset of another dementing disorder like AD.

PDD Compared with AD

The dementia of PD has distinct characteristics and is marked by a different pattern of impairment from AD [11, 27, 111]. Patients with PDD have impaired immediate memory as in AD; however, cued recall and recognition memory remain commensurate with immediate recall, whereas on successive tests, patients with AD retain less information with each trial. The memory deficit in AD can be thought of as impaired encoding or consolidating information. The memory deficit of PD may be a retrieval deficit and could reflect loss of executive function, specifically the ability to systematically search memory. Similarly, the impaired verbal fluency of PDD may represent loss of systematic retrieval and generation of language compared with AD. There is relative preservation of delayed recall and delayed recognition memory, naming, and orientation [112]. Relative impairments are summarized in Table 4.2.

Role of Neurotransmitters

As indicated, the cognitive impairment of PD has been hypothesized to correlate with the dopaminergic compromise of subcorticofrontal circuits. Impaired visuospatial and executive function were observed in patients with 1-methyl-4-phenyl-1, 2, 3, 6-tetra-hydropyridine (MPTP)-

Table 4.2 Neuropsychological impairments in Parkinson's disease, dementia, and Alzheimer's disease

	PD	PDD	AD
Executive function	++	+++	+++
Attention	0	++	++
Vigilance	0/+	++	++
Orientation	0	0	++
Reaction time	+	+	+
Visuospatial function	++	++	++
Memory			
Free recall-immediate	+	++	++
Free recall-delayed	+	++	+++
Delayed recognition	0	0/+	+++
Language			
Naming	0	0/+	+++
Verbal fluency	++	+++	++

induced parkinsonism compared with age- and education-matched controls [113]. In one study, patients with PD, off levodopa therapy or never treated, were impaired on complex choice reaction times; patients on levodopa did not differ significantly from normal controls. This suggests that processing concurrent cognitive information requires intact dopaminergic circuits [114]. Cholinergic deficits emerge, supported by pathological findings of degeneration in the nucleus basalis of Meynert. Long thought to be a late phenomenon, recent work demonstrates reduced acetylcholinesterase activity in PDD at all phases and association with impaired attention and executive function [115, 116]. Depression in PD may reflect spread of pathology beyond the dopaminergic pathways. Cerebrospinal fluid (CSF) 5-hydroxyindoleacetic acid (5-HIAA) is decreased in PD with major depression [117]; another report documented reduced CSF 5-HIAA in PDD [118], which argues that serotonergic degeneration plays a role in both the depression and dementia of PD.

Clinical Significance of Neuropsychological Impairment

Cognitive impairment may be overlooked in PD. DSM-IV criteria for dementia require memory impairment, which may be subtle and could possibly only manifest on complex memory tasks. Incipient dementia can be mistakenly attributed to bradykinesia, depression, apathy, or confusion.

Clinical criteria for probable and possible PDD have been proposed by the Movement Disorder Society Task Force on Dementia in Parkinson's disease [8]. These criteria were operationalized to Level I, with an eight-item clinical assessment that can be conducted in the office; and Level II, which includes a range of neuropsychological testing [119]. Level II testing is appropriate when the diagnosis is uncertain, when it is clinically necessary to assess severity and pattern, and for research. Of note, memory impairment is included as a possible but not mandatory feature of PDD in these criteria.

The diagnosis of PMCI is complicated by the use of instruments not specifically designed for use in PD. A recent review of 33 studies using various assessment tools observed that two scales, Scales for Outcomes of Parkinson's Disease-Cognition (SCOPA-COG) and Parkinson's Disease-Cognitive Rating Scale (PD-CRS) have been extensively validated [120].

Imaging Studies

Single-photon emission computed tomography (SPECT), positron emission tomography (PET), magnetic resonance spectroscopy (MRS), functional magnetic resonance imaging, and volumetric MRI have been used to study the neuroanatomical changes in PDD in cross-sectional studies. Several studies in which demented patients with PD were compared with non-demented PD patients and normal controls have found patterns of abnormal activity in the patients with PDD. Non-demented patients with PD were not significantly different from controls [121–124]. One investigator compared 13 demented and 13 non-demented patients with PD to 10 unaffected controls using SPECT. Regional cerebral blood flow in non-demented subjects with PD was not significantly different from controls. Of the 13 demented patients, 4 demonstrated bilateral frontal hypoperfusion; 8 had frontoparietal

hypoperfusion, and 1 had parietal hypoperfusion alone [122]. However, a study of non-demented PD patients found temporoparietal hypometabolism with both MRS and PET, suggesting that both glycolytic and oxidative pathways are impaired in PD [125].

Patients with PDD, when compared with non-demented patients with PD of similar motor disability, showed decreased dopamine uptake in the anterior cingulate gyrus, ventral striatum, and right caudate nucleus when measured with 18F-dopa (FDOPA)-PET [126]. This finding supports the hypothesis that dementia in PD is associated with greater impairment of mesolimbic and caudate dopaminergic function.

A series of 18 patients with PD, 13 with PDD, and 24 healthy controls compared rates of brain atrophy by volumetric MRI over a 1-year period. Rates of brain atrophy were significantly increased in PDD ($p = 0.015$) vs. PD and controls; there was no significant difference between PD and controls ($p = 0.79$) [127] As most studies published to date have been cross-sectional, additional prospective studies that assess patients with PD periodically with neuropsychological testing and functional imaging might help to identify the biological correlates of clinical progression to dementia.

The development of PET using acetylcholine analogs such *N*-[11C]methylpiperidine-4-yl acetate (MP4A) permits the quantitative measurement of acetylcholinesterase (AChE) activity in the brain. Comparison of patients with PD and PDD has demonstrated greater cortical cholinergic dysfunction than in AD [128], and loss of cortical cholinesterase activity in PDD is correlated with poorer performance on tests of attention, working memory, and executive function [115]. One series performed both MP4A-PET and FDOPA-PET for evaluation of cholinergic and dopaminergic transmitter changes in 17 non-demented PD patients and 10 PDD patients and compared them to 31 controls. Striatal FDOPA uptake was significantly decreased in both PD and PDD patients vs. controls; global cortical MP4A binding was reduced in PDD (29.7%, $p < 0.001$ vs. controls) more than in PD (10.7%, $p < 0.01$) [129].

Treatment

Cognitive Complications of PD Therapy

Treatment of PD may be linked with confusion and psychosis, and patients who develop these signs should be assessed for cognitive impairment. Often, the patient and physician, and in later stages, the caregiver, must choose between better motor control and better cognitive function. Antiparkinsonian agents, particularly levodopa, dopamine agonists, and amantadine, may cause or exacerbate hallucinations. When a patient has symptoms or signs of dementia, it is advisable to reduce or eliminate medications with pure or high-anticholinergic activity. Amantadine, which often increases confusion in demented patients, may be reduced or eliminated. Finally, dopaminergic agents should be reduced to the lowest tolerable dose. Moreover, patients may become unresponsive to levodopa with the development of dementia; these medications may no longer be useful.

Pharmacological Treatments of PDD

The FDA has approved rivastigmine for the treatment of dementia associated with PD [17]. Of 541 subjects enrolled in the EXPRESS trial, 410 completed the study. At 24 weeks, moderate improvement was seen in global measures of dementia, cognition (executive function and attention), and behavioral symptoms [18]. Clinically meaningful improvement was observed in 19.8% of patients in the rivastigmine group vs. 14.5% in the placebo group. In the extension phase, treatment was continued to 48 weeks with all participants receiving the active drug; the mean ADAS-COG score improved by 2 points [130]. Patients with visual hallucinations may benefit more than non-hallucinators [131].

A randomized crossover study of patients suffering from PD with later onset of cognitive impairment, treated with donepezil for 20 weeks, showed a mean increase in the MMSE score of 2.1 (SD = 2.7), a significant effect when compared

with placebo ($p<0.013$ [132]). In an open-label study of 11 patients with PDD who were treated with tacrine [7] and donepezil [4], there was significant cognitive improvement, as measured by the Alzheimer's Disease Assessment Scale, without motor worsening [133]. A study of rivastigmine with slow-dose escalation showed improved cognitive function, along with reduced behavioral problems and visual hallucinations, in PDD without notable adverse effects [134]. A randomized, double-blind, placebo-controlled trial of rivastigmine in DLB demonstrated statistically and clinically significant behavioral effects [135]. A tremor assessment of patients before and after 12 weeks of rivastigmine found a modest mean increase in tremor amplitude, although tremor was increased in fewer than half the subjects, and UPDRS and ADAS-COG measures showed overall improvement [136]. Two randomized controlled trials of memantine in PDD have failed to show benefit, although the sample sizes were small [21, 22].

Trials of piracetam, phosphatidylserine, and olanzapine have not demonstrated improved cognitive performance [137, 138]. Selegiline and tocopherol in the DATATOP trial did not significantly delay progression to dementia [139].

Cognitive Effects of Surgical Treatment

The advent of surgical treatment for PD has raised new questions about patients with dementia or cognitive impairment. Surgical lesioning of the internal globus pallidus is related to improved motor control [140]. Surgical experience with has provided additional evidence for the existence of distinct frontosubcortical circuits within the basal ganglia. A series of 26 patients were studied after lesioning of the globus pallidus. Lesions in the anteromedial region were associated with increased cognitive impairment. In the posterolateral region, improvement in category-cued fluency and the Paced Auditory Serial Addition Test were noted. However, performance on other neuropsychological tests was inconclusive [141].

More recently, deep-brain stimulation (DBS) of the subthalamic nucleus (STN) has provided variable, reversible means of controlling motor symptoms [142]. Patients can then function on lower doses of levodopa and dopamine agonists with concomitant reduction in cognitive adverse effects of these drugs.

Longitudinal data on the cognitive effects of chronic DBS has begun to be reported. Up to 6 months after implantation and initiation of DBS, 62 consecutive patients were assessed with a neuropsychological battery including 25 cognitive variables. Under stimulation, patients' performance improved on parts A and B of the trail making test, but deteriorated on literal and total verbal fluency [142]. In another series, patients were followed for up to 12 months after surgery. At 3–6 months, patients demonstrated significant declines in working memory, speed of mental processing, bimanual motor speed and coordination, set switching, phonemic fluency, consolidation of verbal material, and encoding of visuospatial material, never returning to baseline performance. The effects were more pronounced in patients older than 69 years [143]. A longitudinal study of 57 consecutive patients, followed for 3 years, found that 24.5% converted to dementia, consistent with published dementia incidence rates in nonoperated patients with PD, and the remainder remained cognitively stable [144]. Motor circuits may be preserved at the expense of circuits subserving cognitive tasks. Seven patients suffering from PD demonstrated improved motor symptoms but impaired letter fluency with DBS "on"; the reverse was true in the "off" state [145]. Future investigations may focus on the possible cognitive benefit of "off" periods of DBS.

Longitudinal studies suggest that in carefully selected, non-demented patients, cognitive effects are modest. A cohort of 11 patients was followed for 5 years after DBS of the STN. At 1 year, there was a marginally significant decline on a letter verbal fluency task ($p=0.045$) and significant improvement on the MMSE ($p=0.009$). At 5 years, only letter verbal fluency and abstract reasoning had showed significant decline. No patient had developed global cognitive deterioration [146]. A meta-analysis of 28 cohort studies (including 612 patients) that met prespecified

criteria, small but significant declines were noted in executive function, verbal learning, and memory. Moderate declines were noted in semantic and phonemic verbal fluency [147]. These studies were published between 1998 and 2006, and not all studies reported dementia as an exclusion criterion; moreover, most studies did not have a control group, and therefore it is not clear how much of the decline is attributable to the surgical intervention versus disease progression.

Prognosis

Dementia in PD is associated with poor outcomes. Hip fractures occur more frequently (OR for men = 3.4, 95% CI = 2.5–4.8; OR for women = 2.5, 95% CI = 2.1–3.1) [148]. Dementia is a risk factor for nursing home placement, and caregivers of demented patients with PD report increased distress [149, 150]. In a longitudinal study of patients with PD, dementia was a significant risk factor for institutional placement [58]. In a cross-sectional study of elderly people in southwestern France, the prevalence of dementia in PD was 16.7% among people living at home, compared with 33.3% in those living in institutions. MMSE scores were lower for institutionalized PD patients than for community dwellers [4].

Early epidemiological studies showed low prevalence relative to incidence, which implies shortened life span for demented patients. Subsequent longitudinal studies confirmed that patients with PDD have an increased risk of death in comparison with both non-demented patients with PD and normal age-matched controls [16, 31].

Conclusion

Dementia is a common feature of PD and is associated with institutionalization and increased mortality. The biological substrate is not well understood, as there is significant overlap with DLB and AD. Published diagnostic criteria can guide the clinician. Patients with confusion, psychosis, depression, or apathy should be evaluated for dementia. Loss of levodopa responsiveness may be associated with dementia; reduction of dopaminergic therapy may benefit cognition. Rivastigmine is FDA-approved for PDD, and other cholinesterase inhibitors and memantine may be beneficial.

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Psychosis

5

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Abstract

An important unmet need in the care of Parkinson's disease (PD) is the prediction, prevention, and satisfactory treatment of PD-associated psychosis (PDP). Psychosis in PD is predominantly medication induced and all antiparkinsonian drugs in current use are capable of producing PDP. Dementia and depression are strong predictors of risk for the development of PDP. Hallucinations and delusions can occur at any time in the course of PD, but they are most commonly seen as a later complication in susceptible individuals. Visual hallucination is the most common feature of PDP, although other types of hallucination have also been reported. Delusions, particularly paranoid type, are less common but represent a more serious clinical problem. The mechanisms responsible for producing PDP are not fully elucidated but important advances have been made. Treatment should be approached in a stepwise manner. A triggering factor, such as infection, should be excluded first. Then careful tapering of antiparkinsonian medication, starting with adjunctive medication, should be undertaken. If increased motor disability prevents adequate dosage reduction, quetiapine is a reasonable first-choice antipsychotic agent followed by clozapine.

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The development of levodopa therapy for Parkinson's disease (PD) in the late 1960s gave rise to great optimism that dopamine replacement therapy might provide a cure or, at least, an enduring reversal of symptoms. It was soon realized, however, that levodopa therapy, though dramatically effective in controlling symptoms, was not a cure and that there were a number of long term disabling complications associated with its use. Among these problems were drug-induced behavioral and psychiatric syndromes. The one that may be considered the most important is PD-associated psychosis (PDP) [1]. Despite the impact of dopaminergic therapy on the development of PDP, it is becoming increasingly clear that this is not simply a drug-related adverse effect. Rather, it is the result of a complex interaction between drugs and disease. Studies have demonstrated that hallucinations in PD are a major risk factor for increased caregiver stress and strain [2] as well as nursing home placement that is often permanent [3]. The occurrence of drug-induced psychosis is also an independent and potent predictor of mortality [4], particularly in the nursing home setting [5, 6]. These outcomes are consistent, even when PDP is treated appropriately, indicating that they represent the occurrence of an advanced stage of the disease. These facts become more alarming when one considers that recent studies have estimated that PDP may currently affect up to 130,000 PD patients in the USA [7] and almost 75% of PD patients surviving 20 years after diagnosis [8].

Since the 1999 demonstration by the Parkinson Study Group that clozapine is effective in the treatment of PDP [9, 10], there has been disappointingly little additional progress. Several newer atypical neuroleptics have been proposed as safe and effective alternatives to clozapine. Although quetiapine generally has been accepted in practice, no agent other than clozapine has been proven effective in controlled clinical trials. Thus, there has been growing recognition that psychosis, its impact on quality of life in the short term and independence and mortality in the long term, represents a major unmet need in the treatment of advanced PD. In this chapter, we will review the history, clinical features and mechanisms of PDP, analyze recent literature concerning the treatment of PDP and outline an updated, practical approach to its treatment.

Definitions and History

In the past, the terms levodopa psychosis, drug-induced psychosis, and dopaminomimetic psychosis have been used interchangeably to describe several different psychiatric syndromes occurring in PD. The broad application of these terms has hindered our understanding of the frequency, pathophysiology, and treatment of these disorders. It is now clear that there are several distinct psychiatric syndromes with psychotic features that occur in PD and it is probably no longer accurate to refer to these syndromes as the levodopa psychoses [11]. Levodopa is not the only drug capable of precipitating psychosis and whether psychosis is purely a dopaminergic phenomenon has also been questioned; therefore, the term "dopaminomimetic" also may be inaccurate. However, for the

most part, when psychosis does occur in idiopathic PD it is in patients already treated with PD medications. For the sake of clarity and consistency with proposed National Institute of Neurological Disorders and Stroke/National Institute of Mental Health (NINDS/NIMH) diagnostic criteria [12], we will use the term PD-associated psychosis (PDP) from here forward.

It is useful to divide these syndromes into two broad categories: those associated with a clear sensorium and those occurring on a background of confusion or encephalopathy. Patients with a clear sensorium may suffer from hallucinations, delusions, or both. By Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R) criteria, these correspond to an organic delusional syndrome or an organic hallucinosis, respectively [13]. Another term utilized in DSM-III-R is organic confusional psychosis, which is seen in patients with a clouded sensorium and can vary in intensity from a mild confusional state to frank delirium with varying degrees of coexistent encephalopathy. Although these terms are no longer utilized in DSM IV, we feel they are still useful in the discussion of psychosis in PD. There seems to be a general agreement that, although all these syndromes can be induced by dopaminergic medications, they are distinct in their epidemiology, pathophysiology, and response to treatment [11, 14–16]. Our use of the term PDP will refer to psychotic symptoms (hallucinations and delusions) occurring on the background of a clear sensorium.

A historical review of psychosis in PD from the pre-levodopa era indicates that not all psychotic symptoms are drug related. Coexistent and premorbid psychiatric disease can occur, including schizophrenia [11]. There is also little question that psychiatric symptoms, including psychosis, can be a prominent feature of secondary parkinsonism, particularly the postencephalitic form [17]. In dementia with Lewy bodies (DLB), psychosis can be a presenting feature [18] prior to any exposure to PD drugs. In all likelihood, those cases of "PD" with early prominent psychosis described in the 1960s and 1970s were this disorder. Whether hallucinations, delusions, and other psychotic symptoms can occur as part of the natural history of untreated idiopathic PD is controversial [19, 20].

In James Parkinson's original description of the disease he concluded, "…by the absence of any injury to the senses and to the intellect, we are taught that the morbid state does not extend to the encephalon" [21]. This view of PD as a process that spares the intellect and psychological functioning was held for almost a century. However, in 1903, Regis [22] categorized the mental disorders associated with parkinsonism and specifically mentioned depression as an early phenomenon and hallucinations as a symptom associated with advanced disease. In 1922, 146 patients with PD were reviewed, with an attempt to exclude postencephalitic parkinsonism patients [23]. Depression was found in these patients and thought to be reactive in nature, but no mention of psychotic symptoms was made. Another review in 1923 presented several patients with "paralysis agitans" and prominent symptoms of psychosis [24]. Early features, such as sleep disturbance, withdrawal from social situations and suspiciousness, were mentioned. Also discussed were more dramatic symptoms, such as paranoid delusions and even hallucinations that were "… generally limited to the organic sensations and tactile sense…" In 1950, Schwab et al. [25] described a number of psychiatric symptoms in "Parkinson's disease," including paroxysmal depression, paranoia, and schizoid reactions. However, it is clear from a review of the case histories in this paper that all the patients described had a history of encephalitis or oculogyric crisis, or both, and likely had postencephalitic parkinsonism rather than PD.

Fenelon et al. reviewed the historical literature on PD and found evidence that hallucinations may be a part of PD itself, in the absence of pharmacological treatment, particularly in those with late dementia or depression [26]. Thus, it appears that psychosis may have occurred in PD prior to the levodopa era. However, it must have been rare and a number of these cases might have had secondary forms such as postencephalitic parkinsonism.

During the initial levodopa trials in the 1960s, it became apparent that various psychiatric

syndromes were occurring with a much higher frequency than in untreated PD patients. Unfortunately, it is difficult to determine the incidence with which these problems occurred because the early studies varied with regard to the inclusion criteria, the dosages of levodopa employed and the classification of the psychiatric side effects reported. Studies that included patients with postencephalitic parkinsonism reported incidences of psychiatric symptoms as high as 55% [27]. Most of the studies reporting a significant incidence of psychosis used levodopa dosages in excess of 4 g/day or did not specify the specific dosages utilized [28–35]. In contrast, Cheifetz et al. [36] reported no incidence of psychosis in 34 patients treated with 4 g of levodopa per day or less. Some authors included patients with preexisting psychiatric symptoms in their data; others excluded these patients. When reporting side effects, confusional states were lumped with other forms of psychosis in some studies; others attempted to be more specific in their definitions.

Despite these limitations, in 1971, Goodwin attempted to retrospectively review the psychiatric adverse effects that occurred in 908 PD patients treated in the early clinical trials using levodopa [37]. He reported an average incidence of 20%, but the range was quite large, 10–50%. Confusional states, including delirium, were most frequent, with an overall incidence of 4.4%. Psychosis, including delusions and hallucinations, occurred in 3.6%. These numbers are fairly low but only include patient reports where the psychiatric side effects were clearly defined.

Epidemiology and Risk Factors

In the last two decades, several studies have examined the point prevalence of hallucinations and psychotic symptoms in various PD patient populations and a recent review has been published on the topic [38]. Table 5.1 summarizes the 13 prevalence studies, including clinic- or population-based prospective designs from 1990 to 2008 [39–51], prior to the publication of NINDS/NIMH diagnostic criteria for PDP [12]. There were 2,292 patients overall. Variations in prevalence figures were the result of differences in subject populations and in the definition of psychotic symptoms—some primarily included hallucinations; others had a wider definition that included minor features such as presence hallucinations, passage hallucinations, and illusions. Less common symptoms, such as tactile and gustatory hallucinations are not often included, but there are data to suggest they may be more frequent than perceived [52]. Some studies excluded patients with delirium or DLB; others did not. Different tools also were used for gathering the data regarding the presence of psychotic symptoms. The results varied widely from 20 to 75%, with the average incidence of psychotic symptoms overall being 31.9%. Visual hallucinations were most commonly examined in these studies with frequencies ranging from 20 to 38%; auditory hallucinations were noted in 0–22% [46]; minor phenomenon were examined in only three of the studies and ranged from 17 to 72% [46, 50, 51]; and delusions were described in up to 7% [43, 51]. Since the development of the NINDS/NIMH criteria, three studies have examined the frequency of psychotic symptoms and their findings are as disparate as the prior studies. The first was a meta-analysis of nine studies in which the enrollment criteria matched those of NINDS/NIMH and the investigators reported that 23% had psychosis [7]. A second study examined the frequency from a health claims database of a large managed care population and reported that only 4.5% of patients met the diagnostic criteria. However, this low frequency could be the result of several problems: Medicare cases were not used, this was a retrospective study, only about 23% of the cases were examined by a neurologist or psychiatrist, and there were no codes for minor hallucinatory phenomena [53]. Finally, in a cross-sectional analysis of 116 cases in a movement disorders clinic population, 60% met criteria for psychosis [54].

There have been a few longitudinal studies to examine lifetime frequency of hallucinations in PD. One of these was the Sydney multicenter study where 136 de novo PD patients were followed over 20 years in a clinical trial. At 15 years

Table 5.1 Frequency of psychosis in PD

Author/year	Patient population	# Patients or # Subjects	% Psychosis[a]
Factor 1990	Clinic	78	22
Sanchez-Ramos 1996	Clinic	214	26
Barclay 1997	Clinic	227	31
Graham 1997	Clinic	129	25
Inzelberg 1998	Clinic	121	37
Aarsland 1999	Population based	235	25
Fenelon 2000	Clinic	216	46
Holroyd 2001	Clinic	102	29
Schrag 2002	Population	124	23
Paleacu 2005	Clinic	276	32
Pacchetti 2005	Clinic	289	30
Papapetropoulos 2005	Clinic	166	20
Williams 2008	Clinic	115	75
Total		2,292	31.9

[a]Some studies included lifetime and recent occurrence. Lifetime numbers are shown

50% of 52 survivors and at 20 years 74% of the 30 survivors had hallucinations and 57% of all patients experienced psychotic symptoms before death [8, 55]. Goetz et al. followed 60 PD patients who did not have hallucinations at baseline for 10 years and 93% ultimately had hallucinations at some time during the 10 years [56]. Both studies demonstrate the frequent occurrence of this non-motor problem.

Risk Factors: Pharmacological

All of the antiparkinsonian drugs in current use are capable of precipitating PDP and clinical trials have demonstrated this clearly [11, 14, 57–65]. Pramipexole and ropinirole have shown a greater tendency than levodopa to cause psychotic symptoms in early and advanced PD [66–68].

These phenomena were long considered to be primarily drug induced; hence the term drug-induced psychosis. The paucity of data from pre-levodopa times supported this notion but it is becoming increasingly clear that psychosis is the result of a complex interaction of disease and treatment [26]. There is now substantial data to suggest that medications are not the only factor required for the development of psychosis in PD. First, hallucinations are a frequent symptom of DLB in its early stages, prior to treatment of motor symptoms with dopaminergic agents [69]. This is pertinent since many consider this disorder to be the pathological equivalent of PD with late-onset dementia [19]. There have been some reports of hallucinations in untreated PD patients as well although this is rare [38, 70, 71]. It also is clear that not all patients treated with PD drugs develop psychotic symptoms. There is no simple dose relationship; in comparing patients with and without hallucinations, no difference related to levodopa equivalent doses has been noted [38, 45, 51]. Finally, a study in which hallucinating patients were switched from oral to intravenous levodopa and dosage levels pushed upward did not show a worsening of symptoms; in fact, the symptoms cleared [72]. Hence, disease-related factors are clearly important.

Disease-Related and Genetic Risk Factors

Several disease related risk factors have been suggested for psychosis in PD, including cognitive dysfunction, severity of PD, age, depression,

and visual dysfunction. Several authors from the early literature mentioned dementia as a risk factor [32, 33, 37, 73] and it was usually described as a confusional psychosis. This association has been confirmed in several recent cross-sectional and longitudinal studies [38, 41, 42, 45–47, 74]. Several prevalence studies also have demonstrated that the frequency of psychosis is much higher in demented populations [39, 46, 75]. This is true in early PD as well, in which an inverse correlation between the Mini-Mental State Examination (MMSE) and the occurrence of psychosis has been described [68]. Although depression [41, 45, 47, 74] was considered to be a strong predictor of one's risk for the development of hallucinations, other studies have now indicated otherwise [46, 76]. This will require further in-depth study. More advanced age was found to be a risk in some studies [39, 41, 45, 74], but not others [42, 77]. Similarly, duration or severity of PD was associated with the presence of PDP in some reports [42, 46, 47, 74], but not all [41, 47, 77]. Several studies have suggested that there is a correlation between motor disability and psychosis using the Unified Parkinson's Disease Rating Scale (UPDRS) [39, 45, 47] and Hoehn and Yahr stage [39, 41, 75]. One study examined specific clinical features of PD [39] as possible risks and found that lower tremor scores and higher rigidity, bradykinesia and postural instability scores were associated with PDP. They also demonstrated more dyskinesia and wearing off in hallucinatory patients. However, these latter findings did not remain significant with multivariate analysis. Two studies have also found a significant association with freezing of gait [78, 79]. In relation to these disease-related motor correlates, recent studies have suggested that hallucinations are specific for Lewy body pathology and hence are far less common in progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) [50].

Sleep disorders long have been considered to be closely related to hallucinations [41, 46, 74, 80] and that vivid dreaming indicated hallucinations were imminent [81]. Although long-term longitudinal data has suggested that sleep problems and hallucinations co-occur, recent data demonstrate that they progress independently and are not necessarily linked. Altered dreaming, acting out dreams, and severe sleep fragmentation are correlates of hallucinations, but none of them are predictive of the development of hallucinations [56, 82]. Excessive daytime somnolence was associated with hallucinations in one study [46] but this is not consistent [56].

Similarly, visual dysfunction, such as reduced contrast sensitivity and color discrimination or lower acuity, has been linked to hallucinations in PD patients [46, 47, 83]. The fact that visual hallucinations occurring in the visually impaired (Charles Bonnet syndrome) [84] clinically resemble those occurring in PD patients has fostered speculation that visual impairment may contribute to the pathophysiology of PDP [38, 46, 74, 85]. In a recent prospective evaluation, the factors predictive of new onset hallucinations over a 1-year period were severe sleep disorder, visual impairment, and axial motor symptoms, suggesting that involvement of non-dopaminergic regions is likely to increase the risk of developing psychosis in PD [86].

There have been several attempts to evaluate the occurrence of genetic risk factors for hallucinations, but we are still early in the game. One paper analyzing dopamine transporter gene polymorphisms found that a particular variant allele was more frequent in levodopa-treated PD patients experiencing dyskinesia and psychosis [87]. However, the authors warned that this was a preliminary finding and that they could not exclude the possibility that other determinants, such as ethnicity, might account for the differences observed. In general, the studies examining this gene have been inconsistent [38]. Another group looked at the cholecystokinin (CCK) promoter polymorphisms. They found a trend towards more frequent representation of CCK-T in combination with the CCKAR-C polymorphism in hallucinators, but the statistical comparison to non-hallucinators was not significant [88, 89]. One small study demonstrated that *ACE* II genotype was an independent risk factor of psychosis in PD but this requires confirmation [90]. No association has been evident with $5HT_{2A}$ receptor or transporter genes [91], *ApoE4* or

ApoE2 [92] (Factor, unpublished data), COMT [92], *MAPT*, or *SNCA* REP1 (Factor, unpublished data).

Clinical Features

The clinical features of PDP have been described in numerous publications. In 2007, an NINDS/NIMH working group published a report in an effort to standardize diagnostic criteria for PDP [12]. The definition requires the presence of one or more of the following characteristic symptoms: illusions, false sense of presence, hallucinations or delusions. These must occur in a patient after the onset of idiopathic PD and be present continuously or recurrently for at least 1 month. Other causes of parkinsonism and psychosis must have been ruled out.

Hallucinations

Hallucinations can be described as spontaneously fabricated perceptions occurring while awake (perceptions without stimulus). In PD, hallucinations usually occur on a background of a clear sensorium. However, a concomitant confusional state is not uncommon in more severely demented patients [14, 15]. Usually, hallucinations are fully formed, nonthreatening images of people, animals or inanimate objects and tend to be recurrent, stereotyped, and reflecting past experience for each patient [14, 15]. For many, the fabricated figures seem familiar and friendly, such as family members or friends who have died; for others, they appear to be innocuous strangers or foggy shadows seen in dim light. Some patients will see adults sitting around their home as if they belong there. Others have described children wandering around the house. Another common scenario occurs when patients peer outside through a window and see children playing in the yard or men working (so called kinetic scenes). One patient of ours reported seeing a parade passing in front of her home on several occasions; another described a construction site in the backyard. Visions of animals are also common. Cats, dogs, and other benign furry creatures are typical, but small bugs and reptiles may also be seen. Occasionally, there will be an erotic overtone to the visions [41] and about 28% of the time hallucinations will have a threatening or frightening quality [81]. Although hallucinations tend to occur more frequently in the evening or overnight hours, they can occur at any time of the day. Visual hallucinations are typically brief, lasting seconds to minutes, and with variable frequency. They may be in color or black and white and figures may occasionally be distorted in size or shape. In one recent case report, the patient described hallucinatory background scenery while the people she saw in the foreground were quite real [93].

Oddly, many patients will claim to realize the fabricated nature of these images, and yet describe them to family members and physicians in such neutral terms that they seem to be no more extraordinary than a visit from a neighbor. More severely affected patients may insist they are real and, as a consequence, the hallucinations will impact on their behavior. One patient of ours was setting rat traps; another was spraying bug spray to ward off the insects. Such patients often will argue with their caretaker about the real nature of the hallucinations. In most patients, these hallucinations are fleeting and may disappear if they look directly at the image, move toward it, blink their eyes, or try to touch it [41]. In most cases, visions of people are silent and relatively passive. Some patients will be upset because the silence makes them feel like they are being ignored.

Two other minor forms of visual hallucinations have been well described. The “passage” hallucination is one seen out of the corner of the eye and passes by quickly, such as a person or animal. When the patient looks in that direction, it is usually gone. Another is the “presence” hallucination (extracampine), in which the patient usually has a sense someone standing behind or nearby. Although they don’t actually see anyone, they describe it as if they had [41, 46, 94].

Pure auditory hallucinations are rare in PD, but a secondary auditory component has been reported in up to 40% of patients with visual hallucinations [43, 46]. They are usually unrelated to the visual hallucinations despite occurring at

the same time. In one report, auditory hallucinations accompanied visions in 8% of patients [44] and were described as human voices, which were "non-imperative, non-paranoid, and often incomprehensible," like the background of voices at a party. In one longitudinal study, older patients were more likely than younger PD patients to have auditory or mixed hallucinations be the first they experience [95]. In our own experience, we have had two patients who, in addition to benign visual hallucinations, also reported hearing music periodically, unconnected to their other hallucinations. Both claimed that the music was of a particular style but could not identify a specific tune. One of these patients heard the music along with muffled voices that seemed to emanate from the air-conditioning ducts in her house. She actually attempted to tape record the sounds and play them back for her husband, who could not hear them. Music was heard by 14% of patients in more formal surveys of PD patients [44, 46].

Other less common types of hallucinations have been reported. Tactile and olfactory hallucinations can occur but appear to be rare. Friedman et al. reviewed the data collected on 160 patients in two separate controlled clinical trials on the treatment of PDP in PD and reported that they were more frequent than previously perceived, 23% for tactile and 16% for olfactory [52]. Nine percent of patients in one study and 22% of in the other reported olfactory hallucinations; 21% and 24% reported tactile hallucinations. Those with tactile hallucinations are often seen to be taking something out of their hand and putting it down. This is more likely to occur in individuals with dementia. In one report, a patient was described as "…feeling as if her bowels and bladder extruded from the distal parts of her upper limbs" [96]. The authors interpreted this as a somatic hallucination of visceral origin (cenesthetic hallucination). We had a patient with advanced PD and dementia who was certain he had been shot in the stomach. He described to his wife (who thought his stomach looked normal) that he could see and feel the bloody wound with his hands as well as the pain in his abdomen.

True illusions, which are distortions or misperceptions of actual visual stimuli, can also occur in some patients and represent another so-called minor form of psychotic symptoms in PD [81]. Typically, patients may report seeing faces in patterned fabric, misinterpret a curtain blown by the wind as a person moving, or mistake crumbs on a tablecloth for small bugs. One of our patients has intermittently reported that other peoples' faces appear to be distorted in grotesque ways. Illusions often occur in patients who also experience bona fide visual hallucinations [46].

Delusions

Delusions are not as common as hallucinations in PD but they usually constitute a more serious problem for the patients, caregivers, and physicians because their occurrence carries a greater risk for injury or hospitalization. Delusions are false beliefs that are based on incorrect inference, are held despite evidence to the contrary, and are not ordinarily accepted by other members of one's culture [13]. In PD, delusions are usually paranoid in nature. They most often occur on a background of a clear sensorium without other elements of a thought disorder, such as is present in schizophrenia [15]. Klawans [15] indicated that about 3% of patients treated with levodopa for 2 or more years would experience this type of organic delusional syndrome. Friedman et al. [52] found that the most common delusional themes reported by patients with PDP participating in a clinical treatment trial involved stealing, spousal infidelity, abandonment and the conviction that their spouse was an imposter or that they were not in their real home. In our own experience, delusions of spousal infidelity and elaborate conspiracies on the part of family members and even physicians are particularly common forms of delusions. The delusion of spousal infidelity, so-called Othello's syndrome [97], was found in one review to occur more commonly in middle-aged non-demented patients who were usually not on high dose medications or experiencing severe motor symptoms. In some instances, delusions can be associated with aberrant sexual behavior and violence. One of our patients was loading guns because he believed people he was

seeing in the street were sleeping with his wife. Other less common examples mentioned in the literature include fears of being injured, poisoned, or filmed and even delusions of grandeur.

Delusional misidentification syndromes are also well described. These include the belief that family members or friends have been replaced by identical-appearing impostors (Capgras phenomenon) or a familiar person appearing in the guise of a stranger (Fregoli syndrome) [98]. Capgras is the most common of these syndromes [99–101]. In one unusual case report, a patient experienced Fregoli syndrome closely linked to PD medication changes and without any other elements of psychosis such as hallucinations [102]. One patient of ours, who was an artist, thought his paintings were being stolen and replaced by cheap reproductions. These patients tend to have hallucinations with no insight. They are cognitively impaired with more severe dysfunction of verbal memory, semantic verbal fluency, and language deficits on neuropsychological testing. Although initially described in schizophrenia, this syndrome is particularly common in neurodegenerative disease, occurring in 17% of PDD patients and in up to 40% of individuals with DLB [99–101].

Another interesting delusional syndrome rarely described in PD is Cotard's syndrome [103]. It is a fixed and unshakable belief that the person does not exist. Another interpretation is that the person thinks they are dead. Jenkins and Groh described one such case in 1970 [34]. This patient became psychotic and had the delusion that her husband was dead. "It was pointed out to her that she had been speaking to him, thereupon she developed the delusion that she herself was dead." We have seen a similar case [104]. The patient was admitted by ambulance to the hospital because she was immobile. She had stopped taking her PD medications and when asked why, she claimed that she was dead and no longer had need for them. Her syndrome reversed with quetiapine therapy and PD medications were re-instituted.

The literature indicates quite clearly that the psychosis of PD is very different than that of schizophrenia. In the study by Holroyd of 102 PD patients with DIP, none had a schizophrenic-like syndrome [47]. Verbal commands and ego-dystonic critical commentaries typical of schizophreniform psychosis are extremely rare. However, we have seen two such cases [104]. Both had advanced PD. One woman heard voices telling her that she would be punished by having her PD medications withdrawn. This was very frightening to her since the "off" times were characterized by severe immobility. The other individual, also a woman, was hearing the voice of god commanding her to stop all medications or she would be punished. Neither patient had typical visual hallucinations, overt dementia, or a history of premorbid psychotic disease. One was hospitalized. Both were treated successfully with atypical antipsychotics. These syndromes can occur in isolation without hallucinations or other psychiatric issues [105].

Mechanisms of Psychosis

The mechanisms responsible for producing PDP are poorly understood. In some patients, PD medications precipitate acute psychiatric symptoms by unmasking a premorbid psychiatric state. This has been shown to occur in schizophrenics [106] and patients with manic-depressive illness [37] who were exposed to levodopa. For the vast majority of PD patients, however, there is no premorbid psychotic disorder. Thus, other characteristics peculiar to PD patients, PD medications, or both must be important.

It has been known for many years that drugs that are structurally similar to dopamine, such as lysergic acid diethylamide (LSD), mescaline, and amphetamines, can cause elaborate hallucinations and other psychotic symptoms in otherwise healthy individuals [106]. The discovery that levodopa could also precipitate psychiatric symptoms in animals and man coupled with the dramatic efficacy of dopamine receptor blockers (neuroleptics) in treating endogenous psychosis has formed the basis for the dopamine theory of psychosis [106]. Clinical evidence that supports this hypothesis includes the de novo, dose-related appearance of hallucinations in PD patients treated with dopaminergic medication, the

reliable disappearance of these symptoms with dose reduction, and the efficacy of traditional neuroleptics (dopamine receptor blockers) in treating this problem. Another supporting clue that dopaminergic circuits may be involved in hallucinations is that visual hallucinations were reliably induced by deep brain stimulation of the subthalamic nucleus (STN-DBS) in a postsurgical PD patient off of medications [107], which suggests a role of the STN.

More recent theories have been based on the altered dopamine receptor physiology associated with PD and the varied effects of dopaminergic drugs on different dopamine mediated systems in the brain. Dysfunction of the nigrostriatal dopamine system with consequent insufficiency of dopamine at the receptor sites of otherwise normal striatal neurons is responsible for the motor symptoms of PD. This also results in denervation hypersensitivity of striatal dopamine receptors. The early appearance of psychotic symptoms in patients treated with dopaminergic medications has been attributed to stimulation of these hypersensitive receptors [81].

In order to explain the late appearance of psychosis in PD, Klawans et al. [108] introduced the concept of levodopa-induced dopamine receptor hypersensitivity. They showed that in animal models chronic stimulation of dopamine receptors can cause stereotyped behavior to appear with sub threshold doses and with a shorter latency than in animals not chronically exposed to dopaminergic stimulation. Thus, chronic exposure to dopamine agonists causes hypersensitivity of dopamine receptors rather than the expected result, down regulation. In applying this model to levodopa-induced psychosis, Moskovitz et al. [81] have proposed that two populations of dopamine sensitive neurons exist in the striatum and limbic cortex. These are the so-called dopamine-facilitated and dopamine-inhibited neuronal populations. Dopamine-inhibited neurons predominate in the striatum and exhibit down regulation and hyposensitivity with chronic dopaminergic stimulation. In contrast, dopamine-facilitated neurons respond to chronic stimulation by becoming hypersensitive. This dopamine-facilitated neuronal population might predominate in limbic cortex and thus be responsible for the psychotic symptoms that may occur with chronic levodopa treatment.

Although the literature supporting the central role of dopamine in PDP seems compelling, Goetz et al. have performed an elegant experiment that cast some doubt on this concept [72]. They gave five non-demented PD patients with daily visual hallucinations high-dose intravenous infusions of levodopa, utilizing both steady and pulse infusion paradigms. None of the patients experienced hallucinations in response to the infusions but some did experience increased dyskinesia. The investigators concluded "Visual hallucinations do not relate simply to high levels of levodopa or to sudden changes in plasma levels." This doubt is enhanced by epidemiological studies that show no relationship between daily dose of levodopa and the risk of hallucinations [41, 46].

Dysfunction of central serotonergic pathways has also been explored as a possible cause of PDP. Postmortem studies have shown that patients with this complication have lower brainstem levels of serotonin (5-hydroxytryptamine, 5-HT) [109]. Acute administration of levodopa reduces brain serotonin levels by several possible mechanisms: interfering with the transport of L-tryptophan across the gut and blood–brain barrier, inhibiting tryptophan hydroxylase, and replacing serotonin in presynaptic storage sites leading to increased dopamine formation [37, 109]. In animals, levodopa caused a decrease in serotonin levels but increased 5-hydroxyindoleacetic acid (5-HIAA) levels, suggesting an increase in release and turnover of serotonin that, in turn, leads to increased receptor stimulation [110]. Dysfunction of serotonergic systems is also suggested by the frequent association of PDP with sleep disturbance and altered dreaming, both of which are thought to have a serotonergic basis [41, 80, 109]. Comella et al. [111] compared PD patients with and without hallucinations using polysomnography and found that hallucinators had reduced sleep efficiency, reduced total rapid eye movement (REM) sleep, and reduced percentage of REM sleep. In another recent study, 24-h ambulatory polysomnography was performed on 20

PD patients experiencing visual hallucinations [112]. The investigators found a close temporal link between 33% of the hallucinations and the occurrence of non-REM sleep during the day or REM sleep patterns at night. These findings suggest that serotonergic neural mechanisms involved in generating sleep and dream phenomena may play a role in the occurrence of hallucinations in PD. The serotonin hypothesis is further strengthened by a report of postmortem tissue analysis in parkinsonian patients who had experienced visual hallucinations. The analysis showed increased 5-HT_{2A} receptor binding in the inferior lateral temporal cortex [113]. Clinical trial data showing that ondansetron, a selective 5-HT_{3} receptor antagonist, markedly improved psychotic symptoms in PD patients [110] also support the role of serotonergic dysfunction in PDP.

Cholinergic pathways have also been implicated. Older studies [114] suggested this for several reasons: the occurrence of hallucinations as an adverse effect of anticholinergic drugs, the awareness that anticholinergic drug therapy was a risk factor for the occurrence of psychosis, and the description of cholinergic deficiency in the brains of patients experiencing these symptoms. The recent finding that cholinesterase inhibitors provide some relief of psychosis in PD also supports this possibility [115]. Perry and Perry [116] have advocated a more comprehensive appreciation of the role of cholinergic pathways in the organization and maintenance of normal consciousness. Based on findings in DLB, they propose that decreased cortical acetylcholine leads to breakdown of the boundaries maintaining the clarity of normal conscious thought. This, in turn, results in intrusion of subconscious intrinsic thoughts and sensory phenomena into consciousness, i.e., hallucinations and delusions.

Further insights into the pathophysiology of hallucinations have come from studies that suggest that hallucinations occurring in PD are similar to those of the Charles Bonnet syndrome [46]. This syndrome, first described in 1769, is characterized by fully formed hallucinations in patients who are blind from macular degeneration or other causes. Hallucinations occur in 21% of blind patients [83], possibly as a result of denervation hypersensitivity of the visual cortex [84]. PD patients may be prone to this phenomenon because they develop retinal disorders with abnormalities of contrast sensitivity measures and have a number of age-related visual problems, such as macular degeneration. The results of studies looking to confirm this hypothesis have been inconsistent. Fenelon et al. found that ocular pathology in PD was an independent risk factor for hallucinations [46]. However, a more recent study compared PD subjects with and without hallucinations and found that, although hallucinators performed worse on measures of visuoperceptive performance, there was no difference between the groups on multiple measures of ocular pathology [117].

The idea that visual processing circuits are dysfunctional in PDP is supported by several recent studies utilizing modern functional and volumetric neuroimaging techniques. Stebbins et al. compared functional magnetic resonance imaging (fMRI) responses to stroboscopic and kinematic visual stimulation and found that PD subjects with hallucinations showed an activation shift from posterior brain regions (visual processing areas) to more anterior regions, such as the inferior and superior frontal gyri, compared with non-hallucinators [118]. Another study with fMRI, however, suggested that different regions are abnormal depending on the type of hallucinations. For instance, facial hallucinations were associated with temporal lobe abnormalities; objects and kinetic scenes were associated with occipital lobe changes [119]. Matsui et al. utilized the [^{123}I] IMP single photon emission computed tomography (SPECT) perfusion technique and found not only decreased perfusion in visual processing cortex in visual hallucinators with PD but also decreased perfusion in auditory processing cortex in parkinsonian patients with verbal auditory hallucinations [120–122]. One volumetric MRI study in hallucinators with PD, utilizing voxel-based morphometry, showed decreased gray matter volume in associative visual processing cortex such as the midbrain tectum and lingual gyrus [123]; another showed widespread volume loss in visual association cortex in DLB

but only left orbitofrontal lobe volume loss in PD subjects [124].

Pathological studies have attempted to elucidate the pathological anatomy of hallucinations in parkinsonian disorders. Harding et al. [125] systematically reviewed the clinical features and neuropathological findings in 63 patients with DLB or PD with dementia. They found a striking association between the density of Lewy bodies in the temporal lobe and the presence of hallucinations in patients with DLB. The density of Lewy bodies was particularly high in the amygdala and the parahippocampus. These regions are also important for dementia and the overlap is obvious. This paper looked specifically at DLB, a disorder of dementia and parkinsonism. The fact that psychosis is so much a part of this disorder brings up the question of what the relationship is between dementia, and its associated pathology, and the occurrence of hallucinations. Dementia is the most robust risk factor for onset of hallucinations in PD and hallucinations represent a possible risk factor for dementia [6, 41]. Dementia may, in fact, be a necessary comorbidity because it may promote misinterpretation of visual stimuli. In DLB, hallucinations often occur without medications, but otherwise the hallucinations are similar in DLB and PDD. Indeed, it may be that Lewy body pathology itself is specifically associated with hallucinations in parkinsonian disorders. Strongly supporting this is a large retrospective autopsy study that showed visual hallucinations are specific to Lewy body parkinsonism as opposed to other pathological forms of parkinsonism [126].

The task of assimilating the various neurochemical, neuroanatomical, and clinical observations presented here into a single coherent explanation of the pathophysiology of psychosis in PD seems daunting. However, Diederich et al. [85] have made an admirable attempt by incorporating these disparate findings into the theories of consciousness developed by Hobson [127]. They suggest that visual hallucinations result from the dysfunction of cortical and subcortical systems responsible for the proper gating and filtering between external conscious perception and internal image production. They are able to incorporate factors that reduce normal input into the system, such as primary ocular, retinal, and cortical visual dysfunction related to PD. Neurochemical changes in the brainstem also are postulated to enhance the emergence of internally generated images via the ponto–geniculo–occipital system (cholinergic) and the intrusion of REM dream imaging into wakefulness (serotonergic). Finally, impaired modulation and separation of these external and internal stimuli result from the effects of the cortical dysfunction associated with dementia and exogenous dopaminergic overactivation of mesolimbic systems. Although much supportive research remains to be done, this integrative model represents a major step forward.

Treatment of Psychosis

General Considerations

There are some PD patients with psychotic symptoms that do not require antipsychotic therapy. Those patients with hallucinosis on the background of a clear sensorium may not need or want therapeutic intervention, especially when the hallucinations are intermittent, brief, nonthreatening and when the patient has preserved insight. In fact, some patients actually claim to gain pleasure from the symptoms. These patients should be watched carefully, however, since escalation of psychotic symptoms may occur without apparent provocation.

In patients with a sudden onset of psychotic symptoms, it is important to investigate for triggering events such as urinary and pulmonary infections, metabolic disturbance, cerebrovascular events, or traumatic brain injury. Treatment of these underlying conditions is paramount and, if initiated immediately, will be sufficient. Postoperative psychosis is another situation that may not require specific therapy. In one study [128], psychosis occurred in up to 60% of PD patients who had surgical intervention. Our own experience with this situation suggests that once patients are allowed to increase activity and, more frequently, when they are discharged home, the psychosis will usually improve spontaneously.

Other possible causes of postoperative psychosis include the effects of anesthetics, pain medications, an unfamiliar environment, and superimposed metabolic encephalopathy or infection.

If the patient has PDP and requires intervention, the first step is to decrease PD medications and this remains standard practice. It is clear from experience that lowering medications can be helpful and is usually well tolerated. Marsden and Fahn [129] suggested decreasing and then removing adjunctive medications first, before lowering levodopa. However, as medications are stripped away one by one and psychosis persists eventually the patient will experience intolerable worsening of motor symptoms. It is at this point that the addition of antipsychotic medication is usually considered.

Treatment with Clozapine

Clozapine (CLZ) is a unique drug that remains the treatment of choice for PDP. CLZ is considered to be an "atypical" antipsychotic because it does not cause catalepsy in laboratory animals (i.e., increase in muscle tone and postural abnormalities) [130] and is associated with minimal risk of drug-induced parkinsonism, dystonia, and akathisia [130, 131]. It is this unique ability, to be able to effectively treat psychosis without causing or worsening parkinsonism that led to the initial attempts to use this drug in PD two decades ago. Since then its safety and efficacy in PDP has been demonstrated in numerous open-label studies [132]. This accumulated experience with CLZ has been remarkably uniform and has shown that it can be used in small, well-tolerated doses to rapidly reverse symptoms of psychosis.

In 1999, the results of two-multicenter, 4-week, double-blind, placebo-controlled trials were published, which have confirmed the results seen in previous open-label trials. The first was a North American trial organized by the Parkinson Study Group [9]. In this study, 30 patients with PDP were treated with CLZ and 30 were randomized to placebo. CLZ was started at a very low dose of 6.25 mg. at bedtime and increased as needed according to a standardized schedule to a maximum dose of 50 mg. Psychotic symptoms were measured with (1) a 7-point clinical global impression scale (CGI); (2) the Brief Psychiatric Rating Scale (BPRS); (3) a modified form of the BPRS to remove four items thought to be more reflective of parkinsonism than psychosis; and (4) the Survey Assessment of Positive Symptoms (SAPS). The motor subscale of the UPDRS was used to assess parkinsonism. Psychotic symptoms were significantly improved in the CLZ group compared with placebo at a mean dose of 27 mg/day, without worsening of motor function. The double-blind study was followed by a 3-month open label extension that confirmed this effect [10]. These results were confirmed in a second double-blind, placebo-controlled study organized by the French Parkinson Study Group [133]. They used similar methodology and reported very similar results. This drug remains the only one proven with controlled trials to improve PDP without worsening motor symptoms. This is why it remains the gold standard to which other agents are compared.

Sedation is the most common adverse effect of CLZ but its occurrence may be used to therapeutic advantage. Frequently, patients with PDP also have sleep disruption and some degree of reversal of their normal sleep–wake cycle. These patients often spend nights awake, agitated, hallucinating, and engaged in paranoid behaviors such as looking through their house for intruders. As a result, they will be sleepy and more disoriented the next day. Caregivers also become sleep deprived, emotionally stressed, and physically exhausted. When CLZ therapy is started as a bedtime dose, the most dramatic initial benefit is usually restored restful sleep and normalization of the sleep–wake cycle. This is a result that is greatly appreciated by all involved and generally also is a sign that the CLZ dose is at, or very near, an effective antipsychotic dose as well. Dosing should begin at 6.25 mg at bedtime and increase every few days by 6.25–12.5 mg. Most patients will obtain benefits with 50 mg or less. Occasionally, acutely psychotic patients will need to be given doses as high as 150–200 mg/day until their symptoms are under control. Then, a smaller maintenance dose can be used to prevent recurrence. Some patients

on a single bedtime dose will experience breakthrough symptoms the next day in the late afternoon or early evening. In this situation, a small additional daytime dose (usually ≤12.5 mg) is sufficient. If sedation is a problem in the morning, the bedtime dose can be lowered or moved 1–2 h earlier in the evening.

Once psychotic symptoms are adequately controlled and the patient is sleeping through the night, it is usually possible to carefully increase antiparkinsonian medication doses to improve motor functioning. Small increases in daytime levodopa doses are possible but it is best to keep nighttime doses to the absolute minimum. Adjunctive medications such as dopamine agonists, selegiline or COMT inhibitors will usually have been dramatically reduced in dose or eliminated prior to starting CLZ. These medications need to be used with caution in patients requiring antipsychotic therapy; in patients with significant dementia, they should be avoided.

The adverse effect of most concern with CLZ is agranulocytosis (Agran). In 1975, the occurrence of 8 deaths from septicemia out of 16 patients who developed Agran in Europe [131, 134] delayed the marketing of this drug in the USA. The estimated risk of Agran in schizophrenic patients treated with CLZ is 1–2% [135], which is higher than standard psychotropic medications. This figure is about the same in PD [10], indicating that this adverse effect is idiosyncratic and not dose related. An apparent prodrome of 29 days, characterized by a gradual decrease in white blood cell (WBC) count, has been observed [135]. However, precipitous drops in the WBC count from the normal range can also occur.

Current guidelines in the USA require weekly monitoring of the WBC count for the first six months of CLZ therapy, every other week monitoring for the next six months and monthly thereafter. Therapy should be interrupted if the WBC count drops to less than 3,000/mm^3 or the absolute neutrophil count drops to less than 1,500/mm^3. These patients may be rechallenged with CLZ but must undergo weekly blood testing for the first 12 months. Permanent discontinuation is recommended if the WBC count is less than 2,000/mm^3 or the absolute neutrophil count becomes less than 1,000/mm^3. Patients with a baseline WBC count of less than 3,500/mm^3 or a neutrophil count of less than 2,000/mm^3 or a history of immune deficiency should not be treated with CLZ.

Apparently, these guidelines have been effective in reducing the risk of Agran. Honigfeld et al. [136] reviewed the incidence of Agran in 99,502 patients treated with CLZ according to these guidelines between 1990 and 1994. They found that 382 cases of Agran (0.38%) and 12 deaths had occurred and that this was dramatically reduced from the 995 cases of Agran and 149 deaths that would have been predicted based on the pre-guideline incidence of 1–2%.

Other hematological adverse effects that may occur with CLZ include mild asymptomatic eosinophilia, chronic leukocytosis that may be associated with a low-grade fever, and lymphopenia (less than 600 lymphocytes/mm^3) that is usually asymptomatic or may be associated with diarrhea and fever [130]. The etiology of these problems is unknown [137]. One other adverse event of concern is neuroleptic malignant syndrome. Although CLZ causes few extrapyramidal adverse effects, neuroleptic malignant syndrome has been reported rarely. One case was described in a patient with CLZ and carbamazepine therapy; the other in a patient with CLZ combined with lithium therapy [138].

CLZ can cause several other adverse effects of concern in PD patients. Sialorrhea and delirium follow sedation in frequency [11, 130]. These appear to be dose-related adverse events and are a common cause of dose limitation. Orthostatic hypotension can also be a problem with PD patients, since many already suffer from this problem caused either by PD medications or autonomic dysfunction as part of PD itself. Seizures are of concern in schizophrenics, occurring in up to 4% of these patients [130, 139, 140], often with EEG changes that have been well described. Both seizures and EEG changes are dose-related phenomena. This would explain why no seizures have thus far been reported with the low doses used in PD. The incidence of seizures is less than 1% at

Table 5.2 Summary of distinguishing characteristics of atypical antipsychotics

Characteristics	CLZ	RSP	OLZ	QTP	ZIP	ARI
Fails to induce catalepsy or antagonize amphetamine stereotypies	+	–	–	+	–	–
Inc. 5HT/D-2 binding	+	+	+	+	+	+
No prolactin elevation	+	–	+/–	+	–	+
Mesolimbic selectivity	+	–	+	+	?	–
Loose D-2 binding	+	–	–	+	–	–[a]
Improves negative symptoms	+	+	+	+	+	+
Decreased EPS	+	–	+	+	+	+
Not associated with TD	+	–	+/–	+	?	?

EPS extrapyramidal side effects, *TD* tardive dyskinesia, *CLZ* clozapine, *RSP* risperidone, *OLZ* olanzapine, *QTP* quetiapine, *ZIP* ziprasidone, *ARI* aripiprazole
[a]Has partial dopamine agonist effects as well as antagonist effects

doses under 300 mg/day, 2.7% at daily doses of 300–600 mg, and 4.4% at doses greater than 600 mg/day [139].

Serious, but thankfully rare, medical complications associated with CLZ use include venous thromboembolism [141], myocarditis [142, 143], and possibly sudden death [144]. The treating physician must be vigilant for these effects. There also have been several reports of poor blood sugar control in diabetics and increased risk of new-onset type 2 diabetes with this drug [145, 146]. These reports involved schizophrenics treated with high doses. The same increases in blood glucose were not seen in one study of PD patients treated with much lower doses [147]. Olanzapine and other neuroleptic medications also have been implicated; thus, this may be a class effect [148–151].

The main obstacle to long-term success with CLZ therapy in PD is progression of underlying disease, particularly dementia. Greene et al. [152] found that of four patients with marked dementia treated with clozapine, only one improved and the rest experienced adverse events. Factor et al. [153], in a long-term trial, showed that as dementia progressed (illustrated by a decrease in MMSE score) psychosis began to re-emerge and adverse effects became more of a dose-limiting problem. Non-demented patients can tolerate long-term therapy well; in those with significant dementia, efficacy and tolerance will decline.

Treatment with Other Atypical Antipsychotics

Safe and effective alternatives for the treatment of PDP have been sought because of the small but significant risk of Agran associated with CLZ and the need for mandatory blood monitoring. Six additional antipsychotic medications are now available that have an "atypical" pharmacological profile and do not seem to carry the risk of Agran. Four have been utilized in the treatment of PD: risperidone (RSP), olanzapine (OLZ), quetiapine (QTP), and aripiprazole (ARI). It is their "atypical" pharmacology that makes these drugs potential alternatives for PD patients. But, what is the definition of "atypical?" This has not been clearly defined pharmacologically. CLZ remains the prototype of this class of drugs and that to which all others are compared. It is distinguished from typical antipsychotic drugs by its strong antipsychotic effect coupled with freedom from extrapyramidal syndromes. That, in essence, is the clinical definition of "atypical" and the goal in developing new atypical agents. But what are the pharmacological properties that differentiate these drugs?

The features most often discussed as defining the atypical classification of drugs, based on the unique pharmacology of CLZ, are listed in Table 5.2, along with how all currently available atypical agents fulfill these standards [154].

Table 5.3 Summary of open label reports with risperidone in the treatment of psychosis in PD

Author/reference year	# Patients	Dosage[a] (mg/day)	# Psychosis imp	# PD worsened
Meco 1994	6	0.67	6	0
Ford 1994	6	1.5	6	6
Rich 1995	6	0.5–4	4	5
Allen 1995	3	0.5–1	3	0
McKeith 1995	3	1	0	3
Meco 1997	10	0.73	9	3
Workman 1997	9	1.9	8	0 (est)
Leopold 2000	39	1.1	33	6
Mohr 2000	17	0.5–3	16	0[b]

est estimated number based on available information in the publication
[a]Dosage is given as a mean or a range
[b]Ten of 17 patients reported "hypokinesia" as an adverse event and 1 withdrew due to worsening of gait

Although RSP and OLZ share some features defining atypicality, it is QTP that is the most similar to CLZ in these respects. However, there does not appear to be a single pharmacological trait that strictly defines this class of agents.

A recent and compelling theory of the neurophysiological basis of atypicality has been derived from studies looking at the way in which CLZ interacts with dopamine receptors. In vitro experiments using cloned human dopamine D2 receptors have shown that CLZ and QTP are loosely bound and easily displaced from these receptors [155]. All other antipsychotic drugs tested with this method, including RSP, OLZ, and traditional neuroleptics, show prolonged and tighter binding to D2 receptors (see Table 5.2). A second study utilizing in vivo positron emission tomography (PET) scanning in 12 patients treated with QTP [156] demonstrated only transiently high dopamine D2 receptor occupancy. The atypical clinical and pharmacological features seen most prominently in CLZ and QTP may be due to this "loose" binding and fast dissociation from D2 receptors. Loose binding also may allow a more physiological response to surges in endogenous dopamine, thus preventing the usual neuroleptic adverse effects such as drug-induced parkinsonism [157]. This feature may also contribute to mesolimbic selectivity and may be the reason for a faster relapse of psychosis in schizophrenia when the drugs are discontinued. If loose binding does define atypical behavior, then it would help predict which agents are safer in PD. Based on the limited clinical data available now, it appears to.

Risperidone and Olanzapine

A summary of open-label studies published on the treatment of PDP with RSP and OLZ is shown in Tables 5.3 [158–166] and 5.4 [167–174] respectively. With both of these medications, early open-label reports were generally positive, but these were followed by several additional publications that reported significant, and sometimes serious, worsening of PD motor symptoms. Although the literature is somewhat conflicted, most PD specialists are in agreement that RSP and OLZ are not well tolerated in this setting. The few double-blind trials published on the use of these two drugs for PDP confirmed that these were not appropriate choices [175–178].

Quetiapine

Perhaps the most useful "atypical" antipsychotic medication introduced as an alternative to CLZ for PD is QTP, which was approved for schizophrenia in 1998. There have been several open-label studies in which it appears to be effective in treating PDP at doses of 50–400 mg/day with minimal impact on motor features. A summary of published open label studies is shown in Table 5.5 [179–189].

Table 5.4 Summary of open label reports with olanzapine in the treatment of PD with psychosis

Author/reference year	# Patients	Dosage[a] (mg/day)	# Psychosis imp	# PD worsened
Wolters 1996	15	6.5	15 (est)	0
Jimenez 1998	2	5	1	2
Friedman 1998	19	N/A	7	10
Friedman 1998	12	4.4	12	7
Weiner 1998	21	5	13	9
Graham 1998	5	5	5	4
Molho 1999	12	6.3	9	10
Stover 1999	22	N/A	12	8

est estimated number based on available information in the publication, *N/A* data not available
[a]Dosage is given as a mean or a range

Table 5.5 Summary of open label reports with quetiapine in the treatment of PD with psychosis

Author/reference year	# Patients	Dosage[a] (mg/day)	# Psychosis imp	# PD worsened
Evatt 1996	10	50	10 (est)	0
Parsa 1998	2	200,400	2	1
Juncos 1998	15	70	15 (est)	0
Juncos 1999	40	25–800	40 (est)	8 (est)
Samanta 1998	10	37.5	6	7
Fernandez 1999	35	40.6	25	0
Friedman 1999	15	62.5	12	4
Targum 2000	11	25–300	6	0
Reddy 2002	43	54	35	5
Fernandez 2003	106	60	87	34
Juncos 2004	29	12.5–400	18	NS

est estimated number based on available information in the publication, *NS* no significant worsening overall. Individual results not reported
[a]Dosage is given as a mean or a range

In the largest cohort, Fernandez et al. provided long-term data in 106 PD patients treated in an outpatient clinic [188]. The mean duration of therapy was 15 months and the average dose was 60 mg/day. Psychosis partially or completely remitted in 82%; no improvement was evident in18%. Some degree of motor worsening was seen in 32% of patients, but only 9% discontinued QTP because of this problem. The presence of dementia was associated with an increased likelihood of motor worsening as well as nonresponse in terms of psychosis.

In our own open-label evaluation [187], 43 consecutive PD patients with PDP (mean duration 13 months) were treated with QTP at a mean dose of 54 mg/day for a mean duration of 10 months. Eighty-one percent (35 patients) had improvement of psychotic symptoms but it was not complete in all (23 complete amelioration; 12 partial). Five patients (12.5%) experienced mild worsening of motor symptoms and two had to stop therapy. Twenty of the patients were demented and the rest were not. There was no difference in antipsychotic effect between the groups, but mild worsening of motor symptoms was only seen in the demented group as measured by UPDRS. All five of the patients with definite worsening had some degree of dementia. None of the non-demented patients had a worsening of motor symptoms.

Unfortunately, as with other potential alternatives to CLZ, placebo-controlled clinical trials with QTP have had disappointing results. In each case, efficacy measures did not reach statistical significance, but this may in part be related to the small size of the studies and poor statistical power. Fortunately, none of the trials showed significant worsening on measures of motor function [190–194]. It is likely that larger controlled trials are needed to more fully evaluate the role of QTP, but there are impediments to doing so. These include the lack of sensitive and reliable scales for PDP, psychosis symptom fluctuation, placebo effect, difficulty recruiting adequate numbers of study subjects, and poor tolerance of higher doses of QTP in this setting. Future trials of any antipsychotic in PD will have to address some of these issues and an effort to evaluate the utility of the various psychiatric scales used thus far is underway [195, 196].

Although some worsening of motor symptoms has been reported with QTP, judging from this preliminary literature and our own experience it seems unlikely that this will constitute a significant clinical problem, unlike the case with RSP and OLZ. QTP, however, appears to be less potent than CLZ in relieving psychosis and some suggest that it works well for hallucinations but not for delusions. The dose may need to be pushed aggressively into the range normally used to treat schizophrenia (400 mg/day or higher) in some patients. Even then, some patients with PDP may not respond. We have also seen the occasional patient in our practice who has experienced a paradoxical worsening of agitation and psychosis when QTP was added at the usual starting dose of 25 mg at bedtime. Increasing the dose only exacerbated the problem in these rare patients. There also has been one case report of rhabdomyolysis in a PD patient treated with low dose QTP for PDP [197].

Other Atypical Neuroleptics

The two newest "atypical" antipsychotic medications available are ARI and ziprasidone. No published results exist regarding the use of ziprasidone for PDP. However, it has dopamine receptor binding similar to RSP and other typical antipsychotics and thus it is expected to have a similar impact on PD [155]. ARI has been viewed as theoretically promising because of its pharmacology as a partial dopamine agonist. However, the one large scale controlled clinical trial using low dose ARI for PDP was ended early due to a high dropout rate and worsening of PD motor symptoms in some patients [198].

An experimental antipsychotic agent, pimavanserin, is currently in phase 3 clinical trials and is being tested specifically in PD patients with PDP. This agent is an inverse agonist without any dopamine receptor-blocking properties. In a small double-blind preliminary safety study, this drug was found to be safe and well tolerated in 12 PD patients [199]. No worsening of motor symptoms was evident. In two more recent controlled clinical trials, improvement in psychosis was noted, but formal primary endpoints were not met. Again, pimavanserin was well tolerated and no worsening of motor symptoms occurred [200, 201].

In April of 2005, the USA Food and Drug Administration issued a health advisory warning of increased risk of death with the use of atypical neuroleptics in patients with dementia, based on the results of clinical drug trial adverse event reporting, much of which was unpublished. In a published meta-analysis of randomized trials, Schneider et al. [202] also found a small but significantly increased mortality risk with atypical neuroleptics; no apparent distinction between the various agents was available. The authors recommended that this risk be considered in the context of medical need, efficacy evidence, medical comorbidity and the relative lack of alternative treatments. Conventional neuroleptics, for example, are not safer in this regard when compared with atypicals [203]. Adequate data do not yet exist specifically for the PD population. However, in this special population there is a well-documented morbidity associated with the occurrence of psychosis in PD, including hospitalization and nursing home placement [3, 5]. There are also substantial risks associated with the alternative approach of PD medication reduction to the point of immobility such as parkinsonism–hyperpyrexia syndrome, deep venous thrombosis, aspiration

pneumonia, pulmonary embolus, falling and loss of independence. At this point, experts favor a rational weighing of these risks and still recommend the careful use of CLZ or QTP in the treatment of PDP, provided PD medication has first been reduced appropriately [204].

Non-neuroleptic Therapies

The cholinesterase inhibitors are a promising class of medication that has been investigated for the potential to treat both cognitive and psychiatric symptoms in PD. Donepezil (DPZ), rivastigmine (RVS), and galantamine (GLN) have all been shown to be beneficial in mild to moderate Alzheimer's disease in large, double-blind, placebo-controlled trials [205–207]. The rationale for using these agents in parkinsonian disorders is based on the finding that more severe cholinergic deficits are present in the neocortex of patients with DLB than in Alzheimer's disease [208].

The results of preliminary studies have been encouraging. RVS has been the most thoroughly studied of these agents. Initially, McKeith et al. [115] investigated the utility of RVS in DLB and reported improvements in delusions and hallucinations in a double-blind, placebo-controlled trial involving 120 patients. Patients were treated with up to 12 mg/day of RVS for 20 weeks. Improvements were noted in subscores of the Neuropsychiatric Inventory (NPI) scale. In PD specifically, three open-label trials examining psychotic symptoms have demonstrated similar improvements in a small number of patients [209–211]. Significant worsening of motor symptoms was not noted in any of these studies. In the only large, controlled clinical trial reported to date, Emre et al. reported the results of blinded, placebo-controlled treatment with RVS in 541 patients over 24 weeks [212]. Modest, but statistically significant, improvements were evident in cognitive function and psychiatric symptoms, as measured by the NPI. Increased tremor was noted in the active treatment group, but this was not reflected in any change in the UPDRS motor score.

Donepezil was used to treat PDP in PD in two small open-label studies [213, 214]. Bergman and Lerner reported on six patients who were treated with 10 mg/day for 6 weeks [213]. Five of the six patients experienced "clinically significant" improvement in symptoms of psychosis. No worsening of motor symptoms was observed. Fabbrini et al. reported similar results in eight non-demented PD patients with PDP. In this study, however, two of the eight patients experienced worsening of motor function (40% and 60% respectively), as measured by the UPDRS [214]. A single open-label trial has examined the use of GLN in PDP [215]. Aarsland et al. treated 16 patients for 8 weeks with 8 mg twice daily and reported that hallucinations improved in seven of nine patients. Here, too, some worsening of parkinsonism was noted in three patients, but a formal motor scale was not used and it is unclear how significant the worsening was. Larger, well-designed trials are needed to fully assess the utility and safety of these medications in this setting.

Voon et al. have reported on the treatment of PD patients with psychosis and comorbid depression and anxiety. They found that eight of ten patients had improvement of psychotic symptoms with antidepressants [216]. They suggest this as first-line therapy for such patients.

The cannabinoids are an intriguing group of compounds in this regard. Based on preclinical evidence, cannabidiol was looked at specifically by a Brazilian research team as a treatment for PDP [217]. In an open-label pilot trial, they treated six PD patients and reported significant improvement in psychosis, as measured by the Brief Psychiatric Rating Scale and the Parkinson Psychosis Questionnaire; no motor worsening was observed. Given the disparity between open-label and blinded assessments evident in trials with other agents, these results should be viewed as preliminary and will likely motivate more serious study.

Electroconvulsive therapy (ECT) may be useful in the treatment of PDP [11, 218]. Hurwitz et al. [218] treated two PD patients suffering from chronic non-confusional psychosis with bilateral ECT (one received six treatments; the other

three). It not only cleared the psychosis but also allowed for the use of higher doses of dopaminergic medications. After five months, one patient had no recurrence and in six months the other had only occasional visual illusions. Ueda et al. have demonstrated the same effects in five elderly PD patients, with benefits lasting 5–30 weeks. ECT appeared to be safe in this patient population [219]. It is likely that patients with confusional states will not achieve the same benefit and, in fact, confusion is considered a contraindication for ECT [11, 220]. There also is interest in using ECT to treat PD patients because of its ability to improve motor symptoms [221–223]; this improvement may be due to enhancement of dopamine transmission caused by the ECT [224]. It is hard to explain the antipsychotic effect of ECT on the background of increased responsiveness of dopamine receptors, and Hurwitz et al. [218] suggest that improvement in psychosis may be due to an effect via non-dopaminergic mechanisms.

The improvement of motor features of PD by ECT is most likely transient [221, 222]. The antidepressant effects of ECT also are temporary and patients should be treated with antidepressant agents for long-term maintenance. In general, this would not make ECT a logical choice as a primary agent in the treatment of PDP. The adverse effects of memory loss and delirium also are of concern. However, in those situations where CLZ does not improve psychosis, or when significant side effects occur at dose levels that are otherwise ineffective, ECT can be used as an adjunct and then low-dose CLZ may help maintain the benefit [225].

Treatment Summary

The treatment of PDP can be approached in a stepwise fashion. First, it is necessary to search for and treat any triggering factors, such as infection, that may have precipitated decompensation in an otherwise stable patient. If no such triggers are present and the symptoms are mild, a modest reduction in antiparkinsonian medication dose will usually be sufficient. In more severely affected patients, the next step is to decrease or stop adjunctive medications. This should be done one drug at a time and in order of decreasing risk-to-benefit ratio. If psychosis continues, an attempt should be made to decrease the dose of levodopa. There is data to support the fact that a substantial percentage of PD patients with psychosis will improve with these first steps [226]. If at any point there is a meaningful increase in disability, then an antipsychotic medication will be required.

CLZ is the only antipsychotic medication that has been proven in controlled clinical trials to effectively control PDP without worsening parkinsonism. However, based on existing evidence, our own experience, and ease of use, we feel that QTP is a reasonable alternative as a first choice agent. An American Academy of Neurology Practice Parameter published in 2006 concluded that there was Level B evidence that CLZ was effective and "should be considered" for the treatment of PDP. It was also stated that there was level C evidence that QTP was effective and "may be considered" and that olanzapine "should not be considered" for use in this setting [227]. QTP is usually started with a bedtime dose then daytime doses are added if necessary. If QTP is not effective, or if adverse effects prevent further increases in dose, we recommend CLZ as the antipsychotic of second choice. We have had patients treated with up to 400 mg/day of QTP without benefit then respond to as little as 6.25 mg of CLZ. It is important to remember that PD patients are particularly prone to sedation with these medications and therapy should be initiated with a low dose and increased in small increments. Frequent communication between physician and the patient's caretakers is paramount during this difficult period. Once PDP is controlled, a smaller maintenance dose is usually possible and a careful optimization of antiparkinsonian medications can be attempted.

In the rare patient who does not respond to either of these medications, a trial of one of the other atypical agents may be justified, but the patient should be monitored carefully for worsening parkinsonism. In PD patients with dementia,

cholinesterase inhibitors may be a useful adjunct by helping to control both symptoms of psychosis and dementia. Occasional patients will not respond to the above measures and more drastic reductions in levodopa will be necessary. This will usually be associated with severe worsening of motor features and should be done in a hospital setting under the supervision of a movement disorder specialist. Finally, in non-demented patients, a course of ECT may be considered.

Long-Term Outcomes

It has been suggested that, with the onset of hallucinations, the prognosis of PD declines significantly. Related issues that have been examined are persistence of hallucinations, nursing home placement (NHP), and mortality. The question of whether treatment with atypical antipsychotics alters the outcome of hallucinating patients has been addressed in a limited way. With regard to persistence of hallucinations, several studies have demonstrated that once hallucinations occur, they remain an issue even with appropriate treatment. One study examined the persistence of hallucinations in 59 patients 22 months after enrollment in a clinical trial of CLZ for the treatment of this problem [6]. Sixty-nine percent had persistent hallucinations. A recent study following 89 patients for 10 years showed that if hallucinations were present at baseline there was a high likelihood of them persisting; severity also increased with time, often progressing from visual hallucinations with insight to loss of insight and delusions [56]. Even in patients in whom the symptoms resolve with antipsychotic therapy, any attempt to withdraw the therapy may lead to a rapid, severe rebound [228]. There also is a greater likelihood that dementia will follow, if not already present [6].

With regard to nursing home placement and mortality, a few studies examined the outcomes of patients prior to the availability of atypical agents. Sweet et al., in 1976, looked at the outcome of 18 PD patients followed for about 6 years [229]. Five (27%) were placed in nursing homes, five (27%) died, six (33%) were incapacitated but living at home, and only two (11%) were home and semi-independent. In 1993, Goetz et al. performed a case-control study to specifically examine the most frequent reason for nursing home placement in PD [3]. They studied 11 patients who had been placed and compared them with 22 who were still living at home. Hallucinations were significantly more common in patients placed in a nursing home; motor impairment and dementia did not differentiate between the two groups, indicating that hallucinations were an independent cause of nursing home placement. This study was succeeded by a 2 year follow-up to examine outcome; 100% of the nursing home patients had died with a mean duration of survival of 15.6 months [5]. Nursing home placement in these patients was permanent. These studies focused on hallucinations in relation to nursing home placement and likely involved the most severely affected cases. In their 10-year longitudinal study, the investigators also documented a trend for hallucinations at the previous visit to increase the odds of death [56].

Two studies have examined outcome after the availability of atypical antipsychotics. In the first, Juncos et al. examined 27 PD patients treated with either QTP or CLZ for hallucinations [230]. Over the 36-month observation period 50% were placed in nursing homes. Mortality of patients in nursing homes was 62%, compared with 52% in those still living at home. Factor et al. [6] evaluated 59 patients who were originally enrolled in a double-blind, placebo-controlled clinical trial examining CLZ therapy for PDP in PD. Long-term outcome data were collected a mean of 22 months after enrollment. Over the follow up period many switched to other agents or came off antipsychotics completely. They were not the most severe of these cases because enrollment included those who could withstand a month of placebo therapy. At baseline, 12% were living in a nursing home, 95% had hallucinations, and 60% had paranoia. On follow up, 25% were dead and nursing home placement had occurred in 42%. Of those in a nursing home, 28% had died

over the 2-year period, including two of the seven in a nursing home at baseline.

Comparison of the studies before and after the availability of atypical agents is limited but there is data to suggest that they do have a positive effect on long-term outcome. The death rate in nursing home patients is clearly diminished, suggesting improvement in survival. Factor et al. [6] demonstrated that antipsychotic therapy leads to a significant decrease in the percentage of patients with paranoia, a symptom complex associated with increased nursing home placement. Goetz et al. also demonstrated that use of antipsychotics for mild early hallucinations will prevent development of paranoid ideations or delay onset by as much as 27 months, hence likely delaying nursing home placement [231].

Factor et al. [6] also examined possible risk factors (from baseline data) that might predict poor outcome in PD patients with PDP. Older age and the presence of paranoia were the risk factors for nursing home placement. Older age, older age of onset, and lower baseline MMSE scores conferred greater risk for developing dementia; younger age of onset and longer duration of disease were the risk factors for persistent psychosis.

In combination, the data indicate that older patients tend to end up in nursing homes with paranoia or to develop dementia with poor survival; younger onset patients tend to continue to have hallucinations and remain in the community. Our goal should be to alter the outcome of PD patients with PDP and the examination of predictors for the individual outcome measures might lead to improved treatment approaches. This was the first study to determine modifiable risk factors that could lead to such an alteration, but this is clearly a fertile area for future research. Certainly, preliminary study has shown that aggressive treatment of hallucinations with appropriate atypical antipsychotic agents has a positive short- and long-term effect.

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Postsurgical Behavioral Changes

6

Jay A. Van Gerpen, John A. Lucas, and Julie A. Fields

Abstract

Parkinson's disease (PD) is the second most common neurodegenerative disease (Twelves D, Perkins KS, Counsell C. Mov Disord 18:19–31, 2003) and afflicts more than four million people worldwide (Dorsey ER, Constantinescu R, Thompson JP, et al. Neurology 68:384–386, 2007). Neurosurgical treatments for the debilitating symptoms of this movement disorder are implemented when medical therapy no longer provides sufficient benefit. Lesioning techniques initially utilized decades ago have been supplanted, for the most part, by deep brain stimulation (DBS) because of its potential reversibility should DBS prove to be unsuccessful or result in undue adverse events. Additionally, stimulation parameters can be adjusted as needed to optimize benefit (from both motor and neurobehavioral standpoints), and when bilateral procedures are necessary, DBS procedures are considered a safer alternative or adjunct to ablation. Stimulation of the subthalamic nucleus (STN) is currently the target of choice because it relieves most of the cardinal symptoms of PD and greatly reduces the amount of medication needed.

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Evaluation of postsurgical behavioral changes is complex because there is no universal methodology that allows direct comparisons among studies, which not only results in disparate findings across studies but precludes generalizability. Nevertheless, it is necessary to document change, be it beneficial or detrimental, in order to guide informed decision making regarding future treatment and/or rehabilitation. Although modern-day techniques are often deemed "relatively safe" from a cognitive and behavioral standpoint, there is mounting evidence that cognitive and psychiatric morbidities do occur quite frequently. Decline in verbal fluency is the most common finding, regardless of ablation or DBS techniques, but studies provide evidence of wide-ranging deficits in other aspects of cognition as well, albeit often not clinically significant for the patient. In contrast, psychiatric and mood disturbances observed with alarming frequency especially after STN-DBS, significantly compromise patients' daily functioning and quality of life (QOL), and may even lead to death. So the question remains as to whether we can really say with certainty that surgical treatment is "safe." Optimal cognitive and behavioral outcomes depend on appropriate selection of surgical candidates informed by detailed pre- and postoperative assessment of cognitive and psychiatric status.

Keywords
Parkinson's disease • Neurosurgery • Thalamotomy • Thalamic stimulation • Pallidotomy • Pallidal stimulation • Subthalamotomy • Subthalamic stimulation • Deep brain stimulation • Cognition • Mood • Psychiatric symptoms

Introduction

Surgical treatments of movement disorders can be traced back to the late 1800s [3–5], but they fell out of favor due to unacceptable adverse effects, limited benefit in relieving motor symptoms, and the advent of levodopa therapy in the late 1960s [6]. Despite the remarkable benefit of pharmacologic treatment, drug-resistant movement disorders and limited long-term benefits proved that levodopa was not a panacea. Ablative surgeries reemerged in the 1980s [7] with advances in the understanding of neuroanatomic structures and underlying pathophysiology, in combination with improved surgical, radiological, and stereotactic techniques, and have led to greater symptom relief and significant reductions in postoperative morbidity [8, 9]. In 1987, high-frequency stimulation made a successful foray into the treatment of movement disorders [10], and because of its relative safety and potential reversibility, it is currently the treatment of choice. Nevertheless, these improved procedures are not without risk, and with the benefits come costs. Included in those costs are adverse neurobehavioral changes, such as declines in cognition, mood, and quality of life (QOL), and the emergence of new psychiatric symptoms. Behavioral changes in patients with PD are the important determinants of QOL and survival. As such, any deleterious or protective consequences secondary to surgical therapy for PD may have a profound impact on further treatment recommendations.

Ongoing investigations attempt to identify, explain, and predict postsurgical change, but interpretation of existing studies and their clinical significance is hindered by methodological limitations and procedural differences. Patient

characteristics (e.g., age, preoperative cognitive mood, and psychiatric variables), selection criteria, small sample sizes, lack of appropriate control groups, ill-defined impairment cutoffs, and statistical methods for assessing change are all issues that contribute to discordant findings across studies and prevent generalizable conclusions. The surgical procedure itself also creates a great deal of variability: for example, size and location of surgical target, stimulation versus ablation, unilateral versus bilateral procedures, single versus staged bilateral procedure, dominant versus nondominant hemisphere surgery, mixed diagnostic samples, multiple lesion sites, different lesioning techniques, and even the experience of the neurosurgeon. "On" and "off" stimulation and medication dosing, as well as stimulation parameters, are also issues that need to be considered when interpreting findings.

This chapter presents a brief overview of the neuropathological and neurophysiological correlates of motor dysfunction in PD and the rationale for specific surgical targets. The overview is followed by a more comprehensive evaluation of the current literature examining neurobehavioral changes associated with ablation and DBS at various target locations, with focus on the thalamus, globus pallidus (GP), and subthalamic nucleus (STN). The neurobehavioral sequelae associated with transplantation and promising new surgical therapies are also addressed. Finally, implications for clinical practice are discussed, and suggestions for future scientific investigations are provided.

Neuropathology and Neurophysiology of PD

Idiopathic PD is a neurodegenerative movement disorder characterized by symptomatic onset of resting tremor, rigidity, bradykinesia, and postural instability, typically in the sixth or seventh decade of life. The basal ganglia are involved in the automatic execution of learned motor movements [11]. The motor dysfunction associated with PD results from a disproportionate loss of dopaminergic cells in the substantia nigra (SN) pars compacta that likely begins perhaps a decade prior to symptoms. The subsequent disruption of normal excitatory and inhibitory influences within the basal ganglia, initially most dramatic in the dopaminergic neurons of the ventrolateral tier of the SN that innervate the posterior putamen, causes abnormal activity in associated thalamocortical circuits. Inputs to the basal ganglia originate in various cortical regions and project to the striatum, SN, GP, STN, and thalamus via a system of five parallel segregated cortico–striato–thalamo–cortical loops [12]. Within the direct pathway, the striatum receives excitatory input from cortical regions and projects inhibitory efferents to the globus pallidus interna (GPi)/SN pars reticulata (SNpr) complex. These structures in turn have an inhibitory influence on the thalamus, which ultimately projects excitatory efferents back to the cortex [13]. There is also an indirect pathway, in which inhibitory efferents project from the striatum to the globus pallidus externa and extend to the STN, which then projects excitatory efferents back to the GPi–SNpr complex [14]. The loss of dopamine within the direct pathway leads to a decrease in the normal inhibitory activity from the putamen to the GPi, resulting in an excessive inhibition of the thalamus and net decrease in cortical excitation. DeLong [15] has proposed that this net inhibition of thalamocortical projections within the motor circuit may account for motor signs such as bradykinesia in PD. With this model in mind, several neuroanatomical targets (thalamus, GPi, and STN) and surgical techniques (ablation, stimulation, and transplantation) have been explored in an attempt to alleviate the motor symptoms associated with PD (see ref. [16] for a more comprehensive review of the scientific basis for surgical targets). Through collateral projections of the parallel segregated loops, the basal ganglia also play a role in the control of cognition, affect, and behavior/motivation [14, 17] through dorsolateral, orbitofrontal, and cingulate circuits. This chapter is devoted to describing the effects of surgical treatment for PD on those neurobehavioral aspects.

Neurobehavioral Outcomes by Surgical Target

Thalamus

Surgical Lesioning: Ventrolateral/Ventral Anterior Nuclei

Postoperative Changes in Cognition

Early studies of thalamotomy in PD demonstrated neuropsychological morbidity [18]. Evidence from those studies suggested that preexisting cognitive impairment [19] and bilateral lesioning increased the risk for cognitive decline following thalamotomy [20]. From his review of earlier studies, Burchiel [21] estimated that 39% of thalamotomy patients demonstrated declines in speech, language, and/or memory, with declines being more common among bilateral than unilateral operates (60% versus 31%).

Modern thalamotomy appears to be accompanied by less cognitive morbidity. Several recent studies have not found extensive postoperative cognitive deficits [22–24], yet others have [25]. Several earlier studies reported changes in global intellectual functioning, especially after left thalamic lesions [26–29]. Compared with pallidotomy, unilateral left thalamotomy was associated with slightly greater decline in verbal IQ [30]. Other studies reveal no significant change in IQ [31, 32]. Transient declines in attention were also noted after left and bilateral thalamotomy in earlier studies [33, 34]. One study reported adverse effects (including dysphasia) in 8% of thalamotomy patients [35], though fewer cognitive adverse effects (1.5–2% complication rate) were associated with gamma knife thalamotomy [36].

Numerous early studies examined language and speech, and reductions in verbal fluency were frequently observed following left thalamotomy [27, 37, 38]. Riklan and Levita [33] observed that declines in letter and category fluency following left and bilateral thalamotomy resolved within 5 months. Dysnomia was observed after unilateral left but not right thalamotomy [39, 40]. In a mixed sample of PD, essential tremor, and multiple sclerosis patients undergoing thalamotomy or thalamic stimulation, Schuurman et al. [41] found that semantic verbal fluency was decreased following both left-sided thalamotomy and thalamic stimulation. Most of the morbidities associated with early thalamotomy appear to have diminished with more advanced techniques and methodology. However, verbal fluency deficits after left thalamotomy continue to be observed. In a more recent study of 31 PD patients who underwent unilateral thalamotomy, Nijhawan et al. [25] noted a significant decline in phonemic verbal fluency for left-operated patients but no changes in any other cognitive domain assessed. Others, however, have not observed laterality following thalamotomy. Hugdahl and Wester [42] concluded after a review of five studies that there was no laterality effect associated with stereotactic thalamotomy saves for impairment in listening to dichotically presented speech sounds after left-sided lesioning.

Similar to the laterality of language changes reported in the literature, speech changes historically occurred more commonly after left thalamotomy, although they were more persistent. Quaglieri and Celesia [43] found that, when compared with a nonsurgical PD group, patients who were 8 years post-thalamotomy performed more poorly on measures of speech production but not language. In modern as well as earlier reports concerning thalamotomy, neurobehavioral changes and discrepant findings across studies may be related to lesion size and placement [24, 25, 32]. Yet Samra et al. [18] reported from postmortem data that lesion size was unrelated to postoperative changes on formal measures of speech and language in 27 patients who had undergone thalamotomy.

With regard to memory functioning, early studies generally found that verbal memory declined after unilateral left and bilateral thalamotomy [29–31, 44–49], but not unilateral right [29, 30, 45, 48]. Findings for visual memory were less consistent. Riklan et al. [50], Shapiro et al. [49], and Vilkki and Laitinen [38, 51] observed no changes in visual memory; others reported declines following unilateral left [52] or both unilateral left and right thalamotomy [27]. Improvement in visual memory after right thalamotomy also has been reported [45]. Most deficits appeared soon after surgery and resolved in fewer than 18 months

[32, 53], though Perret and Siegfried [27] observed memory deficits up to 18 months postoperatively. Van Buren et al. [34] also reported that of 78 unilateral operants, four patients who underwent left thalamotomy had significant memory problems postoperatively and were unable to live independently up to 7 years after surgery. More recent studies, however, have not found significant memory changes postoperatively [22–25].

Postoperative Changes in Mood, Behavior, and Quality of Life

Reports of psychiatric complications following thalamotomy are inconsistent. For example, Angelini et al. [54] observed several cases of significant depression following surgery. In contrast, several investigators have reported either reduction in depressive and obsessive symptomatology postoperatively [22, 53, 55] or no change [56]. Persistent neuropsychiatric changes, including "childlike" behavior, decreased motivation, catatonic features, and hallucinations, have been observed following bilateral thalamotomy [57]. Okun et al. [58] described a case of pseudobulbar laughter following unilateral right gamma knife thalamotomy, but symptoms were successfully managed with medication [59].

There are limited data examining QOL following thalamotomy, but the existing literature generally demonstrates postoperative improvements on generic [53, 60] as well as PD-specific [60, 61] measures of QOL. For example, in a 6-month follow-up study of PD patients after unilateral thalamotomy [61], significant postoperative improvements were noted in mobility, activities of daily living, emotional well being, stigma, tremor, and rigidity on the Parkinson's Disease Questionnaire-39 (PDQ-39) [62]. Similarly, others have shown improvements in self-ratings of stigma and bodily discomfort on the PDQ-39 [25].

Deep Brain Stimulation: Ventral Intermediate Nucleus

Postoperative Changes in Cognition

Few studies have examined the cognitive outcomes of ventral intermediate nucleus of the thalamus DBS (Vim DBS) for PD, and often the studies that are documented include mixed samples of PD and essential tremor patients or mixed thalamotomy and Vim DBS procedures. Published studies generally report no change in the overall level of cognitive functioning following Vim DBS for PD [42, 63–65]. In contrast with thalamotomy, thalamic stimulation does not seem to be associated with declines in verbal fluency or memory in PD patients, though when fluency declines are noted they are more likely to be associated with left-sided Vim DBS [41]. Improvements (possibly practice effects) on tasks of problems solving, verbal fluency, naming, and delayed recall have been observed up to 12 months postsurgery [64–66]. Material-specific cognitive changes have not yet been thoroughly examined and will need to be addressed in the future, given the evidence from thalamotomy studies that left-sided surgical intervention carries a greater risk of cognitive morbidity than right-sided surgery.

The interpretation of cognitive changes following Vim DBS surgery is even more challenging than post-ablation changes. In addition to medication and practice effects, neurocognitive changes observed on formal assessment measures may reflect a microthalamotomy effect. Preliminary evidence also suggests that stimulation parameters (polarity, amplitude, frequency, pulse width) could also play a role in cognitive outcome [67]. Indeed, studies employing intraoperative stimulation [42, 48, 68, 69] found lower frequencies (i.e., 60 Hz) more predictive of memory impairment following thalamotomy than higher frequency frequencies (i.e., 200 Hz), the latter of which are typically utilized in chronic Vim DBS. Tröster et al. [70] examined the combined effect of medications and stimulation on postoperative cognitive functioning in a single PD patient under four different conditions: with or without stimulation and on or off medications. Although a decrement in verbal fluency was observed postoperatively, this improved with stimulation regardless of medication condition, suggesting that stimulation may alleviate potential cognitive sequelae associated with the microthalamotomy effect.

Postoperative Changes in Mood, Behavior, and Quality of Life

Studies that include formal measures of mood, behavior, or QOL are also limited. The literature to date suggests that Vim DBS may lead to fewer reported symptoms of depression and anxiety within 1 week [64] and up to 12 months [71] following surgery. No detectable change in depressive symptomatology, however, was detected at 3 months following surgery in a sample of patients who demonstrated significantly improved motor functioning [72]. The relationship between Vim DBS and QOL remains unclear. Straits-Tröster et al. [72] failed to detect changes in QOL at 3 months status post Vim DBS surgery, likely due to the use of a generic QOL measure and small sample size. Indeed, Woods et al. [66] employed a disease-specific measure of QOL and documented that a similar sample of patients reported significant improvements in QOL that were maintained at 12 months post unilateral Vim DBS surgery. Nevertheless, improvements in several aspects of QOL that failed to reach significance highlight the need for investigation of PD patients' QOL following Vim DBS using disease-specific measures in larger samples.

Globus Pallidus

Surgical Lesioning

Postoperative Changes in Cognition

Very few studies before the resurgence of pallidotomy in the mid-1980s examined the effects of this surgery on cognition or behavior, but the data available suggested poor outcomes, at least in a subset of patients. Svennilson et al. [73] reported that among 78 unilateral pallidotomy cases, 4 developed postoperative dementia and 11 developed "a significant memory impairment." A decade later, Christensen et al. [74], using projective personality measures, suggested that pallidotomy was associated with possible "frontal" dysfunction. Krayenbuhl et al. [46] reported on a series of 28 patients who underwent staged pallidotomy and contralateral thalamotomy. They found that speech worsened in over half of the cases after the second operation but improved in 6. They also described "psychomotor disturbances, altered consciousness," and a "more or less marked psycho-organic syndrome" in 17 cases. In three of these cases, the speech impairment was so marked that the patients were incapable of resuming an occupation despite an otherwise nearly normal neurological state.

Recent investigations of neurobehavioral outcomes following unilateral pallidotomy have yielded inconsistent findings. Many studies show no significant cognitive morbidity [75–81]; others show either transient [22, 82–84] or more persistent changes [84–90]. The most consistently reported short-term findings after unilateral pallidotomy are declines in verbal fluency and transient declines in verbal memory, especially for left-sided operants. A few studies reporting long-term cognitive outcomes following pallidotomy again yield mixed findings. Alegret et al. [82] noted significant worsening in phonemic verbal fluency and a line orientation task 3 months after unilateral pallidotomy that returned to baseline by 4-year follow-up. Baron et al. [91] documented stable Mattis Dementia Rating Scale scores in 67% of patients 4 years after unilateral pallidotomy. In contrast, Pal et al. [92] reported a fourfold decrease in Unified Parkinson's Disease Rating Scale (UPDRS) mentation scores 3 years after unilateral pallidotomy. Hariz et al. [93] noted cognitive declines (unspecified) in 3 of 13 patients 10 years post pallidotomy. More recently, Strutt et al. [94] found mild but significant declines in oral and visuomotor information processing speed, verbal recognition memory, and Mini-Mental Status Examination (MMSE) scores 5 years after unilateral pallidotomy, regardless of side operated.

Although declines in verbal fluency are commonly reported after left pallidotomy [78, 83–88, 90, 95–108], the effect is lost when unilateral right pallidotomy patients are included in analyses [79, 81, 109]. Postoperative changes in verbal fluency are unlikely to be related to changes in medication, because the decrements are observed in both the "on" and "off " states [110]. Some evidence suggests that they may be related to changes in underlying executive mechanisms, such as ability to efficiently switch between

phonemic or semantic clusters or categories [88, 89, 108]. Others have shown that declines in verbal fluency may be related to lesion size and placement, because the effect loses statistical significance when patients with lesions extending outside the posteroventral pallidum are excluded from the analyses [84].

More wide-ranging postoperative cognitive deficits after unilateral pallidotomy are also reported [88, 96, 111]. Specifically, postoperative deficits have been observed in verbal learning [88, 96, 112], verbal and nonverbal memory [84, 86, 88, 99, 113–116], working memory and attention [88, 96, 106, 117], visuospatial construction and spatial memory [86], and aspects of executive functioning [88, 99, 102, 117–119]. Dulay et al. [114] explored cognition in depressed and nondepressed PD patients before and after unilateral pallidotomy and found that left-sided operants with depressed mood performed poorer on measures of verbal memory, both before and after surgery, compared with right-sided operants with depression as well as left- or right-sided operants without depression. In a recent meta-analysis, Alkhani and Lozano [120] estimated that transient memory deficits occur in 1.3% of cases after either unilateral or bilateral pallidotomy; persistent memory deficits are present in less than 1% of cases. These results may underestimate the prevalence of memory impairment since not all studies performed or reported results from cognitive testing. Alterman et al. [121] reported progressive dementia in 5 of 60 unilateral pallidotomy cases, only one of whom showed evidence of possible dementia prior to surgery. Esselink et al. [122] reported that one patient in their sample of 14 developed dementia after surgery. Other studies have reported mild *improvements* in memory [85, 86, 88, 102] or executive functioning [84] following right pallidotomy.

Bilateral pallidotomy has been associated with a high incidence of severe complications, but findings are inconsistent and based on small samples or mixed procedures. Scott et al. [87] found significant declines in both category and phonemic verbal fluency among eight bilaterally operated patients, compared with declines in only category fluency, not phonemic fluency, in 12 unilaterally operated patients. Svennilson et al. [73] reported that all three of their bilaterally operated patients had significant memory deficits and dementia after surgery. Ghika et al. [123] noted either profound overall changes (likely reflecting dementia) or marked executive or memory impairments in two of four patients following bilateral pallidotomy. Trépanier et al. [104] reported global cognitive decline after the second operation in two of three staged bilateral pallidotomy patients who had "atypical" cognitive profiles before surgery. Another study found that among 8 of 12 patients with clinical follow-up after staged bilateral surgery, four had poorer speech and one had worse memory [100]. York et al. [124] reported that 9 of 15 patients who underwent staged bilateral pallidotomy and returned for long-term cognitive follow-up displayed declines in cognition 2 years after surgery that were not initially evident 3 months postsurgery. Whelan et al. [126] found that three of six bilateral pallidotomy patients declined on a visual naming task and four of six demonstrated performance decline on a category fluency task. In contrast, one of six nonsurgical PD controls showed improvement in visual naming and three demonstrated improvement on the fluency task. In addition to declines in fluency, naming, and memory, attention-executive [127], and planning [128] declines following bilateral surgical lesions have also been reported. In contrast, others have found no change, or even improvement, after bilateral pallidotomy. Iacono et al. [125], for example, reported that verbal memory scores improved in ten bilateral pallidotomy patients.

Certain factors may predispose patients to cognitive decline following pallidotomy. Older patients, for example, appear to be at greater risk of verbal fluency decline [85, 101], Some studies report that lesion location within the pallidum is an important determinant of postoperative cognitive deficits [112, 130, 131]; others have failed to find a relationship between lesion location and cognitive outcome on select measures [85, 132]. Obwegeser et al. [133] reported that left-sided lesions caused more impairment in semantic fluency than right-sided, and that more impairment occurred following frontomedial lesions.

Severity of motor impairment preoperatively and MMSE scores do not appear to be reliable predictors of cognitive decline [84].

Postoperative Changes in Mood, Behavior, and Quality of Life

Numerous studies have explored mood and psychiatric symptoms following unilateral pallidotomy. Several studies employing formal measures of mood have reported either improvements in depressive symptomatology [66, 72, 78, 84, 86, 100, 103, 134] or no significant change in mood state [75, 79, 95, 96, 101, 104, 135]. Olzak et al. [119] found significant improvements in depression scores as early as 2–3 days after right or left pallidotomy, and Rettig et al. [84] reported improvement in depression scores 3 and 12 months after unilateral pallidotomy. Strutt et al. noted no change in depression scores 5 years after unilateral pallidotomy in 18 patients [94].

Declines in mood have also been observed following unilateral pallidotomy. Bezerra et al. [136] reported persistent depression in 5 of 41 patients after unilateral pallidotomy. In a 4-year follow-up study by Esselink et al. [122], one patient committed suicide 3 weeks after surgery, but no change in depression scores was reported in the 14 patients who underwent unilateral pallidotomy.

Early uncontrolled studies indicated that bilateral pallidotomy increased the risk of postoperative depression [75, 136], though this was not borne out in a subsequent randomized, controlled study comparing postsurgical and waitlist control groups [137]. In fact, Vitek et al. [137] found that the only factor that was associated with increased risk of depression was a past history of depression regardless of side of surgical procedure.

Pallidal lesioning results in other psychiatric sequelae as well; this is especially notable following bilateral operations. Merello et al. [138] discontinued their bilateral-lesioning protocol in an initial study of 12 patients randomized either to bilateral pallidotomy or unilateral pallidotomy plus contralateral GPi stimulation because the first three patients undergoing bilateral pallidotomy experienced severe symptoms of apathy, loss of initiative, motivation, and motor drive that were still persistent at the 3-month postoperative evaluation. Ghika et al. [123] also reported profound personality/behavioral changes and depression in two of four bilateral pallidotomy patients who demonstrated postoperative cognitive dysfunction, as well as another patient who developed obsessive–compulsive features. Psychological symptoms are less frequently reported after unilateral surgery. Trépanier et al. [88, 104] reported that up to 41% of patients' caregivers observed frontal lobe behavioral changes, including lack of insight, lability, impulsivity, poor social judgment, and environmental dependency, after their family member underwent unilateral pallidotomy. In contrast, following unilateral pallidotomy, Junqué et al. [83] reported improvement in scores on a measure of obsessive–compulsive behavior. In a study that employed an objective personality measure (i.e., the Minnesota Multiphasic Personality Inventory (MMPI)), patients reported fewer somatic symptoms and better energy after unilateral pallidotomy [22]; however, it is difficult to determine whether this reflects a surgical effect versus a placebo effect, the latter of which may also have a physiological basis.

Martinez-Martin [139] recently reviewed 61 clinical trials relative to QOL and surgical treatment of PD (including thalamic, subthalamic, and pallidal lesions and stimulation as well as transplantation), and concluded that unilateral pallidotomy (similar to bilateral STN-DBS) was efficacious in improving health-related QOL in PD. Studies utilizing formal measures of QOL generally indicate widespread improvements after pallidotomy [72, 75, 87, 96, 97, 134, 140]. De Bie et al. [97] found that all measures of physical and psychosocial QOL of a disease-specific questionnaire improved after unilateral pallidotomy, with positive effects persisting 1 year after surgery. The studies by D'Antonio et al. [140] and by Martinez-Martin et al. [134] both suggest that improvement in QOL is related to improvement in motor function in the "off " state, and Tröster et al. [141] found that physical aspects of QOL are related to residual motor disability after pallidotomy. Changes in QOL also relate to

changes in anxiety [134], depressive symptoms [72], coping method, and social stressors and resources [142]. Older individuals tend to show less QOL improvement after pallidotomy [141].

Deep Brain Pallidal Stimulation

Postoperative Changes in Cognition

Pallidal DBS is associated with comparatively little risk of cognitive decline overall. In fact, some neuropsychological investigations of pallidal DBS report no change [104, 143, 144]. More specifically, studies of patients undergoing unilateral pallidal DBS have found no significant changes in overall level of cognitive functioning 3 months after surgery [144–146]. Others have observed declines in visuoconstructional ability and/or semantic verbal fluency [146, 147], though these changes were rarely of clinical significance. Looking at individual data, it appears that patients who experience some level of cognitive decrement tend to be older and taking higher medication dosages prior to surgery than patients showing no change or improvement [144].

Cognitive outcomes of bilateral GPi DBS have been addressed in only a few studies that suggest the procedure is relatively safe from a cognitive standpoint. Ardouin et al. [148], found no significant change in average test scores for up to 6 months after bilateral GPi DBS in 13 cases. Pillon et al. [149] noted no cognitive morbidity in a similar group of patients at 12 months postoperatively. Ghika et al. [150] reported no significant change in neuropsychological test scores 3 months after contemporaneous bilateral GPi DBS electrode implantation in six patients. Earlier findings demonstrated that staged bilateral GPi DBS electrode implantation did not appear to pose any significant risk of cognitive decline [143]. A recent study of 42 patients randomly assigned to staged bilateral GPi or STN-DBS, however, revealed declines in verbal fluency and working memory 6 months after unilateral and 15 months after bilateral procedures regardless of surgical target [151]. The verbal fluency declines were significant only after left-sided surgery and were not associated with age. A single case study with MRI-confirmed electrode location reported significant executive dysfunction after bilateral GPi DBS that was partially reversed when the stimulators were turned off [152].

Whether unilateral GPi DBS is cognitively safer than pallidotomy has not been adequately addressed, but studies by Merello et al. [145] and Fields et al. [153] suggest that the safety of these procedures, from a cognitive perspective, is comparable. Gálvez-Jiménez et al. [154] noted that no overt cognitive changes were observed among four patients undergoing GPi DBS after contralateral pallidotomy.

Postoperative Changes in Mood, Behavior, and Quality of Life

Unilateral GPi DBS yields small but significant improvements in self-reported anxiety and "vigor" [72, 143] but does not appear to significantly impact depressive symptoms [72, 149, 150, 155]. Improvement in both depression and anxiety scores has been documented, however, with bilateral GPi stimulation [148, 156, 157].

Relatively little data have been published regarding the occurrence of neurobehavioral changes following GPi DBS. Miyawaki et al. [158] described a single patient who underwent bilateral-staged GPi DBS surgery and developed manic episodes after his second (right GPi) surgery. The patient was eventually able to benefit from stimulation without psychiatric sequelae after a reduction in his levodopa dosage, suggesting that interactions between stimulation and medication may play an important role in neurobehavioral morbidity in GPi DBS. Hypersexuality [159] has also been reported following GPi DBS.

Studies using formal assessment measures have documented significant postoperative improvements on generic measures of QOL. Vingerhoets et al. [160] reported significant improvements in physical, psychosocial, and overall functioning at 3 months post unilateral GPi DBS, with particular gains in ambulation, body care, movement, communication, sleep, rest, and eating. Grace et al. [161] also observed improvements in physical and overall functioning in a smaller sample of nine unilateral GPi DBS patients. Similarly, nine unilateral GPi DBS patients who completed a disease-specific QOL

measure 3 months after surgery noted improved mobility and ability to perform activities of daily living as well as decreased stigma [72]. Rodrigues et al. [162] reported that in a sample of 11 patients (four unilateral, seven bilateral) 8 months after surgery, there were significant improvements in mobility, activities of daily living, bodily discomfort, emotional wellbeing, communication, and cognition subscales on a PD QOL questionnaire and that these changes were not the effect of motor improvement.

Subthalamic Nucleus

Surgical Lesioning

Postoperative Changes in Cognition

Until recently, subthalamotomy (involving the subthalamic nucleus proper) was avoided, owing to fear of inducing hemiballism. Improved ablation techniques and the expense, time for programming and reprogramming, and maintenance of stimulating devices, however, have kept subthalamotomy a viable alternate. Some studies have found no evidence of significant cognitive decline resulting from subthalamotomy [163–165], although one of these [165] noted modest, nonsignificant deterioration in certain attention, memory, verbal fluency, and visuospatial abilities. McCarter et al. [166] studied 12 subthalamotomy patients before and 6 months following surgery (two left, three right, three bilateral, four mixed right subthalamotomy plus left STN-DBS) and found postoperative declines on measures of attention, facial recognition, word list recall, and executive function in patients undergoing unilateral left side surgery. None of the patients with unilateral right-sided surgery demonstrated reliable decrements on any cognitive measure. Verbal fluency decline was noted in one of the patients undergoing bilateral subthalamotomy; postoperative declines in attention and learning efficiency were noted in one patient who underwent right ablation/left DBS surgery. A study of 17 surgical patients (seven left, six right, four mixed left subthalamotomy plus right STN-DBS) yielded similar findings, with diminished attention and memory following unilateral left surgery and in patients with mixed left subthalamotomy and right DBS [167]. Unilateral right subthalamotomy patients had less likelihood of deterioration postoperatively. Together, these studies suggest that modern subthalamotomy probably does not lead to global deterioration in cognition, but that mild deficits in select domains may occur following left side ablation.

Studies by Alvarez et al. [163, 168] describe postoperative stability or improvement in cognitive functioning rather than decline [163, 168]. By 24 months postsurgery, these investigators found significant improvements on measures of initiation/perseveration, attention, executive functioning, and semantic fluency, compared with presurgical abilities.

Postoperative Changes in Mood, Behavior, and Quality of Life

Early subthalamotomy never gained widespread popularity, in part due to adverse neurobehavioral outcomes. Spiegel et al. reported a 30% incidence of "psycho-organic syndrome among 33 patients who underwent subthalamic ablation. In a sample of 58 patients, all six bilateral operates developed a lasting (several years' duration) loss of initiative and spontaneity and diminished interest in the environment [169]. One patient, after a second operation, developed a "jovial, carefree attitude." Over one-third of the patients manifested increased desire for food, and some became obese. Unlike Speigel et al., who performed subthalamic ablations by lesioning Forel's Field H and interrupting pallidofugal fibers (known as campotomy), Mundinger et al. [170] placed the bulk of the subthalamotomy lesion in the zona incerta. Reporting on outcomes in 456 interventions for PD, they noted that 68% of individuals developed "speech symptoms" postoperatively but they did not report any specific neurobehavioral morbidity.

Outcomes from modern-day subthalamotomy are more promising from a mood and psychiatric perspective. For example, depression scores improved 24 months following bilateral subthalamotomy [163, 168]. Significant improvements in apathy scores, as well as small but nonsignificant improvements in anxiety and agitation, also were observed 1 and 2 years postoperatively in ten

bilateral subthalamotomy patients [168]. No significant postoperative changes in depression, apathy, mania, or irritability scores were observed after 1 year in a mixed sample of 15 patients randomized to bilateral subthalamotomy, bilateral STN-DBS, or unilateral subthalamotomy plus contralateral STN-DBS [165].

Negative outcomes are less frequent. One study reports that of 89 patients, one committed suicide 18 months after subthalamotomy [163]. In another study, transient-increased hyperactive behaviors (e.g., disinhibition, hypomania, excessive cheerfulness, talkativeness, etc.) were present acutely in five patients but gradually resolved by 1-year follow-up [168].

Deep Brain Stimulation

Postoperative Changes in Cognition

STN-DBS has gained wide-spread popularity because of its anti-akinetic effect, reduced need for medication, and sustainable improvements in "off" medication conditions [171, 172]. Its effect on neuropsychological and neurobehavioral functioning, however, remains highly debated [173, 174]. Some investigations show no significant cognitive morbidity [148, 149, 172, 175–179]; others show deleterious effects [80, 180]. STN-DBS is generally performed bilaterally. In a meta-analysis of 28 studies carried out between 1990 and 2006, Parsons et al. [181] found small but significant declines in executive function, verbal learning and memory, and phonemic and semantic verbal fluency; they concluded that cognitive deterioration was relatively rare if patients were carefully selected. Others estimate that approximately 40% of bilateral STN-DBS patients experience postsurgical cognitive problems [182]. Older age and moderate levels of baseline cognitive impairment have been shown in some studies to increase the risk of cognitive impairment and neurobehavioral deficits following surgery [104, 175, 183–185]. Longer disease duration also has been associated with more frequent adverse cognitive and psychiatric events [186], which are more common following STN than GPi stimulation.

Although the preponderance of documented change following STN-DBS occurs in both letter [148, 173, 175, 180, 181, 183, 187–193] and semantic [77, 149, 175, 181, 183, 187, 190, 191, 194–196] verbal fluency, studies over the past decade have also shown declines in other cognitive domains, including verbal memory [104, 175, 177, 178, 183, 184, 188, 190], spatial memory [104, 175, 183], visual attention [190, 191], selective attention [190], processing speed [183], executive functioning [104, 191], response inhibition [180, 197, 198], and conditional associative learning [199]. Others have reported stability of general cognitive status [191, 195, 200] or improvements in mental flexibility [175, 198, 199], working memory [199], visuomotor sequencing [148, 149, 188, 199], conceptual reasoning [188, 199], and overall cognitive functioning [188].

Controlled studies have reported greater declines on measures of verbal fluency, color naming, selective attention, verbal memory, and response inhibition following bilateral STN-DBS, compared with nonsurgical PD controls [180, 190, 191]. Zahodne et al. [201] observed declines in verbal fluency at 12-month follow-up in 50% of unilateral STN or GPi DBS patients versus only 11% of nonsurgical PD controls. DBS patients had 8.3 times greater odds of declining on at least one verbal fluency measure (i.e., letter or semantic) than controls. An extension of this study [202] showed that 16 months after surgery a significantly greater proportion of DBS patients demonstrated decline in word list recall and processing speed. In contrast, DBS patients demonstrated improvement in visuospatial functioning.

A multicenter randomized, controlled trial of bilateral STN and GPi DBS ($n = 121$) versus best medical therapy ($n = 134$) found that DBS patients declined on measures of working memory, processing speed, phonemic fluency, and visual delayed recall; the best medical therapy group showed slight improvements on these measures [203]. However, DBS was found to be more effective in improving QOL in patients with advanced PD 6 months after surgery.

Attempts have been made to elucidate whether neurobehavioral declines are due to surgery (i.e., "microsubthalamotomy effect") or stimulation by examining cognition and mood in on- and

off-stimulation conditions. Morrison et al. [177] examined the cognitive effects in 17 STN-DBS patients with PD in both on- and off-stimulation conditions 3 months following implantation, compared with 11 matched nonsurgical PD controls. The STN-DBS group showed a mild decline on indices of attention and language compared with controls; there were no differences between "on" and "off" conditions in the DBS group, except for one individual. This one patient showed a dramatic decline 12 weeks after implantation while on stimulation, and he was only able to complete 5 of the 16 tests. He was older, was one of only two patients who had undergone staged bilateral implantation, and was one of five patients who were tested following medication withdrawal. Okun et al. [192] compared 52 subjects randomized to either STN or GPi DBS, and at 7 months postsurgery found no differences between the groups on measures of cognition at optimal stimulation settings. The STN group, however, exhibited a larger decline in phonemic fluency than GPi when compared to baseline, with an even larger deterioration observed when stimulators were turned off. Similarly, Pillon et al. [149] compared 48 STN-DBS patients with 8 GPi DBS patients after surgery in on- and off-stimulation conditions (most patients without levodopa for 12 h) and found no overall differences between STN and GPi stimulation, but the STN group showed a greater postoperative decline in category fluency that persisted 12 months after surgery, both with and without stimulation. Others have found reduced working memory and response inhibition under challenging conditions during stimulation [204]. One study, however, found that stimulation improved patients' ability to shift cognitive sets [205].

DBS settings (i.e., pulse width, amplitude, and frequency) may play a role in cognitive outcomes and therefore may explain some of the disparate findings across studies. Schoenberg et al. [206] evaluated 20 patients 5 months following STN-DBS and found declines in verbal fluency and improvements in visuoconstructional skills that were significantly correlated with amplitude and pulse width. Another study seeking to determine whether cognitive outcomes are related to stimulation frequency examined verbal fluency performance in high frequency, low frequency, and no stimulation conditions [207] and found that verbal fluency was facilitated at low frequencies whereas high frequencies disrupted word generation. A meta-analysis of 28 DBS studies, however, failed to find a relationship between postoperative decline in verbal fluency and differences in stimulation parameters.

Postoperative Changes in Mood, Behavior, and Quality of Life

With research growing exponentially in the area of STN-DBS, it is becoming evident that psychiatric complications, especially in patients with preexisting morbidities, are more frequent than originally thought. Although estimates vary, psychiatric symptoms are believed to be more frequent in STN than in GPi stimulation [156, 210, 228]. Mood changes following STN-DBS are frequently reported, but it remains unclear to what extent these are due to the effects of stimulation, postsurgical reduction of dopaminergic medication, history of depression, physical symptoms, psychosocial factors, or an interaction among any or all of these variables. Estimates of postsurgical depression with STN stimulation vary from 1.5 to 25% [156, 172, 185, 208–212]. Okun et al. [192] reported that stimulation of either STN or GPi targets resulted in less happy and less energetic behavior. Benabid et al. [213] observed significant depression in 16 of 137 STN-DBS patients (approximately 12%); Tir et al. [214] observed depression in 18% of their 91 patients 12 months after STN-DBS. In the latter study, 72% of those with postsurgical depression also had a prior history of depression. There were two suicide attempts among their depressed cohort, with one suicide completion. Volkmann et al. [156] found that depression occurred more frequently in patients receiving STN than GPi DBS, and Gervais-Bernard et al. [215] observed that depression persisted up to 5 years postsurgery in approximately 40% of their sample of 23 STN-DBS patients.

Of growing concern are reports of an increased suicide rate associated with STN-DBS. Baseline PD suicide rates range from equal to ten times

lower than the general population [216, 217] despite chronic illness, psychiatric disorders, and psychosocial stress. Suicide attempts and/or completions, however, have been reported in from 0.5 to 4% of STN-DBS cases [172, 185, 218–220]. Burkhard et al. [220] observed a suicide rate of 4.3% in a series of 140 STN-DBS patients; all but one of the patients who committed suicide had a preoperative history of major depression as well as prior suicide attempts or suicidal ideation. A retrospective study of 200 STN-DBS patients conducted by Soulas et al. [221] noted that two patients (1%) committed suicide and four (2%) attempted suicide. There were no differences between the suicidal and non-suicidal patients with regard to age, disease duration, preoperative depression, or cognitive status. Suicidal behavior, however, was associated with postoperative depression and/or impulsivity. In a multicenter study (55 centers) on suicide outcomes following STN-DBS, the completed suicide rate was 0.45% and the attempted suicide rate was 0.90% [222]. Identified factors included postoperative depression, being single, a history of impulse control disorders, and compulsive medication use. Younger age, younger age at PD onset, and preoperative suicide attempts were also weakly associated, but gender and preoperative depression were not.

Other studies have reported improvement in depression [148, 149, 156, 183, 184, 188, 195] and anxiety [191] following STN-DBS. One STN group of 36 patients showed fewer depressive symptoms 6 months after surgery; however, they also showed less positive affect and more emotional lability [190]. Saint-Cyr et al. [183] observed no significant mood changes in their total sample of 11 STN-DBS patients; however, significant improvement in depression was noted in the subgroup of six patients who were over the age of 69. Witt et al. [191] found that STN-DBS had a slight positive effect on depression and a significant positive effect on anxiety, compared with patients receiving best medical treatment.

Still others have shown no effect of STN-DBS on mood symptoms [178]. Montel et al. [223] observed no significant change in depression or anxiety 12 months following surgery in 40 STN-DBS patients, compared with 40 dopamine therapy patients. Morrison et al. [177] found no effects on depression scores in 17 STN-DBS patients 3 months after implantation, and York et al. [180] observed no changes in depression, anxiety, or psychological distress scores in 23 patients 6 months after surgery.

Apathy has frequently been observed following STN-DBS, with reports ranging from 8 to 51% of postsurgical cases [200, 224, 225]. It is common for apathy to occur within the first 3 months following surgery. Apathy persists in up to 25% of patients at 3-year follow-up [195] and up to 12% of cases at 5-year follow-up [172]. Interestingly, in the latter study, 80% of the patients with postoperative apathy also developed incident dementia. Esselink et al. [122] reported that of the 18 (out of 20) patients who returned for 4-year follow-up, three experienced persistent emotional lability. Three patients in this study had also undergone previous pallidotomy and, following STN-DBS, all three experienced adverse events, including mild depressive symptoms, dementia, sexual disinhibition, or excessive eating of sweets. The authors note, however, that similar neuropsychiatric problems are observed in medication-only populations [226]. Since STN stimulation generally results in a reduction in dopaminergic medication [227], some have suggested that the depression and apathy observed following STN-DBS may actually be the result of dopamine withdrawal [156].

With regard to other neuropsychiatric sequelae, transient confusion immediately following STN-DBS surgery has been reported in 1–36% of patients [156, 172, 185, 208, 209, 229–234], acute mania/hypomania in 4–15% of patients [172, 188, 209, 235], and emotional reactivity in 75% of patients [185]. Hypersexuality [236], impulsivity [237], pathologic gambling [238, 239], and deficits in facial emotion recognition (especially fear and sadness) [240, 241] and cases of pathological laughter and euphoria [213, 242–244] have also been noted. Saint-Cyr et al. [183] reported increased "frontal" behavior changes on a caregiver-rated personality scale in two of the six patients older than 69 years. Witt et al. [191], however, found that severe psychiatric adverse

events following STN-DBS were only slightly higher than in patients receiving best medical treatment.

Improvements in QOL ratings are generally reported after STN-DBS [190, 245–248], but not always [177]. Capus et al. reported up to 50% improvement in disease-specific QOL in a sample of seven patients at 14.5 months following surgery [249]. A large randomized, controlled multicenter study of 156 patients with advanced PD that compared 78 STN-DBS patients on medication to 78 medication-only PD controls 6 months after surgery reported improvement in mobility, activities of daily living, emotional well being, stigma, and bodily discomfort in the neurostimulation group [226]. In another randomized, controlled trial, QOL was improved after 18 months in the surgical versus the nonsurgical PD control group [250]. Although several studies have shown that improvements in QOL are maintained even longer, i.e., up to 3–5 years postsurgery [172, 251, 252], Volkmann et al. [251] reported that many of the initial STN-DBS benefits in QOL were lost after 3 years.

Ferrara et al. [253] found improvements related to movement and general health (e.g., energy level/enjoyment of life, controllability/fluidity of movement) but no change in QOL items related to general life issues (e.g., occupational function, interpersonal relationships, leisure activities). A study by Derost et al. [254] suggests that changes in QOL following STN-DBS may be age dependent, with younger (age < 65) but not older (age 65+) patients reporting improvement in QOL despite equal improvement in motor function.

Transplantation

Adrenal Medullary Autographs

Intrastriatal implantation of autologous adrenal medullary tissue is no longer considered an option because of lack of benefit [255], and there is evidence that adrenal medullary transplants do not survive in the long term [256]. Although the few studies formally evaluating cognition did not report any significant morbidity [257–260], significant psychiatric morbidity was reported [261, 262].

Fetal Mesencephalic Transplantation

Intrastriatal grafting of fetal mesencephalic tissue purports to show lasting motor benefit in some patients, with clinical benefit predicted by 18-fluorodopa uptake (an index of graft viability) [263, 264]. Differences in tissue preparation, site (unilateral versus bilateral; caudate and/or putamen), and number of implants, however, make these data difficult to interpret. Later prospective, double-blinded, placebo-controlled studies of cell transplantation found either no net benefit compared with placebo [265], or net benefit in only a subgroup of younger patients [266, 267], with some of the patients in each of these groups developing severe dyskinesias that could not be ameliorated by reducing medication. Observed neurobehavioral changes may reflect disease progression, medication changes, associated surgical lesion, or the sprouting of implanted tissue (see ref. [268]). Recent studies have also shown that some dopamine neurons present in transplants that have survived longer than 10 years show the presence of Lewy bodies [269–272]. Although there is no clear evidence that Lewy bodies result in functional impairment of grafted cells, this finding does indicate that grafted cells undergo a disease process similar to the endogenous nigral dopamine neurons. From a cognitive standpoint, transient improvements (up to 2 years) in memory have been reported [273] but cognitive (and speech) outcomes vary across individuals [274–276]. Although most individuals have not shown significant cognitive changes after surgery [277], some cognitive decline may occur in patients with preoperative deficits [275, 276].

Psychiatric complications, such as depression, paranoia, and hallucinations, are more common with open [278, 279] versus stereotactic procedures [280]. Unfortunately, a recent well-controlled study (using a “placebo” control group) did not report neuropsychological or QOL outcomes, although such data were gathered [266].

Hagell et al. [281] investigated QOL using a generic rating scale and reported significant improvements in QOL after bilateral grafting, particularly in terms of patients' satisfaction with mobility, energy, and emotional well being.

Goetz et al. [282] conducted an evidence-based medical review on PD treatments, and in the 27 new studies that qualified for efficacy review from 2001 to 2004, in the category for randomized clinical trials, human fetal nigral transplantation (under procedures utilized to that date) were moved from "insufficient data" to "non-efficacious" for the treatment of PD.

New Frontiers

New targets and methods for treatment of PD are being explored [283] but most are still in their infancy, including embryonic stem cell replacement [284, 285], induced pluripotent stem cell-derived dopamine neurons [286, 287], induction of adult human bone marrow mesenchymal stromal cells [288], autotransplantation of human carotid body cell aggregates [289–291], and intracerebral administration of trophic factors for dopaminergic neurons [292, 293].

Clinical trials of cortical stimulation in humans are currently underway, but preliminary results have been disappointing in alleviating the motor symptoms of PD [294, 295]. Some improvement in motor symptoms has been noted, but it appears to be less efficacious than bilateral STN [296], though it may be an option for patients not eligible for DBS. Munno et al. [295] evaluated cognitive and emotional state in three PD patients 1 year after cortical stimulation and found no changes in cognitive functioning or depressive symptoms, compared with 2 days before surgery. Improved QOL was reported in two of the three patients.

Preliminary results from pedunculopontine nucleus (PPN) DBS trials show improvement in gait and postural instability but do not provide benefit to the extent of STN-DBS [297, 298]. Results from larger trials are not yet available, and no cognitive or emotional factors have yet been examined relative to the PPN alone. However, stimulation of multiple targets simultaneously may provide added benefit. A recent study examined nonmotor functioning in six patients who underwent both bilateral PPN DBS and STN-DBS [299]. Neuropsychological tests were performed in the STN-on/PPN-off versus PPN-on/STN-off conditions. Delayed recall, cognitive flexibility, and phonemic verbal fluency were significantly better in the PPN-on/STN-off condition. Stephani et al. [297] found significant incremental motor benefit when both STN and PPN were stimulated, compared with stimulation of either target alone. Although no formal cognitive or mood symptoms were evaluated, the combination of target stimulation resulted in substantial improvement in ability to perform activities of daily living.

The centromedian–parafascicularis (CM/Pf) complex represents another potential DBS target and has shown some benefit in ameliorating tremor [300, 301]. In a small sample of patients, Stefani et al. [301] found that in conjunction with STN ($n=2$) or GPi ($n=6$) stimulation, stimulation of the CM/Pf provided a reduction in tremor without associated cognitive or psychiatric impairments.

Conclusions and Recommendations

Research on the neurobehavioral sequelae of surgical treatments for PD has grown exponentially over the last decade. Unfortunately, the literature reveals a plethora of inconsistencies across study findings that impede generalization of results. These inconsistencies most likely reflect differences in methodologies and patient characteristics across studies. Most studies involve small samples with no control groups, although more recent meta-analyses and a handful of multicenter, randomized controlled trials have allowed increased power to detect change and have involved more sophisticated statistical methods. The most consistent finding, and one that has not changed with the advancement of technology and experience, is that when cognitive declines occur, they most typically involve lexical and semantic verbal fluency regardless of surgical technique or

target location. Declines in verbal and spatial memory, attention, processing speed, executive functioning, and response inhibition have also been observed, as well as improvements in mental flexibility, working memory, visuomotor sequencing, and conceptual reasoning. In general, however, cognitive declines appear to be less frequent for Vim and GPi targets than for STN-DBS.

Cognitive and psychiatric adverse events occur in approximately 10% of DBS patients [303]. Although relatively rare, the most striking psychiatric complications appear to follow STN-DBS. These complications may be diminished, however, by careful selection of surgical candidates [304]. Evidence of preoperative depression, hypomania, "frontal lobe behaviors," and suicide ideation/attempts appear to entail greater risk of neurobehavioral morbidity following STN-DBS. Although mild psychiatric disturbances should not automatically exclude patients from surgery, comprehensive screening and careful follow-up of such patients should be considered. Gathering a detailed psychiatric history is recommended, as some premorbid psychiatric symptoms may be masked or confounded by the patient's parkinsonism and only emerge once STN stimulation is applied [305].

Table 6.1 summarizes potential factors that may influence the risk of cognitive and behavioral morbidity following surgical treatments for PD. In general, more optimal surgical outcomes are typically related to accuracy of PD diagnosis, severity of illness, consistent levodopa response, absence of cognitive impairment, absence of significant psychiatric symptoms, and well-managed patient expectations [306, 307, 311–313]. Older age has been associated with poorer neurobehavioral outcomes [104, 184, 185, 309, 310] leading some to suggest surgical exclusion of patients over age 70 [308]. Age effects likely reflect age-related comorbidities such as increased risk of cognitive dysfunction and dementia with increased age.

Evidence of prominent executive dysfunction or preoperative diagnosis of Mild Cognitive Impairment (MCI) carry a greater risk of postoperative dementia [314, 315]; however, the degree to which DBS surgery itself contributes to time to conversion to dementia remains unknown. Since patients with preoperative dementia are excluded from surgical studies, there are no data to indicate how surgical intervention affects disease course. In clinical practice, however, it has been suggested that cases with preexisting dementia should be evaluated on an individual basis, with pros and cons weighed in terms of caregiving and QOL and all potential risks outlined for the patient and caregivers so they can make an informed decision regarding surgery [308].

As surgical interventions for movement disorders continue to become more refined and more widely available, the need for well designed and controlled studies of cognitive and neurobehavioral outcomes continues to grow. In recent years, a small number of well-powered multicenter and/or randomized, controlled studies have appeared in the literature and have helped clarify some of the prior discrepant findings. The ability to develop reliable guidelines for clinical decision

Table 6.1 Factors potentially influencing the risk of cognitive and behavioral morbidity following surgical treatment of Parkinson's disease

Increased risk
• Age more than 69 years at time of surgery
• Bilateral surgery
• Unilateral surgery involving the language-dominant hemisphere
• Anteromedial lesions of the GPi
• Psychiatric or behavioral disturbance (e.g., untreated depression, mania/hypomania, bipolar disorder, suicidal ideation or attempts)
• Dementia
• Prominent "frontal" behavioral symptoms (e.g., impulsivity, disinhibition, hypersexuality)
• Excessive and pathologic use of dopaminergic medications
No increased risk
• Type of surgical intervention (ablative versus stimulation)
• Surgical target (Vim, STN, GPi)
• Lesion volume (if confined to intended target location)
Uncertain risk (insufficient data)
• Stimulation parameters (amplitude, frequency, pulse width)
• Disease duration
• Medication effects

making will depend on the accumulation of similar studies that identify and improve our understanding of variables that predict or moderate cognitive, psychiatric, behavioral, and quality of life outcomes following surgery.

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Apathy in Parkinson's Disease

7

Oscar Bernal-Pacheco and Hubert H. Fernandez

Abstract

Apathy is a common word used to describe an inner lack of motivation that is distinct from a depressive condition, cognitive impairment, fatigue, or emotional sorrow. Apathy can be an isolated syndrome or a prominent feature found in depression and post-injury events such as stroke or trauma, infectious or metabolic comorbidities in neurodegenerative conditions (e.g., dementias, movement disorders), schizophrenia, and other systemic illness. Because of these, despite its estimated high prevalence, misdiagnosis of apathy as a syndrome is frequent and probably underestimated. Because apathetic patients, by definition, are non-complainers, Parkinson's disease (PD) patients will often first acknowledge the presence of motor impairment, and even other behavioral symptoms, cognitive compromise, and worsening of quality of life before complaining of lack of motivation or loss of interest. The differentiation between apathy, fatigue, and depression also can become a challenge due to the overlap of symptoms

Keywords

Apathy • Parkinson's disease • Loss of productivity • Mini-Mental State Examination • Mild cognitive impairment

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Introduction

Apathy is a common word used to describe an inner lack of motivation that is distinct from a depressive condition, cognitive impairment, fatigue, or emotional sorrow. Apathy can be an isolated syndrome or a prominent feature found in depression and post-injury events such as stroke or trauma, infectious or metabolic comorbidities in neurodegenerative conditions (e.g., dementias, movement disorders), schizophrenia, and other systemic illness. Because of these, despite its estimated high prevalence, misdiagnosis of apathy as a syndrome is frequent and probably underestimated. Because apathetic patients, by definition, are non-complainers, Parkinson's disease (PD) patients will often first acknowledge the presence of motor impairment, and even other behavioral symptoms, cognitive compromise, and worsening of quality of life before complaining of lack of motivation or loss of interest. The differentiation between apathy, fatigue, and depression also can become a challenge due to the overlap of symptoms.

Definition

Although apathy can be a core feature of important disorders like dementia and depression, it must also be understood as an independent, neuropsychiatric behavioral disorder [1]. Apathy originally was discussed in multiple papers as a symptom, but after a redefinition made by Marin et al., it also has been recognized as a distinct syndrome with its own diagnostic criteria (Table 7.1) [2–4]. The etymology of apathy comes from *a* (lack of) and *pathos* (passion). Over the centuries, this concept has remained with minimal modifications, usually inherent to psychiatric conditions or with religious/philosophic connotation. However, the term "passion" has been modified to "motivation." Motivation is defined both as an inner desire, interest, and energy dedicated to a responsibility, and to put forth persistent effort in attaining a goal. Thus, apathy is currently defined as absence of motivation, drop of interest, loss of concern, lack of effort, diminished initiative, or indifference; it is associated with low content of thinking and flat affect, but without cognitive influence, lack of intellectual development, attention drop, diminished level of consciousness, or emotional impairment. Consequently, apathy can lead to decrease in effort, perseverance, and productivity.

Table 7.1 Diagnostic criteria for apathy (adapted from [2])

(A)	Lack of motivation relative to the patient's previous level of functioning or the standards of his or her age and culture
(B)	Presence, while with lack of motivation, of at least 1 symptom belonging to each of the following three domains:
	Diminished goal-directed behavior
	1. Lack of effort or energy to perform everyday activity
	2. Dependency on prompts from others to structure everyday activities
	Diminished goal-directed cognition
	3. Lack of interest in learning new things, or in new experiences
	4. Lack of concern about one's personal problems
	Diminished concomitants of goal-directed behavior
	5. Unchanging of flat affect
	6. Lack of emotional response to positive or negative events
	7. The symptom of apathy causes clinically significant distress or impairment in social, occupational, or other important areas of functioning
	8. The symptoms are not due to diminished level of consciousness or to the physiological effects of a substance

The *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV) does not include apathy as a specific syndrome or disease. According to this classification of diseases, apathy is the change in personality resulting from, or part of, psychiatric or general illnesses. Although based on clinical and physiopathological presentations involving the frontal lobe, basal ganglia and thalamus, apathy can be a consequence of neurodegenerative disorders (such as PD), neuropsychiatric disorders and lesions in the brain, infectious diseases affecting the central nervous system[5], metabolic disorders [6], or even diseases nondirectly related to the nervous system such as osteoarthritis.

Phenomenology

The spectrum of apathy encompasses three main areas: emotional, cognitive, and behavioral. Emotionally, an apathetic person has a flat affect and reduced or absent reaction to affirmative or negative events. Cognitively, apathy is associated with loss of interest in new experiences and with lack of worry. Behaviorally, apathy results in lack of effort, loss of productivity, and reliance on others [7]. Starkstein et al. proposed criteria for apathy that included the clinical description made by Marin et al. [1]. Robert et al., in a task force, proposed that in apathy (1) the diminished motivation must be present for at least 4 weeks; (2) two of the three dimensions of apathy must be present; (3) there should be identifiable functional impairments attributable to apathy; and (4) symptoms and states that mimic apathy must be excluded [8]. As an example, patients with PD often manifest with masked facies and with low self-awareness of their diminished facial expression, yet can express an intense emotional desire to do a job or enjoy life.

Patients with apathy often show a reduced functional level, with diminished response to medications, and have a lower probability of successful relief of symptoms, which often augments caregiver anguish [9]. Apathy may also affect cognition, especially memory and executive function [7, 10], which is one of the principal factors that influences quality of life [11, 12].

Apathy can also be an associated symptom of another disease or condition such as depression, dementia, delirium, post-injury effect of frontal damage (such as stroke and trauma), infectious disease, metabolic influence, and mental retardation. According to epidemiological studies, apathy is a chronic syndrome and, when associated with neurodegenerative diseases, tends to be stable or worsen across time. Patients with PD have a higher probability of developing apathy as the disease progresses; apathy also is a risk factor for developing dementia [13]. In Alzheimer's disease, apathy is associated with a more rapid decline in cognitive function and global disability [14]. The differential diagnosis for the syndrome of apathy includes diseases with overlap manifestations such as depression, dementia, aprosody, bradyphrenia, akinetic mutism, psychomotor retardation, abulic mood, and organic and metabolic diseases [15].

Epidemiology

In a cohort of patients age 50 and above, the prevalence of apathy was 23.7%. It was associated with older age, female gender, lower scores in the Mini-Mental State Examination (MMSE), and disabilities in basic and instrumental functioning at baseline [16]. Apathy can be present in so many neurological disorders that it may be one of the most frequent neurobehavioral manifestations. It is more prevalent in advanced stages of Alzheimer's disease and less prevalent in mild cognitive impairment (MCI) (Table 7.2). In patients with schizophrenia, apathy is the most frequent manifestation and has the highest impact on the presence of severe social disability [17]. In stroke, patients with the highest severity of apathy are less likely to obtain a favorable outcome, and apathy has a negative effect on physical function, participation, and health perception [18, 19]. In patients with amyotrophic lateral sclerosis, apathy is associated with worse behavioral dysfunction [20].

In PD, apathy may be more frequent than depression (60% versus 56% respectively, in a study by Oguru M et al.) and may coexist with depression in approximately 43% of patients [21]. In one study, apathy without depression affected 17% of patients with PD; depression in the absence of apathy was present in 12% [21]. Others report the prevalence of apathy in PD to be between 16 and 51% depending on the scale used [7, 22, 23]. Kirsch-Darrow et al. found apathy to be more frequent and severe in patients with PD than in patients with another movement disorder such as dystonia [24]; they also noted that behaviorally it was the frequency of apathy, and not depression, that differentiated PD from dystonia.

The prevalence of apathy in other neurological, psychiatric and non-neurological conditions

Table 7.2 Prevalence of apathy in some neuropsychiatric diseases

Population	Prevalence (%)	Scale applied	Author	Other symptoms
Normal, older age (>50 years)	23	AS	Okura T [88]	Depression 12%
Alzheimer disease	72	NPI	Youn JC [40]	Irritability 76%, depression 68%
	78.4	NPI	Fernandez-Martinez M [89]	Depression 44%
	42	NPI	Okura T [40]	Agitation 41%
	51	NPI	Di Iulio F [90]	Depression 49%
MCI	50	NPI	Fernandez-Martinez M [89]	Depression 33%
	6	NPI	Di Iulio F [90]	Depression 44%
Vascular dementia	65	NPI	Staekenborg SS [91]	Depression 45%
Normal pressure hydrocephalus	Higher	NPI	Kito Y [92]	Anxiety 2nd place
Schizophrenia	30	AES	Faerden A [41]	
Amyotrophic lateral sclerosis	31	FrSBe	Witgert M [20]	Behavioral dysfunction
Parkinson disease	62	NPI	Pedersen KF[28]	
	38	UPDRS I	Pedersen KF[31]	Depression
PD (drug-naive patients)	23	NPI	Pedersen KF[32]	Depression 37%
	48	NPI	Kulisevsky [23]	Depression 70%, anxiety 69%
Huntington disease	52	Multiple	Naarding P [42]	Depression 12%
Stroke	88		Mayo NE [19]	
Multiple sclerosis	31	NPI	Figved N [93]	Depression 59%
Traumatic brain injury	42	NPI	Ciurli P [94]	Irritability 37%, depression 29%

AS apathy scale, *NPI* Neuro Psychiatric Inventory, *MCI* mild cognitive impairment, *INP* idiopathic normal pressure, *PD* Parkinson disease, *FrSBe* Frontal Systems Behavior Scale

varies widely; it is also present in non-neuropsychiatric diseases. Tumors in the paramedian frontal area have been associated with the presence of apathy in a small series of patients [25]. In a recent study, the prevalence of apathy in a post-hip fracture population was 37%; patients who recovered from apathy also had a better outcome of their fracture [26]. Apathy was more frequent in patients with PD than in individuals with osteoarthritis in another study, prompting the investigators to hypothesize that the higher frequency was due to the neurobiology of the disorder rather than simply a reaction to the level of disability [7].

Risk factors for apathy have been discussed in some papers and include low cognitive levels [27], presence of depression, poorer Unified Parkinson's Disease Rating Scale (UPDRS) motor scores, decline in speech, and greater axial involvement [28]. Apathy can also be correlated with age, age of onset of the disease, severity of the disease, and depression scores. It affects cognition, especially executive function [29]. Apathy creates a stigma, and impairs quality of life and activities of daily living [30, 31]. In another study, apathy was associated with motor and cognitive impairment in PD patients, especially in males [32].

Physiopathology

Anatomically, the orbitofrontal area has associations with the limbic system (amygdala, hippocampus, ventral tegmental area), with visceral-endocrine areas (hypothalamus and periaqueductal gray substance) and sensory areas (olfactory, taste, visual, hearing, and somatic sensory). The prefrontal area has connections with the caudate nucleus; both areas are involved in executive processes, but the premotor cortex is also involved in volitional actions and perseverance of actions and rewards [33]. The neurotransmitters involved in these areas are dopamine, acetylcholine, and norepinephrine.

The cortical–thalamic–striatal–limbic circuit has been implicated in the origin of the symptoms of apathy. Impairment and progressive damage to frontal, basal ganglia, and thalamic structures have been correlated with the clinical manifestations apathy and also with worsening of its symptoms [34]. Bowers et al. measured the response to aversive and unpleasant visual and auditory stimulus in PD patients and demonstrated a blunted response that was not associated with depression, dementia, or medications but rather with disease severity and a decreased (apathetic) motivational state. The investigators suggested that this may be related to amygdala and dopaminergic dysfunction [35].

Multiple studies consistently show a relation between depression and apathy, which suggests that a common pathway is shared at some points. Although apathy also may be present in the absence of depression, frontal and nigrostriatal pathways are involved in both conditions. Positron emission tomography (PET) and single-photon emission computed tomography (SPECT) studies in patients with Alzheimer's disease and apathy demonstrated hypoactivity and hypoperfusion of the anterior cingulate and orbitofrontal cortex and reduced activity in the medial thalamus [36, 37].

Another study showed a close clinical correlation between apathy and olfaction. Patients with PD who were more apathetic had greater impairment in olfaction [38]. Apathy and olfaction share common anatomic and functional areas in the basal, frontal, and temporal lobes of the brain.

Dopamine supplementation may alleviate apathy. The fact that apathy is less likely to be present in the early stages of PD also supports the idea that dopaminergic pathways are involved in the genesis of apathy [19], especially the mesocortical monoaminergic pathways [39]. According to clinical, pathological, and radiological studies, apathy is present in diseases like Alzheimer's disease [40], schizophrenia [41], amyotrophic lateral sclerosis [20], PD, Huntington's disease [42], strokes, depression, and other neurodegenerative disorders (Table 7.2) in which cholinergic, serotonergic, and noradrenergic neurotransmitters and pathways are involved. Therefore, apathy may involve the same pathways and neurotransmitters [43]. However, the description of patients with lesions in the extra frontal and gangliobasal region suggests involvement of other distinct pathways, perhaps involving thalamus and corpus callosum [44]. Strokes in the territory of the anterior cerebral artery further implicate an association between apathy and anatomic structures such as the frontal pole, cingulate gyrus/corpus callosum, and superior frontal gyrus [45].

Diagnostic Procedures and Scales

Since apathy is not yet recognized as an independent psychiatric disorder in the DSM-IV, no official diagnostic criteria exist, other than those proposed by Marin et al. [2–4]. However, behavioral scales have been used in surveys of apathy in PD and other disease entities. For example, apathy is represented in only one item in Part I of the UPDRS, the scale used most frequently in studies of PD patients. Apathy-specific scales also have been developed and used in several PD studies. Examples include the Apathy Scale (AS), the Apathy Evaluation Scale (AES), the Apathy Inventory (AI), and the Lille Apathy Rating Scale (LARS).

The single item in the UPDRS Part I, which evaluates motivation/initiative, has a 5-point range from 0 (normal) to 4 (complete loss of motivation). This item must be used with caution and only for screening for apathy. It is not meant for the diagnosis of apathy or for evaluation of its severity. As a single item, it has acceptable sensitivity but reduced specificity [46, 47].

The AS is a scale designed by Marin [1] with three subscales applied to the patient, the caregiver and the examiner. It was later modified by Starkstein et al. [48], introducing the AES, which has 14 questions with a 4 point range based on the severity of the symptom. This scale has been the most frequently used, perhaps because of its ability to differentiate apathy from depression and anxiety and its sensitivity in detecting change over time after pharmacological and behavioral intervention. The AES is easy to apply and shows good inter-rater and test–retest reliability. Although not meant to be used as a diagnostic

instrument, a cutoff of 14 points has correlated well with the formal diagnosis of apathy (where in a score of <14 implies a non-apathetic state and a score > 14 indicates an apathetic state) with a sensitivity of 66% and specificity of 100%.

The Neuropsychiatric Inventory (NPI), a scale initially used in patients with dementia, is valid and reliable in cataloging behavioral manifestations in various neurodegenerative disorders, including PD. It is a behavioral scale with ten domains, including apathy. The scale is directed to the caregiver in assessing the severity and frequency of the patient's symptoms. In the subdomain apathy, the clinician can quantify the severity and the frequency of the symptom [49]. The NPI has been used in patients with PD in surveys of neuropsychiatric conditions [50] and in pharmacological clinical trials [30].

The LARS is an original French scale, with dichotomous answers, directed to evaluate apathy. It focuses on the patient's own report and is not based on the caregiver response, although it has a version based on caregiver information [51]. The scale has 33 items separated into nine domains. This scale reinforces the cognitive, emotional and behavioral components of apathy, and includes diminished consciousness of self and disabled behavioral adjustment to social life assessments. The LARS can evaluate the severity of apathy and also helps in the differential diagnosis of apathy and depression [52]. Zahodne et al. compared the LARS with the AS in PD patients; the LARS displayed a high sensitivity and specificity but required a higher cut-off [53].

The score of the AI is obtained from information provided by the patient or the caregiver and shows reliability, internal consistency, and high between-rater reliability [54]. However, this scale has been used less frequently in PD.

Treatment

Identification and treatment of the cause can produce relief of apathy. In PD, no medications have been approved for treatment of apathy. Although randomized, powered trials are lacking, several small studies have reported benefit with pharmacological treatment.

Litvinenco et al. demonstrated improvement in apathy (based on the NPI) in patients with PD and dementia following 24 weeks of treatment with galantamine [55]; however, a similar study by Grace et al. did not produce the same result [56]. Rivastigmine, another cholinesterase inhibitor approved for treatment of dementia in PD patients, improved cognition, psychosis, and apathy in one case–control study [57].

Dopamine agonist (D2/D3) medications have shown some efficacy in the treatment of apathy in short trials. Ropinirole improved apathy in seven out of eight patients with previous DBS STN [58]. Apathy also improved with ropinirole in a patient who had suffered a stroke involving the prefrontal cortex; high blood flow in the cerebral cortex and basal ganglia was demonstrated in this patient [59].

Methylphenidate, an amphetamine-related medication that inhibits levodopa uptake, was reported to improve apathy in a patient with PD and a score of 3 (moderate severity) in the item motivation/initiative of the UPDRS; after 1 week on methylphenidate the score improved to zero (normal) [60].

In one study of 23 PD patients with apathy, levodopa treatment produced a reduction in the AS scale scores and an increase in motivation [10]. Tianeptine, a selective serotonin reuptake enhancer, produced no improvement of apathy in patients with PD and depression in a 3-month, open-label, non-comparative trial [61]. Modafinil, a medication that increases dopaminergic transmission, produced improvement in apathy, as measured by the AES, in a patient with dementia and depression [62]. The same authors reported improvement in apathy, with reduction in AES scores of 50–90%, in four patients with various psychiatric disorders who received methylphenidate for 4 weeks [63]. A patient with normal pressure hydrocephalus showed a dose-dependent improvement of apathy when treated with methylphenidate [64].

Donepezil was effective in the prevention and reduction of severity of apathy in patients with moderate Alzheimer's type dementia following 6

months of treatment [65]. Memantine, another medication for dementia, produced improvement of neuropsychiatric symptoms, including apathy, in patients with dementia after 16 weeks of treatment [66]. In another report, three patients with frontotemporal dementia were treated with memantine for 3 months and showed improvement in the NPI scores, especially in the agitation, apathy, and anxiety items [67].

Nefiracetam, a nootropic medication with action in GABAergic, cholinergic, and monoaminergic pathways, was used to treat apathy in a group of patients with post-stroke depression; doses of 600 and 900 mg daily were employed. Patients were evaluated using the AS. The group randomized to 900 mg showed a better response after 4 weeks of treatment than the group randomized to 600 mg. The investigators concluded that nefiracetam was genuinely beneficial in reducing apathy and that the response was dose related [68].

A systematic review by Drijgers et al. identified nine studies with the improvement of apathy as the primary outcome in neurodegenerative disorders and 26 studies with apathy improvement as a secondary outcome. In 26 studies, cholinesterase inhibitors were used; methylphenidate was used in six studies; and, paroxetine, amantadine, memantine, levodopa, tianeptine, and ginkgo biloba were evaluated in individual studies. Thus far, only three studies have been reported in PD patients; none employed improvement in apathy as the primary outcome. Unfortunately, results have not been consistent; some were even contradictory [69].

Selective serotonin reuptake inhibitors (SSRIs), widely used for the treatment of depression, have been reported to worsen apathy. In a case–control study, geriatric-depressed patients were evaluated with depression and apathy scales before and after treatment with SSRIs. Depression improved but apathy worsened [70]. The investigators suggested that age was a risk factor for apathy, but a case report describing two pediatric patients (9 and 16 years) with apathy induced by fluvoxamine argues against this [71].

Studies of deep brain stimulation surgery (DBS) and apathy have shown divergent results. Stimulation or lesioning of the basal ganglia affects not only motor symptoms but also emotional, speech, and behavioral symptoms [72–76]. Placement of the electrode near to frontal, limbic, or even in dopaminergic structures, depending on the spread of current, can affect the function of cortical and subcortical areas [77]. One study utilizing PET in patients following subthalamic nucleus DBS (STN DBS) documented worsening of AES scores after surgery; reduction in glucose metabolism in the right frontal middle gyrus and right inferior frontal gyrus was also present. A negative correlation was found in the right posterior cingulate gyrus and left medial frontal lobe [78]. Deterioration of AES scores post-DBS also has been observed by other groups [79, 80]. A study by Porat et al., using the NPI and the Frontal Systems Behavior Scale, obtained similar results [81], which were replicated by Denheyer et al. and other authors [82, 83]. In contrast, Castelli et al. failed to show any change in the apathy score 17 months following STN DBS [84]. Worsening of apathy has also been described following subthalamotomy [83]. Voon et al. have suggested that apathy may be secondary to withdrawal of dopaminergic medications after STN stimulation, rather than secondary to the procedure itself [85]. Levodopa and DBS had improved depression 3 months following surgery in another study, but apathy had worsened [86].

A pilot single-center, sham-controlled, randomized, parallel-group study using repetitive transcranial magnetic stimulation (rTMS) daily for 2 weeks specifically in PD patients with pure apathy or mixed apathy with depression, has been reported recently in abstract form. Outcome measures included the AS and the LARS. Although the apathy scores improved after treatment in the rTMS group, this was not significantly different from the sham treatment group. The authors concluded that active behavioral modification/intervention could be an effective therapy for apathy in PD [87].

In conclusion, apathy is a major nonmotor manifestation of PD, with high (and probably under estimated) prevalence. Its diagnosis may be complicated because it can be a distinct entity or a symptom of depression and other conditions.

It may be secondary to dysfunction in multiple related neurotransmitters and pathways and carries negative influences in other motor and non-motor symptoms. Thus far, there is no proven definitive treatment for this condition.

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Part II

Autonomic Dysfunction in Parkinson's Disease

Dysphagia

8

Norman A. Leopold

"Whilst at meals the fork not being duly directed frequently fails to raise the morsel from the plate: Which, when seized, is with much difficulty conveyed to the mouth." "… so much are the actions of the muscles of the tongue, pharynx, &c. impeded by impaired action and perpetual agitation, that the food is with difficulty retained in the mouth until masticated; and then as difficultly swallowed." "…the saliva fails of being directed to the back part of the fauces, and hence is continually draining from the mouth, mixed with the particles of food, which he is no longer able to clear from the inside of the mouth."

James Parkinson, 1817 [1]

Abstract

Dysphagia is an often unrecognized complication that occurs in a large majority of patients with Parkinson's disease (PD). Although dysphagia is often asymptomatic at first, with disease progression, a detailed clinical and radiological examination will identify multiple abnormalities in multiple phases of ingestion. Dysphagia treatment options are discussed, but there is inconsistent benefit from medications and limited documented evidence for paramedical modalities.

Keywords

Parkinson's disease • Dysphagia • Swallowing • Ingestion • Videofluoroscopy • Dysphagia therapy

Introduction

James Parkinson unambiguously portrayed advanced dysphagia in "The Shaking Palsy" [1]. Despite his obvious references to aspects of ingestion that precede swallow initiation, early investigators of deglutition in PD attributed dysphagia to esophageal dysmotility, a conclusion supported by numerous radiological observations [2–11] and pathological findings, such as the presence of Lewy bodies in the dorsal motor nucleus of the vagus (DMV) [12] and the esophageal myenteric plexus [13].

Braak et al. observed that, in most cases of sporadic PD, α-synuclein deposition progresses rostrally from the DMV to midbrain and cortex [14]. Miller et al. further quantified medullary α-synuclein, finding the highest levels in the DMV followed by the nucleus ambiguus, which is the somatic efferent innervation to the upper esophagus [15]. Although these findings have been subjected to some criticism [16, 17], they support the idea that esophageal dysmotility may be an early motor manifestation of PD. However, the relevance of this pathology to symptomatic

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dysphagia is not clear. Instead, the numerous motor abnormalities of pre-esophageal transport in PD [18–22] endorse a principal role for basal ganglia pathology in directing bolus movement and spawning dysphagia.

Definition of Dysphagia

Dysphagia is commonly defined as a disorder of swallowing, whether overt or covert (identified by radiological or physiological testing). However, the standard lingual, pharyngeal, and esophageal stages of swallowing inadequately incorporate other motor and cognitive behaviors that may impact swallowing efficiency and safety. Therefore, dysphagia is most inclusively not merely a disorder of the swallow but of ingestion [23], a complex motor cascade beginning prior to the swallow and terminating when a bolus passes the lower esophageal sphincter.

Anatomic Considerations

Reflexive deglutition begins in utero [24, 25] and is likely driven by a medullary central pattern generator (CPG). This functional center includes, but is not limited to, the nucleus solitarius, the dorsal and ventral vagal nuclei, and the intervening reticular activating system [26–28]. Exposed by neuroanatomic labeling techniques, additional polysynaptic connections that assist control and coordination of complex oromotor behaviors extend throughout the brainstem, from the hypoglossal nucleus to the substantia nigra pars reticulata [29–33]. With brain maturation and development of volition over reflex behavior, suprasegmental innervation supercedes the reflex swallow and merges it into the final phase of ingestion. Recent reviews of the supranuclear control of swallowing highlight a complex anatomic network that initiates and supports non-reflexive swallowing [34, 35]. Identified by transcortical magnetic stimulation, functional brain imaging (PET and fMRI) [28, 29, 36], and movement-related cortical potentials (MRCP), the most predominant activated regions include the cingulate, premotor, prefrontal, and primary motor and sensory cortices, along with the insula, cerebellum, and the basal ganglia–thalamic–cortical circuitry [36–40]. Therefore, many integrated neuronal systems, including those known to be defective in PD, control both bulbar and extremity automatic and commanded movements. Recent animal research also places the basal ganglia in position to modify some autonomic medullary motor functions [41]. This extensive functionally related circuitry provides robust evidence against the concept of hierarchial control of ingestion in favor of modular or distributed governance [40].

Prevalence of Dysphagia in PD

The prevalence of dysphagia in PD remains unknown but may range from about 50 to 100% [20, 42, 43]. Disparate results among studies relate in part to inconsistent criteria used to define dysphagia. Eadie and Tyrer [43], in the first systematic investigation of dysphagia in PD, claimed that 47% of their cohort had "symptomatic" dysphagia. Edwards et al. [44] using a more extensive questionnaire, reinforced this conclusion. An additional 28% of both study cohorts had sialorrhea, a complaint often due to an abnormality of swallowing and not to dysautonomic salivary overproduction [45, 46]. Indeed, compared with controls, hyposialorrhea may be an early autonomic feature of PD [47].

The prevalence of dysphagia in PD also increases if its definition, in addition to drooling, also encompasses those asymptomatic patients with radiological abnormalities of swallowing. Logemann et al. [48] reported that 95% of the PD patients referred for dysphagia therapy in their study had cineradiographic swallowing disturbances, but only 15–20% were clinically symptomatic. Other investigations of dysphagia in PD, using varying inclusion criteria, also demonstrate disparity between symptomatic and radiological dysphagia [18–21, 44, 49, 50]. These examples of diminished awareness of dysphagia in PD force the conclusion that responses to the Unified Parkinson Disease Rating Scale (UPDRS) Part II, which queries only about

Ingestion questionnaire

1. Do you have difficulty swallowing _____
2. Do you choke or gag on food? _____
3. Do you choke or gag on liquids? _____
4. Do you choke or gag on your own saliva? _____
5. Do you have difficulty starting to swallow? _____
6. Do you drool?. If so, only during sleep? _____
7. Do you have difficulty chewing? _____
8. Do you have difficulty moving food about in your mouth? _____
9. Does food feel like it gets stuck when you go to swallow? If so where – mouth, throat, chest?

   _____
10. Do you have heartburn? _____
11. Do you have reflux? _____
12. Do you belch frequently? _____
13. Do you get full at meals too quickly? _____
14. Do you have a poor appetite? _____
15. Do you have a fear of swallowing food or pills? _____
16. Does your mouth feel too dry? _____
17. Does it take too long to eat? _____

Fig. 8.1 Ingestion questionnaire

sialorrhea and choking/gagging during meals and even more detailed questionnaires are incomplete markers of dysphagia (see Fig. 8.1). Other scales to measure dysphagia clearly have more clinimetric value [51, 52].

The relationship between the prevalence of dysphagia in PD and the severity of the disease has received limited attention. Several studies report a correlation between disease severity and symptomatic dysphagia [20, 21, 44, 53, 54]. However, these results also hinge on the definition of dysphagia, e.g., whether drooling is included. In one study, all PD subjects reporting drooling had abnormalities of the oral stage of swallowing [55]. Barone et al. also noted that drooling increased along with disease duration and severity [56]. In a cohort of patients with dementia with Lewy bodies, dysphagia characteristics correlated with UPDRS-related severity of disease [57]. Conversely, Kalf et al., in a review of sialorrhea in a community-based PD population, thereby excluding those with more advanced disease, found prevalence rates to be higher in those with more mild PD [58]. Other investigators not only found no correlation of dysphagic symptoms with disease severity [21, 59] but also instead discerned that patients with most advanced disease professed fewer dysphagic symptoms

Table 8.1 Abnormalities of ingestion in Parkinson's disease

Phases of ingestion				
Preoral	Oral preparatory	Lingual	Pharyngeal	Esophageal
↓ Movements to mouth	↓ Lip seal	↓ Peristalsis	↓ Peristalsis	
Impulsive feeding	↓ Bolus movement	Hesitant or delayed transfer	↓ Laryngeal elevation	Tertiary waves
Dysregulation of feeding rate	↓ Mastication	Premature transfer	↓ Hyoid elevation	Reverse peristalsis
	↓ Lingual-centering movements	Segmented bolus transfer	↓ Epiglottic tilting	↓ Transport
		Lingual tremor	Vallecular retention	↓ Emptying
		Lingual "freezing"	Pyriform sinus retention	↓ LES closure
		↓ Lingual seal	↓ Laryngeal closure	GE reflux, hiatal hernia

↓, Slow or impaired; LES, lower esophageal sphincter; GE, gastroesophageal

than those less debilitated by their PD [21, 48]. These unanticipated results were posited to possible dementia, another complication of PD whose prevalence increases with advancing disease. A similar argument is proposed for the underreporting of symptomatic dysphagia when compared to radiological results in patients with corticobasal degeneration [60].

Clinical Dysphagia

The neurologic examination routinely incorporates a detailed cranial nerve examination but no observation of swallowing capacity. A simple bedside screening test of swallowing, although no substitute for the rigorous examination of the clinical dysphagia specialist, provides a rapid estimate of water swallowing capacity [61, 62]. Patients are asked to drink as quickly and as safely as possible 150 ml. of cold water. Observations include the number of swallows, the time to empty the cup, and any aberrant swallowing behavior such as coughing, gagging, or a post-test wet voice. Patients with PD require more swallows and are slower to complete the task than controls; both parameters decline with advancing disease [63]. However, a normal test does not exclude dysphagia since only water swallowing is monitored.

Clinical dysphagia specialists also conduct a detailed examination of cranial nerves 5, 7, 9, 10, and 12 as they relate to ingestion. They also analyze self-feeding by presenting a variety of food substances with varying textures, temperature, and tastes and record atypical feeding behaviors that might precipitate or exaggerate dysphagia. The more common feeding deficits in PD include reduced self-feeding capacity, abnormal neck and body postures while eating, impulsive feeding behaviors, difficulty regulating the quantity of food eaten, slow mastication, and hesitant swallow initiation [21, 64].

Radiological Dysphagia

Numerous videofluoroscopic studies of food and liquid ingestion have been conducted on PD patients. However, methodological and nomenclature differences have yielded incomplete and inconsistent observations of bolus movement (see Table 8.1). In early studies, patients swallowed only liquid barium while lying prone or standing erect [6–11, 65]. Pre-esophageal bolus preparation and transit were largely ignored. The modified barium swallow (MBS) administers test substances including barium impregnated foods of varying quantities and consistencies in the upright seated position. Unfortunately, the MBS

is an example of regional procedural blindness in that it scrutinizes oral preparatory, lingual, and pharyngeal phases of ingestion but ignores the esophageal phase.

Oral Preparatory Phase

The oral preparatory phase of ingestion prepares food or liquids and positions the bolus on the tongue prior to lingual transfer. Once in the mouth, food is captured by a firm lip seal anteriorly and compression of the posterior tongue against the hard palate posteriorly. The tongue squeezes food against the hard palate and then, with the cheeks, guides it onto the teeth for mastication. Once masticated, the tongue properly sizes and centers the bolus prior to the swallow, while any excess is temporarily squirreled between the teeth and cheeks. Prolongation of this phase is a generalized and commonly described abnormality in PD. More circumspect observations include one or several of the following: slow oral acceptance of the bolus, reduced bolus oral manipulation, inadequate or dysfunctional mastication, and poor bolus formation [18, 19, 21, 22, 48, 49, 66–68]. Less frequently observed aberrations include an insufficient lip seal so that oral contents slip from the mouth and lingual tremor [19, 21].

Lingual Phase

The lingual phase of ingestion is the first stage of the swallow. Although there are minor individual variabilities, contraction of tongue blade or tongue dorsum forces the bolus against the hard palate and generates a lingual peristaltic wave that propels the bolus from the mouth into the oropharynx. During this phase, PD patients manifest difficulty initiating the swallow, often displaying repetitive "pumping" movements [18, 19, 21, 49] approximating the leg hesitancies seen in freezing of gait. Segmented or "piecemeal" bolus swallowing is also common. These defective tongue movements may result in the bolus escaping over the tongue to invade the oropharynx and instigate a premature swallow [18, 19, 21, 49, 68]. An inefficient lingual phase also imparts a weakened bolus propulsive force that in turn compromises pharyngeal motility.

Pharyngeal Phase

The pharyngeal phase begins almost simultaneously with swallow initiation. The pharynx elevates and then contracts to surround the bolus, the hyoid bone and laryngeal cartilages rise, the epiglottis tilts to cover the laryngeal vestibule, the vocalis closes, and respiratory muscle activity pauses. A large majority of PD patients evaluated for dysphagia manifest slow or uncoordinated pharyngeal transport [19, 22, 49, 66–68]. The most frequent abnormalities include slowed pharyngeal peristalsis (>45%), bolus retention in the vallecular (>50%) and pyriform sinuses (>30%), and glottic aspiration (>15%) [22]. Because of its more proximate position to the laryngeal vestibule, spillage from pyriform sinus retention is more likely to cause laryngeal penetration or aspiration.

Although ignored in most studies of dysphagia in PD, epiglottic displacement is adversely affected in nearly 50% of patients [22]. When coupled with impaired extrinsic (laryngeal elevation) and intrinsic (vocal fold closure) laryngeal muscle movements during the swallow [69], the risk of aspiration increases significantly. Those PD patients with more advanced disease are most likely to display three abnormalities of the pharyngeal swallow that increase bolus aspiration risk: pyriform sinus retention, absent epiglottic inversion, and defective true vocal cord closure.

The pharyngo-esophageal sphincter (PES) is the anatomic transition between the pharynx and esophagus. This sphincter is pulled open during the pharyngeal phase, which allows unobstructed bolus transfer into the esophagus. Despite the opinion that dysphagia in PD is "…caused simply by clinical cricopharyngeal achalasia" [70] and several reports of PES dyssynergia with the advancing wave of pharyngeal peristalsis [13, 71], radiological studies of large numbers of PD patients do not support significant PES dysfunction. Together, Eadie and Tyrer [3] and Leopold

and Kagel [22] found only 1 of their 143 PD patients to have PES dysfunction. Manometric and electrophysiological evaluations of PES activity have also yielded contradictory results, with either increased or normal PES pressures, respectively [71–73]. These studies likewise failed to discern any radiological PES dysfunction during videofluoroscopy.

Esophageal Phase

Once past the PES, the bolus traverses the length of the esophagus and exits through the lower esophageal sphincter (LES) into the stomach. Bolus movement during the final phase of ingestion is generated foremost by the continuing progression of pharyngeal peristalsis and supplemented by local neuromuscular networks stimulating secondary peristalsis. Whether recorded during videofluoroscopy or inferred by esophageal manometry, more than 85% of PD patients have demonstrated slow, uncoordinated, and ineffectual esophageal bolus transport [22]. Defective peristalsis ranges from minor slowing to aperistalsis [7, 11, 22, 74]. Other esophageal aberrations include tertiary contractions, reverse peristalsis, "spasms," and patulency [4, 75]. Delayed transport and reverse peristalsis are statistically more common in patients with more advanced PD [23],. a finding unconfirmed by esophageal manometry [74, 75].

The lower esophageal sphincter (LES) transitions bolus transport from the esophagus to the stomach. Functionality of the LES in PD has not been examined as extensively as other anatomic regions of ingestion. Those few such studies describe a prevalence of gastroesophageal (GE) reflux that ranges from 26% to 57% [3, 22]. In PD patients studied by Eadie and Tyrer, GE reflux was three times more frequent than in control subjects [3]. Hiatal hernias also are seen but their prevalence may be no more than that of control subjects [76]. In another study of esophageal motility in PD patients (without a control population), both GE reflux and hiatal hernias were common, but no significant differences were uncovered based on disease severity [22].

Implications of Dysphagia

Dysphagia consequences are often both psychosocial and physical [77–79]. Symptomatic dysphagia often goes unrecognized by the PD patient. However, observant family and friends may find aberrant feeding behavior disturbing and withdraw from or become less tolerant of the patient during meals. For those dysphagic patients with insight into their frailties, mealtimes may provoke more anxiety than provide satiety [77]. As dysphagia advances, patients or their caregivers reduce food selection for safety and time constraints [80]. Mealtimes serve for both enteral and emotional nutrition, and neither goal will be satisfied if meals are exceptionally prolonged by slowed feeding, mastication, and swallow initiation. The end of this spiral is a socially isolated and often malnourished patient.

The burden of advancing PD includes an increased aspiration risk or frank aspiration. Choking and coughing may be absent or minimal [18]. The absence of aspiration during a MBS in dysphagic PD patients might suggest that their symptoms are of little consequence. However, the MBS is artificial and does not represent the automatic motor behavior so impaired in PD. Additionally, the MBS directs patients to sit with head and neck to sit erect. During typical daily meals, PD patients tend to eat with their head and neck anteroflexed [21], a posture that prepositions pharyngeal and tracheal structures to self-protect the airway. Disease and dysphagia progression eventuates in respiratory symptoms, with pneumonia as the most common cause of death in PD [81–83].

Treatment

Overview

Reviews of effective therapy for oropharyngeal dysphagia, the most common dysphagia in PD, find no consensus [84–87]. Minimal dysphagia with relatively low risk of aspiration presents historically as isolated sialorrhea. If nocturnal and

mild, such patients often require no specific intervention and therapeutic decisions should be based on other PD symptoms or manifestations. More severe drooling, even in the absence of additional dysphagic symptoms is a sign of more seriously compromised ingestion. Treatment decisions then follow a more considered examination of ingestion by a MBS plus esophageal fluoroscopy administered under the direction of an experienced clinical dysphagia specialist. Fiberoptic endoscopy during swallowing may also be informative.

Compensatory Techniques

During a diagnostic MBS, the dysphagia specialist introduces a variety of compensatory techniques and observes the responses. The result is a collection of facilitory and compensatory strategies taught to the patient and caregiver, intended to remediate abnormalities in one or several phases of ingestion. Direct therapy methods may include changes in body positioning during meals, altering the quantity, taste, temperature, and texture of food permitted, and cued instructions to reduce the automaticity of meals by inserting repetitive cycles of mastication, breath holding, and chin tucking before swallowing to narrow the airway prior to swallow initiation. Swallows may be followed by intentional throat clearing, a more effortful supraglottic swallow [88] and the Mendelsohn maneuver, a technique that prolongs laryngeal elevation during the swallow [89]. Some of these behavioral interventions have been systematically applied to PD patients with statistical improvement, but no single preferred treatment has emerged [59, 90–92].

Indirect strategies, such as stimulation techniques and exercises to strengthen and quicken the swallow, may provide benefit. Lee Silverman voice treatment improved some temporal measures of the oropharyngeal swallow [93]. Using the Mendelsohn maneuver with other indirect therapies in PD subjects, Nagaya et al. reported significantly reduced swallow initiation time after only one swallowing training session [68]. Cued swallowing can also shorten the duration of oropharyngeal swallowing [94]. Extrapolating from gait therapy research in PD [95], cueing may redirect motor instructions so as to minimize disordered basal ganglia influences over the automatic and sequential components of ingestion.

Notwithstanding any other literature support, dysphagia therapy appears experientially successful in remediating dysphagia in PD patients. However, because dysphagia may result in aspiration, subsequent pneumonia, or asphyxiation, researchers confront ethical barriers to the placebo-controlled studies usually demanded to determine treatment efficacy.

Drug Therapies

Drug treatment may diminish some aspects of impaired ingestion in PD, but the supportive literature is so meager as to suggest that dopaminergic pathways have little impact on swallowing [67, 96–98]. However, accurate quantification of drug-induced ingestive changes is limited. Lingual tremor is uncommon, subsides during swallowing [9, 21] and is without known adverse affects. Deglutory muscle rigidity is immeasurable. Only the ingestive equivalent of bradykinesia can be witnessed at the bedside or during videofluoroscopy with few standards by which it can be judged [41, 96, 99]. Consequently, relative to the scaled improvement of limb movement, even modest drug-induced benefits may be inconspicuous or, if radiologically or electophysiologiclly quantifiable, unappreciated by the patient.

Any medication-related benefit should accrue primarily to the prepharyngeal phases of ingestion, those phases under the greatest volitional control. In the first publication of levodopa therapy for PD, Cotzias et al. [100] noted “striking” improvement in “drooling and dysphagia.” Radiographic confirmation was not attempted. Levodopa therapy improves jaw velocity and amplitude [101] and lessens swallow-related deficits in some PD patients [20, 67, 70, 102–104] but may also increase saliva [105]. However, no levodopa-induced improvement of pharyngeal motility was seen by Calne et al. [42] Their cohort may have been less affected, since none had

vallecular or pyriform sinus stasis or aspiration; prepharyngeal bolus transport was insufficiently documented.

Dopamine agonists ameliorate some symptomatic and radiological swallowing abnormalities. In one study, bromocriptine lessened drooling [106]. In another, apomorphine produced some improvement in the oral preparatory and lingual phases [107]; off-period belching and associated esophageal motility also have been reported to improve [108]. Anticholinergic agents and salivary gland botulinum toxin injections [109] may reduce salivary consistency or volume but have little positive impact on the motor act of ingestion. On a cautionary note, anticholinergic-induced xerostomia may further impair swallow initiation and actually worsen ingestion. However, patients experiencing reduced saliva following parotid gland botulinum toxin injections reported no such problem [110]. Finally, although specific drug treatment for dysphagia was not directly addressed, PD patients may incur a significant slowing of swallowing when dopaminergic medications are withdrawn [63].

Prospective Non-pharmacological Therapies

Swallowing efficiency may improve in response to deep brain stimulation [111]. In that prepharyngeal phases of ingestion are more under volitional control, the report of improvements only in the pharyngeal phase of ingestion is somewhat unexpected. The explanation may be in the small numbers of subjects studied or that DBS activated other than thalamocortical targets to achieve the noted benefit. In potentially relevant research, Hamdy et al. demonstrated that short-term pharyngeal stimulation could drive pharyngeal motor cortex reorganization [112]. Jefferson et al. used transcortical direct current stimulation to enhance pharyngeal motor cortical excitability [113]. Together, these studies suggest that increased stimulation via several routes might kindle motor plasticity leading to symptomatic improvement of one or several phases of ingestion in PD patients.

Summary

In summary, the above review gives testimony in PD to an ensemble of ingestive motor deficiencies, extending from lips to lower esophageal sphincter. These abnormalities are not specific for PD, since many have been reported in other bradykinetic-rigid syndromes [60, 114, 115]. However, the early appearance of significant dysphagia is exceptional in PD and should alert the clinician to an alternative diagnosis [116, 117]. Once recognized, a detailed dysphagia evaluation should be considered.

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Gastric Dysfunction in Parkinson's Disease

9

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Abstract

Parkinson's disease (PD) is a degenerative illness affecting the central, autonomic, and the enteric nervous systems (ENS). Neuropathological changes have been described in all parts of the ENS in PD patients. Gastric dysfunction is common in PD patients and includes delayed gastric emptying (gastroparesis), early satiety, anorexia, abdominal fullness, nausea, and vomiting. Gastric dysfunction may impair drug absorption and thus contribute to motor fluctuations in PD. Moreover, antiparkinsonian medications themselves may exacerbate gastric dysfunction.

To date, there is no satisfactory drug treatment for gastroparesis, and the clinician will need considerable creativity for planning therapeutic management to help the PD patient overcome this disabling syndrome and its consequences. Dietetic interventions, together with prokinetic medications, are recommended. Gastrostomy or jejunostomy feeding tubes should also be considered for patients with severe gastroparesis.

Keywords

Parkinson's disease • Gastric function • Gastric emptying • Motor fluctuations • L-Dopa pharmacokinetics

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Introduction

Parkinson's disease (PD) is a common degenerative illness affecting the central, autonomic, and the enteric nervous systems (ENS) [1]. Common gastrointestinal (GI) manifestations include sialorrhea, probably reflecting swallowing dysfunction, and more severe deglutition problems, resulting in dysphagia, aspiration and possibly weight loss [2–5]. Constipation is very common among PD patients, often antedating the motor manifestations of the disease [6]. Relatively little attention has been paid to dysfunction of the proximal part of the GI system, the esophagus, and the stomach. This dysfunction may be important not only due to its unpleasant clinical symptoms but also because it may affect drug absorption and, therefore, motor manifestations of PD. In one study, impairment of gastric motility (gastroparesis) was found in 70% of PD patients, especially in those with response fluctuations [7]. Conversely, among 146 consecutive patients with gastroparesis seen in a gastroenterology clinic, the condition was related to PD in only 7.5% [8]. Although considerable progress has been made in delineating many aspects of GI dysfunction in PD, therapeutic approaches to these symptoms are lagging behind. A growing body of evidence indicates that GI symptoms mostly reflect direct involvement of the GI tract by the neurodegenerative process, although the effects of PD on skeletal muscle function in the oropharynx, anorectum, and pelvic floor also contribute to the problems [9].

The finding of Lewy bodies in the ENS has prompted the "dual-hit" hypothesis, which proposes the possible entry of a pathogen, probably viral, into the central nervous system (CNS) through the gastric system as a consequence of saliva swallowing with subsequent spread via the vagus nerves to the medulla and eventually the basal ganglia [10].

James Parkinson, in his famous monograph [11], recognized the serious GI features that PD patients manifest. This issue failed to claim proper attention until 1965 when Eadie and Tyrer focused attention on GI dysfunction in PD patients [12]. Since then, a growing number of studies have investigated the anatomical and pathophysiological bases and the clinical manifestations of gastric dysmotility, as well as drug influences on gastric motility, in PD patients.

The regulation of GI motor function by the autonomic nervous system (ANS) is under the extrinsic control of the parasympathetic and sympathetic nervous systems and by the intrinsic enteric plexuses [13]. The ENS plays a key role in the generation and coordination of antral contractions and peristalsis and in the regulation of gastric emptying. Interstitial cells of Cajal, which are located in the greater curvature of the stomach, act as a slow gastric pacemaker. Intrinsic innervation of the ENS consists of a network of neurons within the gut wall that are arranged in two principal plexuses, the myenteric plexus of Auerbach and the submucosal plexus of Meissner. This intrinsic system is activated by vagal fibers and inhibited by the sympathetic system, originating in the intermediolateral column of the spinal cord between the fifth and the ninth thoracic segments. Extrinsic nerves control the striated muscle portions of the esophagus and the external anal sphincter.

Clinical Manifestations

Gastric motor dysfunction is a disorder of the upper gut and typically is characterized by delayed gastric emptying (GE) that may be associated with early satiety, anorexia, upper abdominal fullness, bloating and sometimes pain, nausea, and vomiting [14, 15]. Nausea in patients with PD is most often caused by dopaminergic medications [16, 17], and the results of double blind studies with dopaminergic agonists confirmed that these drugs are, indeed, associated with nausea [18, 19]. The frequency of nausea in one group of patients with PD who were on these medications and another group of patients who were untreated was reported to be similar, however, suggesting that although dopaminergic medications are associated with nausea and vomiting, they cannot fully explain those symptoms in PD [20].

Ancillary Investigations

The gastric symptoms of PD are nonspecific and it was only the introduction of ancillary investigations that allowed their origin to be confirmed. Untreated PD patients have significantly slower GE time compared with controls [21], but the same slowness of GE also is observed in individuals with multiple-system atrophy (MSA) [22]. Abnormalities in gastric myoelectric activity have been documented in PD, and electrogastrography (EGG) reveals frequent dysrhythmias. Gastric motility is especially impaired in patients with advanced disease [23]. PD patients have a significantly slower GE time for solids, regardless of age or gender, and a positive correlation has been reported between rigidity and action tremor with slow GE [24]. However, another group of investigators noted no differences in the myoelectrical activity between PD patients with or without upper GI complaints [25]. There is some similarity between the abnormal EGG patterns of PD patients and patients after the acute phase of a vagotomy procedure; however, there is improvement with time in vagotomized patients but slow deterioration in PD patients, presumably reflecting progressive ENS involvement [26].

The dysrhythmia of GE, which is influenced by food, was examined in a study on subjects in different stages of PD. A significant association between preprandial dysrhythmia of gastric motility and duration of disease, duration of levodopa treatment and, especially, with motor fluctuations was demonstrated. Preprandial dysrhythmia of GE was detected in almost all patients with motor fluctuations, compared with PD subjects without motor fluctuations [27]. This study employed a new method measuring gastric emptying using the C^{13}-sodium octanoate breath test, which entails fewer technical difficulties for advanced PD patients and patients with motor fluctuations than did the older method of obtaining radioisotope images of the GI tract [27].

Pathology and Pathophysiology

Neuropathological changes have been described in PD in all parts of the nervous system responsible for gastric motility, explaining the gastric motility problems in this disease. GI involvement in PD is a good example of the interaction between the CNS and the ANS. The recent demonstration of neuropathologic abnormalities in the ENS, analogous to those regarded as being pathognomonic for the parkinsonian process in the brain, suggests that the ENS, called "the little brain in the digestive system" [28], and the CNS ("large brain") may exemplify parallel pathologic changes [9].

Lewy bodies, a pathological hallmark of PD, were found to be widely distributed in Auerbach's and Meissner's plexuses in the GI tract [29, 30]. Additional supportive proof of a degenerative process taking place in the ENS has been demonstrated by an immunocytochemistry stain for α-synuclein in the submucosal Meissner's plexus, with extension into the gastric mucosa and in proximity to the fundic glands [31].

Neurons immunoreactive for tyrosine hydroxylase (TH) were also shown to exist in these plexuses of normal humans, and a possible relationship between presumably pathological processes involving these catecholaminergic neurons and the occurrence of Lewy bodies in the ENS in PD has been suggested [32]. However, α-synuclein deposits in the brain in PD are not confined to dopaminergic neurons.

Loss of neurons has been reported in the dorsal motor nucleus of the vagus nerve (DMNX) in PD patients with autonomic failure [33]. This nucleus consistently showed early Lewy bodies in PD before similar changes occur in pigmented nuclei of the brainstem [33, 34]. Moderate neuronal loss and the presence of Lewy bodies have been noted in the intermediolateral columns of the thoracic cord in PD patients with autonomic failure, in addition to neuronal loss in the sacral segments [35, 36]. Lewy bodies were present also in sympathetic ganglia, with or without obvious neuronal loss [37]. Comparison of the

pathological findings involving the nervous system that controls gastric motility revealed involvement of the CNS in both MSA and PD patients, but the latter also had involvement of the ENS [22]. The changes involving both the ANS and ENS are considered by some investigators to be the primary cause of GI dysfunction in PD [26].

Recently, Schulz et al. proposed an interesting theory of a possible mechanism that linked PD and *Helicobacter pylori* (*H. pylori*) infection. Cholesterol glucosides constitute part of the lipid profile of *H. pylori* and have some resemblance to cycad-derived sterol glucosides, a substance that induces loss of striatal dopaminergic terminals. This similarity in the sterol glucosides structure might explain how the cholesterol glucosides arising from an *H. pylori* infection may act as neurotoxins, promoting the degeneration of the dopaminergic neurons in parkinsonism [38].

The Effect of Medications on Gastric Motility

The frailty of GI function in old age, and particularly in patients with PD, underlies the very frequent complaints of nausea, gastric fullness, or constipation following drug exposure [39]. The effect of dopaminergic drugs is well known [40], with important influences on gastric motility and gastric symptoms.

Levodopa slowed gastric emptying to a similar extent in both elderly and young normal volunteers [41]. Dhasmana et al. [42] provided evidence that the reduced GI motility elicited by dopamine and dopamine agonists is primarily through activation of dopamine receptors involved in intestinal contractions. Levodopa treatment initially slows down gastric emptying by its peripheral action on the gastric wall. This action results in an indirect effect on the movement of the pyloric sphincter [43]. The peripheral GI effect of levodopa occurs despite cotreatment with a decarboxylase inhibitor, since some peripheral conversion to dopamine occurs in the stomach [44, 45]. In contrast to healthy subjects, PD patients are influenced differently by dopamine derivatives, Apomorphine facilitates swallowing in PD patients [46]. This finding has also been demonstrated in a short-term study with PD patients at mild and moderate stages of the disease [21]. PD patients with a fluctuating type of response had a significantly delayed GE compared with those with a smooth response [7]. Chronic exposure to levodopa also may modify the activity of the DMNX in the medulla oblongata. Several groups have shown that dopaminergic cells are present in the DMNX [47–49]. Following the development of response fluctuations, PD patients had a dramatic shortening of GE time—almost to the rate recorded in healthy volunteers—when measured during the "on" state induced by levodopa. Accelerated GE in PD patients with motor fluctuations (all with long-term exposure to levodopa) also was described by Murata et al. [50, 51], who demonstrated accelerated absorption of levodopa after prolonged exposure to levodopa in intact rats and in PD patients. The ability of chronic levodopa treatment to accelerate its own absorption from the gut was also reported by Abrahms et al. [52] and Muenter and Tyce [53] shortly after levodopa was introduced for the treatment of PD. Such an effect is supported by the clinical observation that taking medications during the "off" state can frequently result in a "delayed on" or a "no on" state. Furthermore, a "delayed on" state, which is often associated with prolonged GE [54], is most frequent after the first morning dose, usually taken after 6–10 h of fasting (and no medications) while the patients is still "off". Yeh et al. [55] showed that the second daily dose of levodopa had a significantly shorter absorption time. These results should encourage patients to take their medications while still in the "on" state in order to accelerate levodopa absorption and improve the absorption of subsequent doses of levodopa.

Dopaminergic agents (e.g., apomorphine and bromocriptine) significantly slow GI transit in rats; this effect is blocked by dopamine antagonists [42]. Although the effect of other antiparkinsonian medications on GI motility may be largely overestimated [56], it is nevertheless worthy of consideration. Gastric relaxation invariably precedes nausea and emesis produced, for

example, by the classical emetic agent, apomorphine [57]. Other dopamine agonists, and possibly selegiline, may produce nausea and vomiting as adverse effects, not only by stimulating catecholamine receptors in the medulla oblongata involved in the emetic response but also due to the direct dopaminergic effects in the GI tract [45]. A comparison study of the influence of entacapone in combination with levodopa/decarboxylase inhibitor to levodopa/decarboxylase inhibitor alone demonstrated increased absorption, especially for salt and acid that could be explained by the basic environment induced by entacapone in the gut [58]. No difference in GE was observed after a one-time administration of entacapone with and without levodopa/decarboxylase inhibitor [58, 59].

Anticholinergic agents, such as trihexyphenidyl and benztropine, also may impair gastric emptying. Trihexyphenidyl decreased levodopa absorption in rats [60], but increased the amount of levodopa absorbed by young healthy volunteers [61]. Thus, the concomitant administration of trihexyphenidyl to patients receiving levodopa may decrease the therapeutic efficacy of levodopa by slowing its absorption [62]. Benzhexol did not change the amount of levodopa absorption in healthy young controls, but it did increase the second peak of absorption at the cost of the initial peak [63]. By their anticholinergic effect, tricyclic antidepressants, and atropine may cause gastroparesis. Vagotomy worsens the "delayed on" and "dose failure" phenomena [60].

Medications with antidopaminergic effects influence gastric motility as well. Metoclopramide is a dopamine antagonist that can reverse the delayed GE caused by a dopaminergic agent [43]. This classical prokinetic drug is, however, not a useful treatment in PD because of its ability to cross the blood–brain barrier, thereby exacerbating parkinsonism. Domperidone, an antidopaminergic derivative with similar prokinetic action [64], does not cross the blood–brain barrier and is in common use in PD patients.

Cisapride, a prokinetic drug with indirect cholinergic activity by means of stimulation of serotonin receptors, also enhances gastric motility, resulting in GI smooth muscle contraction, possibly contributing to its antiemetic effect [65]. Cisapride improves the "delayed on" and "dose failure" phenomena [66], but the use of cisapride has been restricted due to serious safety problems.

Motor Fluctuations and the Gut

The mechanisms responsible for motor fluctuations in PD are not fully understood [54]. Some factors associated with unstable drug effects are pharmacokinetic, including a short half-life, peripheral O-methylation and transport across the blood–brain barrier. Erratic gastric motility also may contribute to the complex pharmacokinetics of levodopa [55]. Djaldetti et al. [60] described a PD patient who experienced "delayed on" and "dose failure" phenomena after a vagotomy and pyloroplasty procedure, which may imply a connection between levodopa absorption and delayed GE.

Erratic gastric motility in PD patients results in periods of effective contractions that induce efficient transit of food into the duodenum causing rapid uptake of levodopa, which may contribute to the motor fluctuations. Although the "wearing off" phenomenon may be due to changes in central pharmacokinetics caused by diminished presynaptic dopamine storage capacity, peripheral levodopa pharmacokinetics, and especially erratic intestinal absorption of oral levodopa due to delayed GE, may account for the "delayed on" and "dose failure" phenomena [54, 67]. The main support for this hypothesis is that these events can often be prevented or ameliorated by taking levodopa before meals on an empty stomach

Kurlan et al. [68] assessed motility and plasma levodopa concentrations in PD patients exposed to levodopa administration in order to clarify the influence of GE on levodopa-related motor fluctuations and demonstrated that it is possible to produce steady plasma levodopa concentrations with a corresponding reduction in motor fluctuations by continuous intraduodenal administration of the drug [69]. Other enteral routes, such as gastric ones, have produced more variable

plasma levodopa concentrations and an acceptable clinical response [68].

It seems that the success of levodopa treatment depends, in part, on normal gastric motility, and that stagnation of levodopa within the stomach due to reduced gastric motility and prolonged transit time may affect the bioavailability of the drug. In a recent study, however, there was no difference in GE time between PD patients under long-term levodopa/decarboxylase inhibitor therapy with and without motor fluctuation [70].

Taking a levodopa dose before or after ingesting a meal is an important determinant of drug absorption. Time to peak plasma levodopa concentration increased threefold (from 45 ± 23 to 134 ± 76 min, $p < 0.001$) when levodopa was administered after meals in a study by Baruzzi et al. [46, 71]. Fatty food can slow GE, at least in non-PD persons [71].

Bypassing the stomach and administering levodopa via nasoduodenal or gastrojejunostomy tubes [60, 68] may be an optimal decision for patients with severe motor fluctuations. Intraduodenal administration of levodopa is thought to be an ideal model for the development of continuous-release preparations of levodopa [68, 69]. The success of modern intraduodenal levodopa/decarboxylase inhibitor intestinal gel infusion makes this the procedure of choice in fluctuating patients.

Therapy for Gastric Motility Disturbances in PD

Nonpharmacological treatment of gastroparesis in PD includes a diet that consists of small, frequent low-fat and low-protein meals. Special consideration must be given to protein intake due to the potential correlation between decreased absorption of levodopa and a protein-rich diet. Astarloa et al. [72] established a positive effect of a diet rich in insoluble fibers on plasma levodopa concentrations (particularly 30–60 min after dosing) and motor function of PD patients following a levodopa dose. Avoidance of anticholinergic medications may also help in the management of gastroparesis. The muscarinic cholinergic agent, bethanechol, enhances gastric contractions but not in a coordinated way to stimulate gastric emptying and, therefore, is limited in terms of acting as a prokinetic agent [73]. The most commonly used prokinetic medication in PD is the peripheral dopamine receptor antagonist, domperidone, first proposed by Agid et al. [74] and by Quinn et al. [75]. Domperidone in a daily dose of 80 mg significantly reduced upper GI symptoms (nausea, vomiting, anorexia, abdominal bloating, heartburn, and regurgitation) and accelerated GE of a solid meal but did not interfere with response to antiparkinsonian treatment [64]. In addition, domperidone has an antiemetic effect by acting on the chemoreceptor trigger zone. Domperidone is not available in the USA but is commonly used in other countries for the management of GI symptoms. It is typically dosed orally at 10–20 mg, three or four times daily. A suppository form is available as well.

Cisapride has no direct antidopaminergic effect and is effective and well tolerated in fluctuating PD patients, in whom it produces a significant shortening of the time from latency to "on" and reduction of the number of dose failures. This effect is related to improved pharmacokinetic parameters of levodopa [66, 76], although exacerbation of tremor also has been reported [77]. The usual dose of cisapride is 10–20 mg four times daily, usually given 30 min before meals. Because of potential cardiac arrhythmias precipitated by numerous drug interactions and medical conditions, cisapride was withdrawn from the open market in the USA and the UK in 2000 but is still in use in a few countries worldwide.

Mosapride is a gastroprokinetic agent that acts as a selective 5HT4 agonist. It was tested in an open label study involving five PD patients with fluctuations; the investigators reported significantly shortened GE time, reduced fluctuations, and improved motor function in all patients, and no adverse reactions were noted [78].

The motilin receptor agonist, erythromycin, may be effective in patients with gastroparesis, especially in relieving acute gastric stasis when given at a dose of 1–3 mg/kg intravenously every 8 h. Oral dosing of 50–250 mg four times

daily may also be effective [28, 73], but our literature search failed to reveal any studies on the use of erythromycin as a prokinetic agent specifically in the setting of PD. The use of prokinetic medications in combination with one another may be beneficial, but that concept has been minimally investigated, and not at all with regard to PD [73].

Despite dietary and medication interventions, some patients will continue to have debilitating symptoms of gastroparesis. Such patients may benefit from the judicious use of dietary supplements as a rich source of energy [79]. Gastrostomy or jejunostomy feeding tubes may provide optimal nutritional and hydration care [73]. Jejunostomy may be preferable for some PD patients because it allows direct infusions to the intestine.

Recent understanding of normal and abnormal gastric electromechanical function has led to the development of an electrical gastric stimulator, similar to devices used to stimulate other dysfunctional organs [80]. It requires the surgical placement of electrodes into the gastric serosa. Patients activate the pacer in the immediate preprandial period and continue its operation for several hours after eating. Gastric electrical stimulation is associated with symptomatic relief and improvements in nutritional status, health resource utilization, and costs and is approved by the FDA for patients with severe nausea and vomiting caused by gastroparesis, offering a new approach for patients with refractory gastroparesis when other options have failed [81, 82]. The methodology of neural electrical gastric stimulation consists of a microprocessor-controlled sequential activation of a series of annular electrodes that encircle the distal two-thirds of the stomach and induce propagated contractions, causing forceful GE. This particular stimulator method has not yet been applied to humans and would need to be clinically tested before it could be considered for PD patients [83].

Some consideration must be taken regarding the eradication of *Helicobacter* species. These bacteria frequently reside in the human GI tract. They are usually harmless, but may be associated with symptomatic infections. In such cases, their eradication (by antibiotics) may be indicated. Dobbs et al. observed clinical improvement in PD patients following *Helicobacter heilmannii* eradication, including reversibility of cachexia and disability in one patient, and significant improvement in GE time and upper abdominal symptoms following eradication of *H. pylori*. Furthermore, it would be reasonable to expect an increase in the probability of being underweight in the presence of the *H. pylori* antibodies [84]. An interesting concept regarding motor fluctuations was recently proposed by Pierantozzi et al. [85], who described six PD patients in whom the area under the curve of levodopa plasma concentrations was augmented with prolongation of clinical benefit after *H. pylori* eradication. The authors suggested that *pylori*-activated gastric alterations may be responsible, at least in part, for the unpredictable absorption of oral levodopa in advanced PD.

Three women with severe gastroparesis were recently treated with intrapyloric injections of botulinum toxin and all were reported to have had significant symptomatic improvement [86].

Conclusion

Gastroparesis is one of the well-recognized manifestations of PD, causing nausea and other symptoms and, importantly, affecting drug absorption as well. Most antiparkinsonian drugs further exacerbate GI manifestations. To date, there is no satisfactory therapeutic approach to gastroparesis, and the clinician will need considerable creativity to help the PD patient overcome this disabling syndrome and its consequences.

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Intestinal Dysfunction in Parkinson's Disease

10

Ronald F. Pfeiffer

Abstract

Intestinal involvement in Parkinson's disease (PD) has been known since James Parkinson's initial description of the disease in 1817. Relatively little attention has been directed toward small intestinal dysfunction in PD, but some evidence has accumulated that small intestinal motility may, indeed, be impaired in PD. However, the clinical consequences of any such dysfunction have not been clearly delineated. Much more information is available regarding colonic and anorectal dysfunction in PD. Diminished bowel movement frequency, presumably reflecting colonic dysmotility with consequent slowed colonic transit, is present in a significant percentage of individuals with PD, reported figures ranging from 20 to 77%. Anorectal dysfunction, characterized by both excessive straining and a sense of incomplete emptying, develops even more frequently in PD, affecting more than 60% of patients. Both central and enteric nervous system dysfunction may have a role in the generation of these intestinal and anorectal abnormalities. Recognition of two components of intestinal dysfunction in PD—slow-transit constipation and anorectal defecatory dysfunction—will hopefully open the therapeutic door to more specific and effective treatment for these troubling and occasionally disabling features of PD.

Keywords

Parkinson's disease • Intestinal dysfunction • Postprandial pattern • Interdigestive pattern • Colonic dysmotility • Constipation • Defecatory dysfunction • Colon transit time • Anorectal dysfunction • Anorectal manometry

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Introduction

James Parkinson indicated quite clearly his awareness of intestinal dysfunction in the setting of Parkinson's disease (PD) in his remarkable 1817 treatise, *An Essay on the Shaking Palsy.* In addition to characterizing other gastrointestinal (GI) features of PD, his description of bowel dysfunction codifies in crystal clarity both constipation ("the bowels which had all along been torpid, now in most cases, demand stimulating medications of very considerable power") and defecatory dysfunction ("the expulsion of the feces from the rectum sometimes requiring mechanical aid") [1].

However, little else was placed in print regarding parkinsonian intestinal dysfunction in the post-Parkinson neurological literature until 1965, when Eadie and Tyrer published their analysis of GI dysfunction in 107 patients with parkinsonism. Of these, 76 had been diagnosed with idiopathic PD, whereas the majority of the remainder carried a diagnosis of postencephalitic parkinsonism [2]. A group of comparably aged persons with "acute orthopedic" disorders served as controls. Constipation (no distinction was made between decreased frequency and dysfunctional defecation), along with other GI features, such as difficulty in chewing, drooling, dysphagia, and frequent "heartburn," were noted to be present more often in individuals with parkinsonism than in controls.

Little else was published for the next 25 years, until Korczyn wrote about autonomic dysfunction in PD and suggested that GI dysfunction is the most frequent autonomic manifestation of the disorder and that constipation is the most common GI feature; he also noted that constipation may precede the development of the motor manifestations of PD [3]. In 1991, when Edwards et al. reported their survey of 98 patients with PD and 50 comparably aged spousal controls [4], additional information regarding GI dysfunction in PD became available. The GI features they identified closely paralleled those described by Eadie and Tyrer, by Korczyn, and by Parkinson himself, including disordered salivation (drooling), dysphagia, nausea, constipation (decreased bowel movement frequency), and defecatory dysfunction (difficulty with the actual act of defecation). In a series of subsequent reports that focus largely (although not exclusively) on bowel dysfunction in PD, these authors further investigated, cataloged, and characterized this surprisingly common, yet complex and troublesome aspect of PD [5–12].

Recent years have witnessed a sustained and ever-growing literature on the subject of intestinal dysfunction in PD (see [13–18] for recent reviews). Using a large retrospective claims database, Makaroff et al. examined the association between the presence of GI disorders and PD-related outcomes and reported that the majority of people diagnosed with PD ultimately acquire at least one GI disorder (65% at 4 years post PD diagnosis) and that PD patients with GI disorders have worse health outcomes and incur higher annual healthcare costs than individuals with PD who do not develop GI disorders [19].

This chapter will focus primarily on bowel dysfunction in PD, along with a brief review of the scarce literature regarding small intestinal function in PD.

Small Intestine

Anatomy and Physiology

The intestine is divided into two primary components, the small and large intestine (or colon), which possess definite similarities, but also serve clearly different functions. In adults, the small intestine reaches the rather astounding length of approximately 4–6 m [20, 21] and is divided into three segments: duodenum, jejunum, and ileum. The small intestine is responsible for absorption of nutrients, salt, and water. Motility within the small intestine is produced by contractions of the circular and longitudinal muscle layers that compose the intestinal walls. Interstitial cells of Cajal (ICCs), which are part of the enteric nervous system (ENS), generate electrical slow waves that serve a pacemaker function and migrate in an aborad direction [21, 22]. When spike bursts are superimposed on a slow wave, actual muscle

contraction occurs, which then travels in either direction along the small intestine. It previously was considered that slow waves traveled only short distances, with small intestinal motility organizing into segmental contractions serving to slowly mix and spread the chyme for digestion [21, 22]. However, a more recent study found that many of the slow waves actually propagated the length of the small intestine [21, 23] and it is likely that the characteristic segmentation patterns of small intestinal motility are the result of limited propagation of individual spikes occurring in the wake of slow waves [24]. The digesting contents within the small intestine are propelled forward at a rate of 5–20 mm/s and it typically takes 3–5 h for chyme to traverse the small intestine [21].

Two distinct patterns of small intestinal motor function have been identified [25]. The fed (postprandial) pattern, which appears within 10–20 min following a meal, is characterized by more segmental, and consequently less propulsive, contractions that assist in the mixing of digestive enzymes with the chyme and maximize mucosal contact, thus promoting nutrient absorption. The second pattern, the fasting (interdigestive) pattern, appears 4–6 h after a meal and is divided into three phases. First is a period of relative motor quiescence, followed by increasingly prominent contractions in the subsequent two phases that presumably serve to "flush" solid residues from the small intestine into the colon, preventing bezoar formation and minimizing bacterial accumulation within the small intestine. This complex pattern of small intestinal motility is under the direct control of the ENS, but modulated by both autonomic and hormonal influences.

Small Intestinal Dysfunction in PD

Little attention has been focused on whether any changes in small intestinal function occur in the setting of PD. Thorough assessment of small intestinal function is rendered very difficult because of its inaccessibility and length; undoubtedly, this has discouraged dedicated investigation. However, some information is available.

Orocecal transit time was shown to be markedly prolonged in 15 patients with PD when compared with 15 age- and sex-matched control individuals [26]. Yet, it must be recognized that this investigative method is a measure of combined gastric and small intestinal transit and does not assess small intestinal function in isolation. Small intestinal manometry has also been employed in the study of PD patients and abnormalities in small intestinal motor patterns have been demonstrated [27]. Small intestinal dilatation has also been observed radiographically [28].

In the laboratory, disruption of the migrating myoelectric complex has been documented in rats following administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), along with reduction in jejunal myenteric plexus dopamine levels [29]. Also in rats, salsolinol, a catechol dopaminergic toxin, does not appear to alter fasting small intestinal myoelectric activity, but it does block changes induced by gastric distension [30]. Studies that evaluate whether similar changes occur in PD have not been undertaken.

The recent development and employment of newer technologies, such as the wireless motility capsule and video capsule endoscopy [31], may permit the accumulation of more detailed information regarding small intestinal function in individuals with PD, but such studies have not yet been reported.

The clinical consequences of small intestinal dysfunction in PD, if it indeed occurs, have not been systematically investigated. Some individuals with PD experience a very uncomfortable abdominal bloating sensation, which is sufficiently severe at times to compel the anguished individual to loosen trousers, even when they are clearly not even tight. This typically develops during "off" periods and resolves with the re-emergence of levodopa benefit. It is conceivable that this uncomfortable sensation might be related to small intestinal dysmotility, but no study has actually addressed this issue. If there is an association, agents that accelerate small intestinal transit time (e.g., the serotonin-4 receptor agonist prucalopride) [32] might provide symptomatic relief for patients with these symptoms. Another potential consequence of delayed

small intestinal transit might be an alteration in intestinal nutrient absorption. This also has not specifically been studied, but some recent investigations have suggested possible roles for both small intestinal bacterial overgrowth (SIBO) and *Helicobacter pylori* infection (which occurs primarily in the stomach, but may also cause duodenal ulceration) in producing problems for persons with PD.

Individuals with impaired intestinal motility are at risk for the development of SIBO. Recently, Gabrielli et al. [33] documented the presence of SIBO in 54% (26/48) of patients with PD, compared with only 8% (3/36) of a comparably aged control group. The presence of SIBO correlated with disease severity, as measured by both Hoehn and Yahr stage and UPDRS-III score. They, too, suggested that SIBO might be responsible for bloating and flatulence and speculated that SIBO-related malabsorption with consequent impaired nutrient absorption might help to explain the weight loss that often occurs in individuals with PD.

Basing his conjecture on a 1965 report by Strang [34] that there was a higher incidence of ulcers in patients with PD compared with controls and the subsequent identification of *H. pylori* as an etiologic agent for peptic ulcer disease (both gastric and duodenal) [35], Altschuler hypothesized that *H. pylori* might play a role in the genesis of PD [36]. In a subsequent extended series of reports, Dobbs et al. have suggested that *H. pylori* infection triggers an autoimmune response, which may be further potentiated by the development of SIBO, that may initially damage the ENS and subsequently be transmitted to the central nervous system and produce PD (for review see [37]). Although this theory has not been widely accepted, a recent epidemiological study using nationwide Danish registers provided increased fuel for the idea by demonstrating that prescriptions for *H. pylori*-eradication drugs and proton pump inhibitors five or more years prior to the diagnosis of PD were associated with a 45% and 23% increased PD risk, respectively [38].

A role for *H. pylori* infection in producing erratic levodopa absorption within the duodenum with consequent motor response fluctuations has also been proposed [39, 40]. Subsequent clinical studies reported that eradication of *H. pylori* infection improved levodopa absorption, shortened the delay to turning "on" and lengthened "on" time in patients with levodopa-induced motor fluctuations [41, 42]. It has been speculated that *H. pylori* may interfere with levodopa absorption as a consequence of delayed gastric emptying, gastroduodenal inflammation, or even by direct utilization of levodopa by *H. pylori* itself [42, 43]. A recent review, however, concluded that there is insufficient evidence that *H. pylori* eradication improves absorption of levodopa and improves motor symptoms [44].

Colon

Anatomy and Physiology

The colon, approximately 1.0–1.5 m in length in adults, is composed of the same two muscle layers—circular and longitudinal—found in the small intestine [20, 45]. The ileocecal valve, which divides the colon from the small intestine, is not a true sphincter but still effectively regulates colonic filling and prevents colo-ileal reflux. The colon stores material marked for excretion and performs an important role in the regulation of fluid, electrolyte, and short-chain fatty acid absorption. It can increase fluid absorption up to fivefold in appropriate circumstances. As in the stomach and small intestine, ICCs perform a pacemaker function in the generation of pressure waves that regulate colonic motility. Motor control of colonic motility is mostly mediated directly through the ENS with modulation via the autonomic nervous system. Parasympathetic innervation of the ascending and transverse colon is vagal in origin, whereas the descending and rectosigmoid regions receive their innervation by the pelvic nerves. Sympathetic supply to the colon originates in the thoracic spinal cord and reaches the colon via the inferior mesenteric and pelvic plexuses. Sympathetic activity produces vasoconstriction of mucosal and submucosal blood vessels, downregulates motility, and inhibits secretion (thus limiting water loss);

parasympathetic activity increases enteric motor activity and colonic motility [45].

Colonic Dysfunction in PD

To the lay public, constipation is a somewhat nonspecific term that may connote both decreased bowel movement frequency (usually with hard stool) and difficulty completing a bowel movement, often with excessive straining, sometimes with inability to evacuate fecal contents entirely, and occasionally with associated pain [46]. However, these two problems are actually quite different, with distinctive physiology and clinical characteristics; hence, a separate classification and discussion of each is needed to fully understand bowel dysfunction in PD. Decreased bowel movement frequency is primarily a consequence of colonic dysmotility and is discussed in this section, whereas defecatory dysfunction is primarily an anorectal anomaly and is discussed in the following section.

Divergence between the public concept and formal medical definition of what constitutes normal bowel movement frequency has also evolved in recent years, representing a source of confusion and sometimes consternation, both within the literature and inside the clinic. In the past, it was standard to label anything less frequent than a daily bowel movement as abnormal, constituting constipation, and this continues to be the concept embraced by many patients, particularly the elderly. The current formal medical boundary of constipation (or colonic inertia), however, has been redefined as fewer than three bowel movements weekly. Some investigators have employed an even more strict definition of constipation as one or fewer evacuations per week [47, 48]. Clinicians realize that not all patients are willing to accept the medical establishment's wisdom in this regard. To further complicate matters, the observation has also been made that estimations of bowel movement frequency reported by patients often conflict with their own diary records, typically in the direction of underestimating frequency [49].

Recognition of this change in what actually constitutes normal bowel movement frequency is important when reviewing reports in the medical literature of constipation in PD. Estimates of the percentage of patients with PD experiencing constipation have descended from the 50–67% range of earlier reports to levels of 20–29% in more current publications. In 1958, Schwab and England reported the presence of constipation in two-thirds of their patients [50], whereas in 1965, Eadie and Tyrer noted that 51% of their study sample of patients with PD did not have daily bowel movements, compared with 13% of their controls with orthopedic disease [2]. They also reported that over 50% of their patients were using laxatives on a regular basis. In notable contrast, using a definition of constipation as fewer than three bowel movements per week, Edwards et al. reported in 1991 the presence of constipation in only 29% of their 98 patients with PD in comparison to 10% of their spousal controls [4]. Siddiqui et al. found its presence in only 20% of patients with PD in their 2002 survey report [51]. In contrast, in a group of PD patients studied recently by Stocchi et al., bowel movement frequency of fewer than three times per week was described by 77% of the 17 patients [52]. The explanation for this divergence is not readily apparent.

In survey studies, the presence of constipation in PD has correlated with disease duration and severity [2, 53]. However, in clinical practice, it is not unusual for patients with PD to recollect the development of some degree of bowel dysfunction even prior to the appearance of the more typical motor features of PD [8]. Constipation occurring early in the course of PD has also been documented by Bassotti et al. [47].

A report derived from data accumulated in the Honolulu-Asia Aging Study has propelled this a step further by suggesting that diminished bowel movement frequency may actually constitute a risk factor for PD development [54]. An association was documented between the frequency of bowel movements and risk of developing PD. Men who reported a bowel movement frequency of less than one per day were found to have a risk of developing PD that was 2.7 times greater than

men who had daily bowel movements and fourfold higher than those with two or more bowel movements daily. The same group of investigators subsequently have reported an association between reduced bowel movement frequency and the presence of incidental Lewy bodies [55] and between reduced bowel movement frequency and reduced substantia nigra neuronal counts (which was independent of the presence of Lewy bodies in the substantia nigra or locus ceruleus and a clinical diagnosis of PD) [56].

Other investigators have added to the recognition that constipation may constitute a risk factor for the development of PD. Using the medical records-linkage system of the Rochester Epidemiology Project in a study involving 196 case-control pairs that included both men and women, Savica et al. reported that constipation occurring as early as 20 or more years before the onset of motor symptoms is associated with an increased risk of PD and may represent a premotor manifestation of the disease [57]. In another study that identified 402 incident female PD cases drawn from the Nurses' Health Study and 156 male PD cases from the Health Professionals Follow-up Study, Gao et al. found that men who have a bowel movement every 3 days or less have an almost fivefold (4.98) increased risk of developing PD in the next 6 years; the corresponding risk in women was 2.15 [58].

Although these findings may simply reflect the fact that the appearance of constipation can precede the emergence of conventional PD motor features, other explanations are possible. Perhaps, rapid transit of material through the GI tract, implied by frequent bowel movements, limits exposure to, and absorption of, toxic substances capable of damaging dopaminergic neurons. Further studies investigating this possibility might prove to be very interesting and informative.

Considerable evidence has now accumulated that implicates slowed colon transit of fecal material as the physiological basis for decreased bowel movement frequency in PD. Employing radiopaque markers, colon transit studies have indicated that as many as 80% of persons with PD may have abnormally prolonged transit times [59]. Jost and Schimrigk initially reported an average colon transit time (CTT) of 5–7 days (120–168 h) in a group of 20 persons with PD, [59] and in a subsequent study of 22 subjects in whom CTT could be measured, the average time was 130 h [60]. Edwards et al. also documented slowed CTT in a study of 13 participants with PD, but the CTT they documented was considerably shorter than that noted by Jost and Schimrigk, finding a mean of 44 h, compared with 20 h in spousal controls [7]. A more recent study further confirms that CTT is slowed in PD, although the times reported (82.4 min in PD patients and 39 min in controls) appear to be incorrectly labeled in minutes rather than hours [61]. Therefore, despite the variance in average CTT in published reports, there seems to be ample agreement that CTT is prolonged in PD. The reason for the widely varying CTTs reported by the various investigators is not clearly evident.

In addition to the earlier survey studies, another study by Jost and Schimrigk in recently diagnosed patients with PD seems to support the idea that constipation becomes more severe as PD progresses. In this study, the average CTT in patients with PD was 89 h [62], in comparison to the considerably longer CTTs reported in their earlier studies cited previously, which included individuals with more advanced disease.

Prolongation of CTT in untreated individuals strongly suggests that it develops as part of the disease process itself; yet the demonstration by Ashraf et al. shows that not all persons with prolonged CTT experience clinically symptomatic constipation [63]. This evidence seems to indicate that delayed CTT may not be the sole determining factor for stool frequency. Other factors certainly may have a role in the genesis of constipation in some individuals, but it is not clear what these factors might be. Medications—not only anticholinergic drugs but also levodopa and dopaminergic agonists—may be responsible for diminished bowel movement frequency in some individuals, but not all individuals with PD who experience constipation are receiving these medications.

The pathophysiologic basis of constipation in PD has not been definitively defined. Evidence has accumulated for both central and peripheral

mechanisms; it is very probable that both are involved.

Animal studies that employ dopaminergic agents have demonstrated that activation of central D1 and D2 receptors stimulates colonic motility by increasing colonic spike bursts [64]. In these studies performed in rats, Bueno et al. found that intracerebroventricular injection of the selective D1 agonist, (+)SCH 23390, the selective D2 agonist, quinpirole, and dopamine itself increased the frequency of colonic spike bursts (indicating increased colonic motility) by 54.8%, 68.7%, and 48.7%, respectively. Additional evidence favoring a central site of action was provided by the absence of any change in colonic spike burst frequency when these agents were injected intraperitoneally. It has been suggested that CNS influences on both bladder and colonic function may be coordinated through Barrington's nucleus (also known as the pontine micturition center), which lies adjacent to, or possibly within [65], the locus ceruleus in the pons [61, 66–68]. Utilizing the pseudorabies virus, Pavcovich et al. were able to demonstrate transynaptic labeling from the distal colon of neurons in Barrington's nucleus [66]. Using similar techniques, other investigators have identified additional sites within the CNS as being potentially involved with central regulation of colonic function, including neurons within the dorsal motor nucleus of the vagus, nucleus of the solitary tract, nucleus ambiguous, and area postrema [68]. Also, it appears that the colonic connections with Barrington's nucleus travel via bulbospinal pathways, whereas connections with the other medullary nuclei are mediated through vagal pathways [68].

Evidence favoring a peripheral basis for slowed colonic transit in PD has arisen in recent years as well. Numerous investigators have noted changes within the ENS in PD. In 1987, Kupsky et al. were the first to document the presence of Lewy bodies in the colonic myenteric and submucosal plexuses of individuals with PD [69]. This was subsequently confirmed by several other groups [70–72], who found Lewy bodies in both dopaminergic neurons and in those containing vasoactive intestinal peptide. Using immunohistochemical methods, Singaram et al. [72] studied colon tissue removed from 11 persons with PD, nine at the time of colectomy undertaken for intractable constipation, and two at autopsy. Lewy bodies were primarily evident in myenteric neurons and only rarely in the submucosal plexus. With immunohistochemical methods, Singaram et al. were also able to demonstrate a very striking reduction in the number of dopaminergic neurons in the colonic myenteric plexus of patients with PD in comparison with both healthy controls and individuals with idiopathic constipation [72].

In more recent years and using more modern techniques, much additional information has accumulated that demonstrates the presence of PD pathology within the ENS in individuals with PD. Braak et al. led the way in this regard by demonstrating the presence of α-synuclein immunoreactive aggregations in the gastric myenteric and submucosal plexuses [73]. Subsequently, Lebouvier et al. documented the presence of phospho-α-synuclein immunoreactive neurites within the submucosal plexus of biopsy samples taken from the ascending colon of four out of five individuals with PD during routine colonoscopy but not from biopsy samples taken from control individuals or persons with chronic intractable (presumably idiopathic) constipation [74]. In a subsequent report, the same group of investigators reported the presence of Lewy pathology in the form of Lewy neurites immunoreactive for phosphorylated α-synuclein within the submucosal plexus in 21 of 29 (72%) PD patients biopsied during colonoscopy, but in no controls [75, 76]. Beach et al. also demonstrated the presence of phosphorylated α-synuclein histopathology within the ENS of autopsied PD patients and noted a marked trend for a diminishing rostrocaudal gradient [77]. Using limited, unprepped flexible sigmoidoscopy rather than full colonoscopy, Shannon et al. demonstrated α-synuclein immunostaining in the lamina propria of the colonic submucosa in all nine early, untreated PD patients they studied in whom adequate tissue was obtained [78]. They also demonstrated increased intestinal permeability in these same individuals and suggested that this might result in

increased exposure to proinflammatory bacteria and bacterial products such as endotoxins, which might then initiate a cascade of proinflammatory events leading to α-synuclein deposition and subsequent development of PD in genetically susceptible individuals [79].

Other abnormalities within colonic tissue have also been documented in individuals with constipation owing to problems other than PD. Serotonin receptor immunoreactivity was recently found to be reduced in colonic tissue (specifically the left colon) of patients who underwent subtotal colectomy for treatment of colonic inertia when compared with those where colectomy was performed for colon carcinoma [80]. Other studies of patients with chronic idiopathic intestinal pseudo-obstruction or slow transit constipation have shown a marked pan-colonic loss of ICCs, which are believed to function as pacemaker cells in the gut [81, 82]. Whether these abnormalities are also present in patients with PD suffering from constipation is unknown.

Treatment of Colonic Dysmotility

The treatment of slow transit constipation in PD can be difficult and frustrating, both for the patient and physician. Formal studies in this patient population are largely lacking with the consequence that treatment is mostly based on clinical experience rather than rigorous clinical investigation [83]. In fact, treatment of parkinsonian constipation has generally simply mirrored practices that are employed in treating idiopathic constipation, and only recently some clinical trials focusing on patients with PD have been carried out. Increased dietary fiber reduces CTT in normal individuals [84], most likely by increasing bulk within the colonic lumen. In their survey study, Edwards et al. [4] had each participant complete a food frequency dietary questionnaire that permitted calculation of the average daily intake of dietary components, including fiber. They found that the mean daily fiber intake in patients with PD was noticeably lower (11 g in untreated patients; 14 g in those on antiparkinsonian therapy) than the 15–20 g generally recommended [4, 85]. However, no distinction was made between constipated and non-constipated individuals regarding fiber intake. In one of the few formal controlled clinical trials performed to date in PD patients, psyllium was found to be effective in increasing stool weight and frequency, but did not alter CTT [63]. Improved motor function, presumably reflecting increased levodopa bioavailability, has also been documented with increased fiber intake [86]. Fiber supplementation can also be achieved by concoctions of high fiber foodstuffs (e.g., a combination of applesauce, unprocessed wheat bran, and prune juice) consumed on a daily basis. It is important to couple increased fiber consumption with adequate fluid intake in treating constipation. A 15 g daily fiber intake, along with at least 1.5 L of water, has been recommended [85]. Adding a stool softener (e.g., docusate) can also be useful. Daily consumption of probiotics, such as *Lactobacillus casei* strain Shirota, may improve stool consistency and reduce bloating, abdominal pain, and the sensation of incomplete emptying in patients with PD [87].

If increased fiber and fluid intake does not sufficiently control constipation, an osmotic laxative, such as lactulose or sorbitol, can be a very useful next step. These agents increase colonic osmotic pressure, which results in increased water content, and consequently bulk, of the stool. A 30-mL lactulose dose once or twice daily can be used initially with subsequent downward titration of dosage if necessary. Because sorbitol is less expensive than lactulose, it might be considered as a cost-effective alternative [88]. The effectiveness of polyethylene glycol (macrogol) also has been demonstrated in patients with PD [89, 90], including in a randomized, double-blind, placebo-controlled trial [91]. Its routine use in large volumes as a colon-cleansing agent prior to colonoscopy is well established, but in individuals with PD experiencing chronic constipation, polyethylene glycol with (e.g., Movicol) or without electrolytes (e.g., Miralax) can be administered in much smaller amounts than those used in conjunction with colonoscopy on a regular or even daily basis. Polyethylene glycol is considered “likely efficacious” for the treatment of constipation in PD by the Movement

Disorder Society Task Force on Evidence-Based Medicine [92]; the Quality Standards Subcommittee of the American Academy of Neurology concluded that polyethylene glycol "possibly improves" and "may be considered to treat" constipation in PD [93].

Patients often turn to irritant laxatives, such as senna-containing compounds, which are available without prescription for relief from constipation. These compounds are often effective, but daily use should be discouraged because of concern regarding potential myenteric plexus injury as a consequence of extended use, even though such damage has not actually been definitively proven. When other measures fail, enemas can be administered as necessary to the patient suffering from PD with severe constipation.

The value of prokinetic agents in the treatment of slow-transit constipation is uncertain. Cisapride is a serotonin (5-HT4) agonist that activates 5-HT4 receptors on motor neurons in the ENS, thus enhancing acetylcholine release and stimulating propulsive motility [94]; it was reported to be beneficial in initial short-term studies in patients with PD, but was less convincingly effective in longer-term studies [95, 96]. Moreover, cisapride is no longer available because of the potential risk of cardiotoxicity. The same fate befell tegaserod, another 5-HT4 agonist that was reported to be effective in improving constipation in two small studies involving patients with PD before cardiotoxicity also prompted its removal from use [97, 98]. Mosapride is a 5-HT4 agonist that does not block potassium channels or dopamine receptors; it has been studied and reported to reduce CTT in a small number of patients with PD [99]. Prucalopride, another 5-HT4 agonist, also has been shown to be effective as a prokinetic agent in patients with severe chronic constipation [32, 100], but its effect in individuals with PD has not been specifically reported. Lubiprostone, a chloride channel activator that promotes intestinal transit by enhancing fluid secretion into the intestinal lumen, is effective in the long-term treatment of chronic constipation [101]; clinical trials in individuals with PD have been initiated but results have not yet been published.

Anecdotal reports have described the efficacy of the cholinomimetic agents, pyridostigmine [102], and neostigmine [103], in the treatment of constipation in PD, but no formal studies of these compounds in patients with PD have been reported. A pilot study of pyridostigmine, administered for 6 weeks to ten patients with autonomic neuropathy, demonstrated improvement in colon transit in some patients; response to neostigmine predicted improvement with pyridostigmine [104]. In these reports, pyridostigmine was taken orally; neostigmine was administered intravenously.

The neurotrophic factor, neurotrophin-3, improved bowel movement frequency, completeness, and ease of passage in a randomized, double-blind study of patients with functional constipation [105]. The efficacy of neurotrophin-3 in a small double-blind study of PD patients with constipation also has been reported [106]. However, further development of neurotrophin-3 was subsequently abandoned.

Misoprostol, an analogue of prostaglandin, can stimulate colonic motility, particularly in the left colon, and has been reported to be effective in alleviating chronic constipation, although adverse effects may pose problems at higher doses [107, 108]; however, it has not been specifically studied in patients with PD [108]. In a small randomized, double-blind trial of 16 patients with chronic idiopathic constipation, colchicine was effective in accelerating colon transit and increasing bowel movement frequency [109]; it also has been reported anecdotally to be effective in treating constipation in PD [110] but further studies in PD patients have not been published. Whether other substances, such as ghrelin agonists, motilin agonists, and cholecystokinin A receptor agonists, will prove to be helpful in treating constipation in PD remains to be determined [111].

Non-pharmacologic approaches to the treatment of slow transit constipation, such as biofeedback therapy, may also be useful, especially in persons who also have outlet dysfunction [112], but have not been studied specifically in individuals with PD. Surgical approaches, such as subtotal colectomy, are considered only as a last resort and rarely are indicated in patients with constipation due to PD.

Complications from constipation may progress beyond simple discomfort in patients with PD. Constipation with fecal impaction triggered the malignant syndrome in an individual with PD, even though antiparkinson medication had not been discontinued [113]. Other potentially life-threatening complications of slow transit constipation in PD include megacolon [28, 85, 114, 115], intestinal pseudoobstruction, volvulus, and even bowel perforation [4, 9, 114, 115]; surgical treatment in the form of colectomy may be necessary in these situations.

Anorectum

Anatomy and Physiology

The rectum is a storage reservoir in which feces are held until a convenient opportunity occurs to evacuate its contents. The internal and external anal sphincter muscles are tonically contracted, thus preventing leakage of rectal matter as feces accumulate. The longitudinal smooth muscle layer, which in the colon had been concentrated into the muscle bands called *taenia*, spreads out in the rectum into an encircling sheath. The internal anal sphincter (IAS) consists of smooth muscle that is continuous with the circular muscle layer of the rectum [45]. In contrast, the external anal sphincter (EAS) is a band of striated muscle distal to the IAS. The IAS is under autonomic control via the pelvic plexus; the EAS is controlled by motor neurons in the sacral spinal cord through the pudendal nerve. The puborectalis muscle is also thought by many to contribute to the maintenance of fecal continence by means of tonic contraction that pulls the rectum anteriorly, forming an anorectal angle of approximately 90–95° that impedes rectal emptying [116, 117]. The anorectal angle formed by puborectalis contraction may be especially important for the retention of semisolid (as opposed to liquid) material [118]. The erect position may provide an additional contribution to the maintenance of fecal continence by further sharpening the anorectal angle to about 80° [117]. However, it should be noted that the importance of this anorectal angle in the maintenance of continence is not universally accepted [116, 119].

The act of defecation is characterized by relaxation of the two anal sphincters and the puborectalis muscle, which results in a straightening or opening of the anorectal angle. Also, it is defined by contraction of the glottic, diaphragmatic, and abdominal wall muscles, which elevates intra-abdominal pressure and encourages evacuation of the rectal contents.

Anorectal Dysfunction in PD

Anorectal dysfunction, characterized by excessive straining, often with a sense of incomplete evacuation and sometimes pain, is actually the more prevalent form of bowel dysfunction in PD. Edwards et al. [4] differentiated between decreased bowel movement frequency and defecatory dysfunction and noted the latter in 67% of patients with PD, compared with only 29% who reported decreased bowel movement frequency. As with slow transit constipation, anorectal dysfunction can also appear early in the course of PD [47].

Clinical neurophysiological and radiographical studies have shed considerable light on the pathophysiological basis for disordered defecation in PD. The act of defecation is not solely dependent on sphincter and puborectalis relaxation, but also demands the coordinated contraction of numerous additional muscles and muscle groups while the sphincters relax to effectively accomplish evacuation. It is now clear from studies, such as anorectal manometry, anorectal electromyography, and defecography, that this does not always occur in individuals with PD, and dyscoordination may actually be the rule. In one study, abdominopelvic (or pelvic floor) dyssynergia was present in over 60% of patients with PD [47].

Lower basal sphincter pressure and difficulty in maintaining sphincter pressure have been documented during anorectal manometry in patients with PD, as have some more distinctive abnormalities, including unusual phasic contractions of the sphincter muscles during voluntary contraction and a “paradoxical” hypercontractile response of the external anal sphincter and

puborectalis muscles on rectosphincteric (rectoanal inhibitory) reflex testing, where sphincter relaxation (rather than contraction) is expected [7, 120, 121]. These abnormalities of anorectal muscle function appear to be distinctive for PD, not simply a general reflection of constipation. Ashraf et al. studied 15 patients with PD, nine persons with idiopathic constipation, and eight control individuals and found these abnormalities only in the patients with PD [122]. Abnormalities on anorectal manometry may already be evident in individuals with early, untreated PD; in one recent study, results of anorectal manometric testing were abnormal in 63% (12/19) of such patients [123].

Failure of the EAS and puborectalis muscles to relax during attempted defecation, producing functional outlet obstruction, was originally observed in patients with PD by Mathers et al. [124, 125] and subsequently confirmed by others [7]. It has been suggested that this is a focal dystonic phenomenon [124, 125]. Moreover, fluctuation in the severity of the anorectal abnormalities in response to dopaminergic medications has been documented with deterioration during "off" periods and improvement in function when patients are "on" [120]. However, paradoxical sphincter and puborectalis contraction during attempted defecation may also occur in healthy controls, leading some investigators to question its correlation with difficult defecation [126, 127].

Evaluation of defecation with rectoanal videomanometry has provided objective confirmation of the subjective sense of incomplete emptying during defecation that is experienced in many patients with PD by demonstrating that incomplete defecation with the presence of significant post-defecation residuals is common in PD [61]. Dynamic transperineal ultrasound has recently been reported to be a simple and accurate method for evaluating the pelvic floor in individuals with defecatory dysfunction [128]. This technique has not yet been applied in the study of patients who have PD. MRI defecography is yet another technique that potentially may provide important information regarding anorectal dysfunction in PD [129], but no studies using this technique in PD patients have yet been reported.

Treatment of Anorectal Dysfunction

It is important to recognize and differentiate anorectal difficulties from colonic inertia when assessing bowel dysfunction in patients with PD. Although softening the stool by various measures will make it easier to expel, such measures do not correct the fundamental defect in muscular coordination that produces the problem. In fact, laxatives and other measures that hasten the arrival of stool to the rectum may sometimes accentuate the problem, creating a situation that might be likened to a frantic crowd trying to leave a burning building through a narrow, or even blocked, exit. Unfortunately, the array of treatment options for anorectal dysfunction is somewhat limited.

Some evidence suggests that dopaminergic medications may improve anorectal function in individuals with PD. As noted previously, improvement in anorectal manometric and electromyographic measures of anorectal function during "on" periods with deterioration during "off" episodes has been described [120]. Additionally, Mathers et al. found some degree of improvement in both electromyographic and proctographic measures of anorectal function following apomorphine injections in most of the patients they studied [125], as did Edwards et al. in some (but not all) of the eight patients with PD they studied with apomorphine [130]. Occasional patients on levodopa will also report that it is easier for them to have a bowel movement when they are "on" than when they are "off." Improvement of anorectal function following institution of levodopa therapy also has been objectively demonstrated by Tateno et al., who documented reduction in the amplitude of paradoxical sphincter contraction during defecation and reduction in post-defecation residuals in individuals with PD [131].

Albanese et al. have pioneered yet another approach to the treat outlet obstruction-type constipation in PD, successfully injecting botulinum toxin into the puborectalis muscle under transrectal ultrasonographic guidance [132, 133]. In their full study [133], 18 patients received the injections and were evaluated by means of anorectal manometry, defecography, and electromyography

at baseline and at 1 and 2 months following the injections. Resting anal tone and maximum voluntary contraction were unchanged, but anal tone during straining was reduced, and the anorectal angle during straining was widened. The duration of benefit was not clearly defined, but improvement in test parameters was still evident at the 2-month mark. In their earlier case report [132], improvement had waned by 12 weeks. In another open-label trial involving 18 patients, Cadeddu et al. noted symptomatic improvement in 56% (10/18); decreased tone during straining was evident on anorectal manometry and improvement in the anorectal angle during straining on defecography [134]. Although these results are encouraging, the risk for producing fecal incontinence is present with this procedure, and perianal thrombosis has also been reported [135].

Functional magnetic stimulation (FMS) also has been reported to be effective in ameliorating defecatory dysfunction in individuals with PD [136]. In this study, patients underwent a 3-week stimulation period of 20-min stimulation sessions twice daily. Significant improvement in the difference in the anorectal angle between resting and straining during evacuation, improvement in the changes in the pelvic floor muscles when straining downwards, and reduction in the amount of barium paste remaining in the rectum after evacuation all were documented. Patients noted increased frequency of bowel movements, reduced use of enemas or suppositories, reduced time to complete evacuation, and reduced frequency of difficult defecation. Improvement continued to be evident 3 months after the FMS intervention. Further study of this treatment modality will likely be forthcoming.

Behavioral techniques, such as defecation training and biofeedback measures, have been successfully employed in the treatment of outlet obstruction constipation [137, 138], but they have not been specifically examined in patients who have PD. Sacral nerve stimulation is a technique that might also conceivably have some application in patients with PD, but this also has not yet been evaluated. Surgical treatment (e.g., colectomy) is rarely necessary in patients with PD.

Fecal Incontinence

Fecal incontinence is considered to be uncommon in PD, but does occur [17, 18, 139]; in a recent questionnaire-based study, 9% of individuals with PD reported wearing protection against fecal incontinence, compared with 3.7% of partner/carer controls [139]. In some patients, fecal incontinence may be related to the presence of an abnormal cough reflex, characterized by a decrease (rather than the normal increase) in rectal sphincter tone with voluntary cough [123]. In others, the presence of fecal incontinence has been associated with laxative use [139]. An association of fecal incontinence with urinary incontinence also has been described in PD patients [53].

Conclusion

As awareness of the nonmotor features of PD has grown in recent years, it has become quite clear that intestinal dysfunction poses a significant problem for a considerable number of patients with PD. Understanding of the pathophysiological basis for this dysfunction is expanding, and more effective management measures are evolving. Recognition and definition of the two components of parkinsonian bowel dysfunction—slow-transit constipation and anorectal defecatory dysfunction—is beginning to foster the development of more effective management measures. However, much more remains to be learned.

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Impaired Sexual Function

11

Cheryl Waters and Janice Smolowitz

Abstract

The incidence of impaired sexual function in adults with Parkinson's disease (PD) is greater than in the general population. Studies have examined different aspects of sexual function among adults with PD and their partners. Comparison groups have included healthy adults matched for age and gender, as well as age-matched controls with chronic, nonneurological disease with motor impairment. Impaired sexual function in PD is most likely multifactorial. Depression, physical disability, and autonomic dysfunction may contribute to the increased prevalence of erectile dysfunction (ED) among men with PD. Given this multifactorial basis, clinicians should routinely assess patient needs. For women with PD, therapeutic interventions and impaired sexual function have not been adequately described. Further research is required to develop treatment for adults with PD and sexual dysfunction.

Keywords

Erectile dysfunction • Hyposexuality • Sexual dysfunction • Reduced libido • Sexual dissatisfaction • Decreased sexual activity • Impaired sexual function

Introduction

Impaired sexual function varies among the populations studied [1–12]. Advancing age is correlated with a decline in sexual activity [1–4, 13]. Sexual function may be altered by chronic illnesses [4, 14, 15]. The presence of impaired sexual function has been found in adults with PD and will be the focus in this chapter. Reports on sexual function in the general population are briefly discussed to provide an overview of the research on patients who have PD with impaired sexual function. Its physiology is briefly explained as a basis for potential therapeutic interventions.

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Impaired Sexual Function in the General Population

Emotional and physical illnesses and aging affect relationships and quality of life and are associated with impaired sexual function [1–5, 13–17]. In men, the repeated inability to achieve or maintain an erection firm enough for satisfactory sexual performance is defined as ED. The term impotence, which has been used interchangeably, describes diminished sexual desire and problems with ejaculation and orgasm that interfere with sexual function [18].

The National Health and Social Life Survey [6] (NHSLS) included 1,410 men between the ages of 18 and 59. Prevalence rates for ED were 7% for men 18–29, 9% for men 30–39, 11% for men 40–49, and 18% for men 50–59 years of age. The Massachusetts Male Aging study [1, 7] also found that sexual function decreased with age. The age-adjusted risk of ED was higher for men with diabetes, heart disease, hypertension, and men with lower education [7]. Studies conducted in the Netherlands, Spain, Germany, and Australia reported prevalence rates of ED between 11 and 33.9% [8–11].

Masters and Johnson characterized four sequential phases in the sexual response cycle: excitement, plateau, orgasm, and resolution [19]. A three-phase model consisting of desire, arousal, and orgasm was subsequently developed in which sexual desire triggers the sexual response cycle [20]. This model forms the basis for the DSM categorization of Sexual Desire Disorders, Sexual Arousal Disorders, and Orgasm Disorders. Hypoactive Sexual Desire Disorder (HSDD) is the persistent or recurrently deficient or absence of sexual fantasies and desire for sexual activity that causes marked distress or interpersonal difficulty [21]. When diagnosing HSDD, age, the context of the person's life, the physiological effects of a substance or a general medical condition and other Axis I disorders, except another sexual dysfunction, are considered.

The prevalence of low sexual desire and associated distress among women has been examined. Forty percent of women in the USA were concerned, and 12% were distressed by sexual problems [22]. Thirty-four percent of 1,134 Swedish women ages 18–74 years reported they experienced decreased sexual interest quite often or most of the time. Forty-three percent of these women reported this was a problem [23]. Witting et al. [24] examined the prevalence of low desire and associated distress in a population-based sample of 5,463 Finnish women ages 18–49 years. Five percent of participants experienced low sexual desire and 23% reported associated distress. Low sexual desire and its relationship to personal and relationship distress were evaluated in American women. Telephone interviews were conducted with 987 women, ages 20–65 years. Women were asked how frequently they thought about sex with interest or desire during the past month. Choices were: not at all, once or twice, once a week, several times a week, and at least once a day. Seven percent of women reported no sexual interest over the past 4 weeks. Women ages 20–35 years were more likely to view their lack of sexual thoughts as distressing to the relationship and to their own sexuality compared with women aged 36 and older [25].

Reports of Sexual Function Among Adults with PD

Validated, self-report questionnaires and interviews were used when evaluating different aspects of sexual function. The subjects were men and women with PD, couples with one spouse affected by PD, men with PD, and women with PD. Comparison groups have included healthy adults matched for age and gender, as well as age-matched controls with chronic, non-neurological disease with motor impairment. As yet, there are no studies with quantitative measures that objectively evaluate sexual function.

Sexual function in men and women with PD has been assessed in four studies. Thirty-six men and 14 women with idiopathic PD and no evidence of mental deterioration completed a structured questionnaire that addressed sexual activity, function, and libido [26]. Mean age of participants was 57.9 years (standard deviation [SD]

10.1 years); mean disease duration was 7.01 years (SD 3.9 years). Sixty-eight percent of participants reported decreased sexual activity, and 26% described decreased libido. ED was reported in 38.8% of men and described more frequently in men over 61 years old.

One hundred and twenty-one adults with PD and 126 controls matched for age and gender participated in a study that compared opinions about public sexual attitudes, emotion from personal sexual practice, personal sexual function, and general health perception [27]. Adults with PD were recruited from a PD self-support organization and physicians' patient lists, and the controls were enlisted for participation from a community registry. A physician investigator examined the adults with PD and reviewed their medical records. The physician completed the motor portion of the Unified Parkinson's Disease Rating Scale (UPDRS) [28] and the Hoehn and Yahr score [29]. Participants were interviewed about disease variables and sociodemographic data. In the presence of an investigator, participants completed a 33-item multiple-choice self-report questionnaire that addressed various aspects of sexuality [30], a depression scale [31], and the Wechsler Adult Intelligence scale [32] to measure the influence of education. All subjects reported they were currently involved in heterosexual relationships. Frequency of intercourse did not differ between adults with PD and the controls. The average age of adults with PD was 45 years. Adults with PD reported greater disagreement with present attitudes about sexuality than did controls. Significantly, more adults with PD were unemployed and depressed, and this group indicated greater dissatisfaction with their personal sexual lives than controls. Greater sexual discontent was described by adults with PD and concomitant depression than by nondepressed adults with PD. In men with PD, a higher level of dissatisfaction was reported in comparison with women. Depressed, unemployed adults with PD were more often unhappy with their current sexual relationship, felt lonely more often, and were less able to enjoy flirtation. The subjects with PD were less satisfied with their lives, felt older than their stated age, and perceived their health to be poorer than the controls.

Interviews with 25 patients with PD (15 men and 10 women) younger than age 56 were conducted to describe sexual function in a sample of young adults with PD [33]. The interview and physical examination were conducted by a female neurologist. Interview content discussed libido, sexual activity, orgasm, penile/vaginal sensibility, and changes in sexual activity owing to motor symptoms. Women were interviewed regarding vaginal dryness and pain, whereas ED was discussed with men. Both men and women were questioned about the influence of urinary incontinence on their sex lives and their partner's acceptance of their physical disability. Depression was measured with the Beck Depression Inventory (BDI) [34]. The mean age of participants was 50.3 years, and the mean age of disease onset was 44.7 years. Libido changes were not statistically different between men and women, although women reported more marked changes in libido. More women reported changes in sexual activity than men. Causes of sexual dysfunction reported by men included ED ($n=3$), reduced libido after the initiation of medication ($n=2$), change in orgasm ($n=2$), and lack of partner's acceptance ($n=1$). Causes of sexual dysfunction reported by women included decline in libido after the initiation of medication ($n=4$), change in orgasm ($n=3$), vaginal dryness ($n=3$), sexual dysfunction from rigidity ($n=5$), and lack of partner's acceptance ($n=1$). Urinary incontinence was reported by four women and four men. One woman reported major depression on the BDI; she was not sexually active. Of the participants in this sample, 55% of optimally treated patients with PD reported changes in sexual function.

Hand et al. [35] examined self-reported sexual and relationship problems among men and women with PD. Participants completed the UPDRS [28], the PD questionnaire-39 [36], the Mini Mental State examination [37], and the Szasz Sexual Functioning scale [38]. Participants in long-term relationships and their partners completed the Golombok Rust Inventory of Marital State [39]. Of the 82 men and 85 women who attended the PD service and were invited to

participate, 46 men and 42 women agreed. Of this group, 47 participants were married, 36 were widowed, 3 were single, and 2 were divorced. Seventy-seven participants lived at home and 11 lived in residential care facilities. Twenty-five percent of participants reported concern about sexual function. Concern was described more frequently by men ($p=0.001$) and younger people with PD ($p=0.001$). Men with PD and adults with PD who had increasing functional problems reported higher levels of relationship problems. An association was not found between disease duration, anxiety, and depression. The authors concluded that sexual and relationship problems were common, but patients did not voluntarily discuss these concerns.

Twenty-two men and 23 women with PD [40], consecutively seen at the outpatient neurology clinic at a University hospital, were interviewed by one examiner using the Arizona Sexual Experiences (ASEX) scale [41]. This scale was also given to age-matched healthy controls. An experienced neurologist examined all PD patients and performed Hoehn and Yahr [29] staging. All study participants were interviewed by a psychiatrist. Depression and anxiety were assessed using the Hamilton Depression rating scale [42] (HAM-D) and the Hamilton Anxiety scale [43] (HAM-A). All study participants were assessed for dementia. Those with mini-mental status examination [37] scores less than 20 were excluded from participation.

The mean age of women and men with PD was 67.52, SD 8.51years and 61.59, SD 8.52 years, respectively. No statistically significant differences between patients and control subjects were found for age, highest level of education completed, marital status, having a partner, or the presence of a chronic disease other than PD. Of the 45 PD patients, 9 were diagnosed with major depression, 3 had depression due to PD, 6 had general anxiety disorder, 4 had obsessive compulsive disorder, 1 had simple phobia, and 1 patient had bipolar disorder. The HAM-A and HAM-D scores were higher for PD patients compared with control subjects. Women with PD reported reduced sexual drive and lower satisfaction with orgasm compared with the control group. Men with PD reported easier orgasms than healthy controls. Regression analysis demonstrated increased age and female gender were predictive of reduced sexual drive and arousal. Among study participants with PD, sexual dysfunction was not associated with stage of disease or severity of anxiety and depression.

Perceptions of patients and spouses pertaining to the affected partner's sexual ability were described in two studies [44, 45]. Thirty-six men and 14 women with PD, along with their spouses, were recruited from a movement disorders clinic to participate in an investigation of the relationship of autonomic nervous system (ANS) dysfunction, depression, medication, motor disabilities, and sexual difficulties [44]. Patients and their spouses completed separate self-report questionnaires and the Geriatric Depression Scale [46] as well as a questionnaire that addressed degree of sexual interest, arousal, and performance skills [47]. They also answered questions about medical history, medications, and symptoms of increased sweating, constipation, or urinary difficulty to evaluate ANS function. ANS dysfunction was defined as the minimum of two of the following symptoms: increased sweating, constipation, or urinary difficulty. Spouses completed a questionnaire regarding sexual interest, arousal, and performance of the affected spouse, as well as their own sexual interests. Patient mean age was 67.3 years, and the mean duration of disease was 6.96 years. Of male patients, 80% stated that their sexual frequency had decreased since the PD diagnosis, and 44% reported reduced sexual interest and drive. Fifty-four percent were not able to achieve an erection; only 14% were able to maintain an erection. Depression was present in 19%, and sexual dysfunction was indicated in 1.7% of these patients. ANS dysfunction was prevalent in 69%, and of these, 70% reported problems with sexual function. Among female patients, 79% stated that their sexual frequency had decreased since diagnosis, 71% reported a decline in sexual interest, and 38% were unable to achieve orgasm. Vaginal dryness during intercourse was found in 38%, whereas 67% felt it was more difficult to be aroused. Frequency of orgasm was reduced since diagnosis in 75%. Depression was present in only one woman. Of all the couples, 78% shared the same bed. A reduction in the affected partner's sexual

interest was noted by 54% of the spouses, and 54% of spouses reported loss of interest in having sexual relations with their partner affected by PD.

The prevalence of sexual dysfunction in patients with PD and their partners was surveyed in young-onset patients with PD and their spouses. In a weekend residential meeting in the UK [45], participants were asked to describe the nature of sexual difficulties experienced and the relationship between sexual dysfunction, psychological morbidity, psychosocial stress, physical disability, and ANS dysfunction. A total of 44 couples attended the meeting; 34 couples and 4 spouses of patients who had PD participated in the study. Questionnaires were completed by 23 male and 11 female patients. Data describing age of PD onset, current medications, and physical disability were collected independently from the patient and partner. Sexual function was assessed by the Golombok Rust Inventory of Sexual Satisfaction [48], a 28-item survey with male and female forms. Marital function was assessed using the Golombok Rust Inventory of Marital Status [39]. Depression and anxiety in patients and spouses were reviewed with the BDI [34] and the State Trait Scale Anxiety Inventory [49]. Patients completed an acceptance of illness scale [50] and their spouses completed a caregiver strain index [51]. ANS dysfunction was rated on a questionnaire, and three neurologists rated the likelihood of ANS dysfunction based on the answers. Male patients (mean age 51.9 years; SD 8.9 years) were notably older and had a later onset of disease than female patients (mean age 44.7 years; SD 7.2 years). A statistically significant difference was not found in the duration of illness or degree of disability for male and female patients. Sexual dissatisfaction and the perception that sexual problems existed were primarily in couples where the patient was male. Marital dissatisfaction was highest in male patients and their partners. BDI scores were highest in the male and female patient groups: 36% of the female patients and 29% of the male patients were depressed. Of female spouses, 15% were depressed; female spouses demonstrated significantly greater trait anxiety than male spouses ($p<0.01$). No major differences were demonstrated in caregiver strain and acceptance of illness. Regarding ANS, 39% of male and 54% of female patients were rated with possible or probable dysfunction. Singer [52] reported on ANS dysfunction, including sexual dysfunction, in 48 men with PD. The patients with PD were compared with 32 healthy elderly men. ED affected 60.4% of men with PD versus 37.5% of controls. ED was not associated with other autonomic features, duration of levodopa therapy, or age.

Erectile function is controlled by the ANS. Nonmotor symptoms associated with ANS dysfunction have been shown to predate the development of clinical PD. The Health Professionals Follow-up Study [53] sought to determine if ED preceded the onset of PD symptoms. This cohort study was established in 1986. In 2000, men who did not have PD at baseline completed a retrospective questionnaire with questions about ability to have and maintain an erection adequate for intercourse during each of the previous study periods. Participants rated erectile function for each study period as very poor, poor, fair, good, or very good.

The primary analysis examined the relationship between erectile function prior to 1986 and PD risk from 1986 to 2002. Secondary analyses examined the association between erectile function at different follow-up periods and the risk of PD during the following 4-year period. Potential interactions between erectile function, age greater than or less 60 years, smoking status, BMI, and report of diabetes mellitus were considered in the analysis. Forty-seven men diagnosed with PD at the time of study enrollment were excluded from the analysis.

The questionnaire was completed by 32,363 men. Response rates were similar for men with PD (80%) compared with men without PD (82.7%). The diagnosis of PD, when reported by a participant, was confirmed by the participant's treating neurologist, internist, or medical record. ED increased with age; men with PD had a higher prevalence of ED relative to men without PD in each age group. In 2000, 68% of men with PD reported ED during the past 3 months compared with 32% of men who did not have PD ($p<0.0001$) after adjusting for age, smoking, and BMI. Men who reported ED prior to 1986 were 3.8 times more likely to develop PD than men who reported good erectile function [multivariate relative risk

(RR) = 3.8, 95% confidence interval (CI) 2.4, 6.0; $p < 0.0001$].

Sexual function was compared in men with PD and with men who had arthritis [54]. Sexual function and its relationship to age, PD severity, and depression were described in 41 married men with PD. The comparison group consisted of 29 married men with arthritis. Men with a history of dementia, illnesses, or use of medications known to cause impotence were excluded from participation. Men with PD were recruited from three neurology clinics; men with arthritis were recruited from arthritis clinics at the same three hospitals. Providers of participants who had PD rated the patients' stage of disease using the Hoehn and Yahr scale [29] and Columbia Parkinson scale [55]. Providers of patients with arthritis rated severity of disease using the Functional Capacity in Rheumatoid Arthritis Scale [56]. Participants completed the Zung Depression Scale [57] and Sexual Functioning Questionnaire [58]. The two groups were well matched for age, but they differed in duration of disease. The average duration of PD was 6 years, compared with 15 years for patients with arthritis. Similarities were found between the two groups. Total scores for sexual functioning and subscores for desire, arousal, orgasm, satisfaction, and frequency of sex per month did not differ significantly between the two groups. Age was notably related to total sexual function score (PD, $r = -0.40$, $p < 0.05$; arthritis, $r = -0.39$, $p < 0.05$). Sexual dysfunction increased with severity of illness, and without depression, was found in both groups.

One report has exclusively addressed sexual function in women with PD; 27 married women with PD and 27 age-matched married women without history of neurological disease participated in the study [59]. Data were collected by a medical student. Demographic information included age, years with PD, ethnicity, educational and employment status, onset and cessation of menstruation, hormone replacement therapy, and concomitant illness. Women with PD were assessed for presence of ANS dysfunction, as evidenced by the presence of significant postural hypotension, and history of urinary or fecal incontinence. To establish severity of disease, according to the Hoehn and Yahr scale [29], neurological examinations of women with PD were conducted when they were in the "on" motor state. All participants completed the Brief Index of Sexual Functioning for Women (BSIF-W) [60] and BDI [34]. The BISF-W is a 22-item questionnaire that measures sexual interest/desire, sexual activity, and satisfaction. Women with PD and women in the control group differed in employment and ethnicity: 22% of patients with PD were employed, 67% were retired, and 11% were unable to work; 37% of control group participants were employed and 63% were retired. Of the 27 patients who had PD, there were 23 Caucasians, 2 Asians, and 2 Hispanics. In the control group, 19 were Caucasian, 1 Asian, 3 Hispanic, 3 African-American, and 1 woman described herself as "other." Approximately 50% of both samples were sexually active. Patients who had PD reported less satisfaction with their sexual relationship than the control group. Women with PD reported greater anxiety or inhibition during sex ($p = 0.04$), more difficulty with vaginal tightness ($p = 0.03$), and more problems with involuntary urination ($p = 0.03$). Patients with PD were less satisfied with their partners than the controls ($p = 0.005$). Also, patients with PD were significantly more depressed than community controls. In women with PD, the Hoehn and Yahr stage of disease was mildly correlated with change in satisfaction and change in sexual activity. In both groups, age was associated with change in sexual satisfaction and sexual activity.

Physiology of Sexual Function

Physiology of Penile Erection

Primary regulation of penile erection is provided by the central and peripheral nervous system [61]. Integration for central control of erection appears to occur in the medial preoptic area (MPOA) of the hypothalamus, where sensory impulses from the amygdala that have input from the cortical association areas are received. Stimuli

to the MPOA include proerectile dopamine-mediated signals and inhibitory norepinephrine-mediated signals. The MPOA provides neural input to the paraventricular nucleus (PVN) of the hypothalamus. Descending pathways from the PVN may have proerectile action through oxytocin-mediated pathways. Neural connections between the MPOA and the brainstem are provided by periaqueductal gray matter, which may have proerectile activity. Neurons from the PVN project to the thoracic and lumbosacral nuclei concerned with erection. Reflex erections are mediated through T12-S3 cord levels, and the penis is innervated by the sympathetic nervous system at T11-L2. Sympathetic input is antierectile; parasympathetic and somatic nervous system innervation of the penis is mediated through the S2–S4 segments and is proerectile. Autonomic input to the penis is integrated in the inferior hypogastric plexus. The cavernous nerves originate in the inferior hypogastric plexus. The lesser cavernous nerves travel along the penis to supply the erectile tissue of the corpus spongiosum and urethra; the greater cavernous nerves innervate the helicine arteries and erectile tissue. Fibrous tissue encases intercavernous nerves, preventing compression during erection. Branches of the intercavernous nerves travel with the prostate vesicular artery branches. Stimuli from the perineum and lower urinary tract mucosa are conveyed by the sacral reflex arc. Branches of the pudendal nerves, ilioinguinal nerve, and the dorsal penile nerves provide sensory input from the glans penis and skin and penile root. In the flaccid state, sympathetic neural activity is predominant, minimizing blood flow into the sinus cavernosa. Intracorporeal smooth muscle is in a semicontracted state. Maintenance of this state is the result of intrinsic myogenic activity, adrenergic neurotransmission, and endothelium-derived contracting factors. For smooth muscle cell contraction to occur, adequate local levels of neurotransmitters, expression of receptors, integrity of the transduction mechanism, ion channel homeostasis, interactions between contractile proteins, and effective communication over gap junctions all must be present. Sexual stimulation causes parasympathetic neural activity to dominate, resulting in increased blood flow into the sinuses of the corpora cavernosa, smooth muscle relaxation, and achievement of erection. Nitric oxide (NO) is the main neurotransmitter mediating penile erection. During nonadrenergic, noncholinergic neurotransmission, NO is released from the endothelium of the corpora cavernosa. NO activates soluble guanylyl cyclase within the muscle cells, which raises the intracellular concentration of cyclic guanosine monophosphate (cGMP). cGMP activates a protein kinase, causing hyperpolarization of the muscle cell membrane, sequestration of intracellular calcium, and calcium channel inhibition that blocks calcium influx. Smooth muscle relaxation, dilation of arterial vessels, and increased blood flow into the sinuses of the corpora cavernosa result from the decrease in cytosolic calcium concentration.

Hormonal and Neurogenic Mediators of Female Sexual Function

Two physiologic changes occur during the female sexual response cycle: vasocongestion of the external and internal genitalia and breasts and myotonia throughout the body [62–64]. Hormones and neurogenic mediators regulate female sexual function. Estradiol levels affect cells throughout the nervous system and influence nerve transmission. Estrogen causes vasodilatation, resulting in increased vaginal, clitoral, and urethral arterial blood flow, which prevents atherosclerotic compromise of pelvic arteries and arterioles and also maintains sexual response. With aging and menopause, women experience decreased sexual desire, less frequency of sexual activity, and a reduction in sexual responsiveness. A correlation between the presence of sexual complaints and estradiol levels below 50 pg/mL has been demonstrated [65]. Estrogen regulates vaginal NO synthase, the enzyme responsible for production of NO [62]. NO is involved in the modulation of vaginal relaxation and secretory processes. NO has been identified in clitoral cavernosal smooth muscle and may be a mediator of clitoral cavernosal and vaginal wall smooth muscle relaxation. Aging results in

decreased vaginal NO levels and increased vaginal wall fibrosis. In women, low testosterone levels are associated with a decline in sexual arousal, genital sensation, libido, and orgasm. The neurogenic mechanisms that modulate vaginal and clitoral smooth muscle tone as well as vaginal and clitoral vascular muscle relaxation are undetermined. Preliminary studies suggest the involvement of vasoactive intestinal polypeptide and NO.

Therapeutic Interventions

In both men and women, impaired sexual function can be caused by psychogenic factors, organic factors, and aging [61, 62]. Organic causes are categorized as vascular, neurogenic, hormonal, disease related, and drug induced. In men, psychogenic causes of ED include depression, performance anxiety, relationship problems, and psychosocial distress [9–11]. Alternatively, in women, issues related to self-esteem, body image, relationship with partner, and ability to communicate sexual needs affect sexual function [62].

Impaired sexual function in PD is most likely multifactorial; depression, physical disability, and autonomic dysfunction may contribute to the increased incidence of ED in PD [66]. In light of the multiple factors potentially responsible for impaired sexual function, the needs of patients, partners, and couples should be individually assessed. Therapeutic interventions can be guided by The World Health Organization definition of sexual health as "the integration of the somatic, emotional, intellectual, and social aspects of sexual being, in ways that are positively enriching and that enhances personality, communication, and love." [67]

Diagnosis and Treatment of Erectile Dysfunction in Men with PD

Nonpharmacological Measures

Recommendations for the diagnosis and treatment of ED were developed by the First International Consultation on ED [68]. Diagnostic evaluation has been described and a stepped approach to treatment is recommended [61, 68]. When possible, prescribed medications associated with ED should be discontinued. First-line therapy includes lifestyle modification, psychological counseling, androgen replacement therapy, and oral therapy. Lifestyle modification includes smoking cessation, avoidance of substance abuse, adequate nutrition, physical activity, and sleep.

In men with PD, there is limited discussion of first-line pharmacological therapies. Treatments with testosterone [69, 70] and sildenafil [71–73] have been described. Erection has been reported as an adverse effect of subcutaneous apomorphine treatment of motor-resistant fluctuations in PD [66].

Testosterone

Testosterone is thought to stimulate libido in the central nervous system [74]. Erections in response to erotic visual stimuli may be partially androgen dependent [75]. Animal and human studies [76] have found that low-normal range concentrations of testosterone are sufficient to maintain sexual activity. Testosterone deficiency [69] is found in 20–25% of men over age 60. Testosterone deficiency can result in depression, fatigue, decreased libido, and decreased work performance.

Okun et al. [69] retrospectively analyzed the effect of testosterone replacement therapy in five men with PD and evidence of plasma testosterone deficiency. The men had not clinically improved with antidepressants and antiparkinson medication. Four of the men were screened initially with the St. Louis Testosterone Deficiency Questionnaire (SLTDQ) [77]. Men who met SLTDQ criteria were screened for total and free testosterone levels. Prostate-specific antigen and digital rectal exam were performed to exclude the presence of prostate cancer. The UPDRS motor score was recorded. Patients with testosterone levels less than 70 pg/mL with no medical contraindications were treated with a topical application of testosterone gel. Patients reported improved sexual function and decreased fatigue, depression, and anxiety 1 month later. To assess the prevalence of testosterone deficiency, total

testosterone levels for 68 men enrolled in a PD registry were sent for evaluation, and 35% had evidence of plasma testosterone deficiency. The risk of testosterone deficiency increased 2.8-fold per decade.

In a subsequent double-blind, placebo-controlled, parallel-group, single-center study [70], patients were treated with intramuscular testosterone therapy or placebo every 2 weeks for 8 weeks. At the end of the double-blind phase, all patients were offered open-label testosterone therapy and then evaluated at 3 and 6 months. Testosterone therapy was well tolerated. There were no significant differences in the motor and nonmotor scales between the experimental and control groups.

Sildenafil

Sildenafil [61], a selective inhibitor of cGMP-specific phosphodiesterase type 5, enhances the effect of NO release into the corpora cavernosa from nonadrenergic noncholinergic nerves of the parasympathetic system and vascular endothelium during sexual stimulation. Sildenafil potentiates the hypotensive effect of nitrates and is absolutely contraindicated in men using nitrates [78]. Sildenafil may be hazardous in men with borderline low blood pressure, borderline low cardiac volume, or receiving medications that can prolong its half-life [79]. Adverse effects include headache, flushing, nasal congestion, dyspepsia, abnormal vision, diarrhea, and dizziness [61]. To optimize treatment outcome, sildenafil should be ingested on an empty stomach. Excessive alcohol consumption should be avoided.

Studies of men [78, 80] with ED of various etiologies have reported on sildenafil. To evaluate the efficacy and safety of sildenafil in men with PD and ED [71], 10 men participated in an 8-week open-label pilot study. The BI [34], UPDRS [28], and a Sexual Health Inventory-M version (SHI-M) questionnaire [81] were administered prior to treatment and at the conclusion of the treatment period. Four 50-mg doses of sildenafil were prescribed for use in four sexual encounters during the first month. At the conclusion of the first month, participants had telephone conversations with a urologist and a movement disorder neurologist. Participants then were permitted to increase the dose to 100 mg for each of four sexual encounters during the second month. All participants took eight doses of medication during the study period. Four men increased the dose to 100 mg during the second month. A statistically significant improvement in total SHI-M scores was demonstrated ($p=0.01$). Significant improvement was demonstrated in overall sexual satisfaction, satisfaction with sexual desire, achievement of erection, maintenance of erection, and orgasm. One patient reported a headache during three encounters. There were no reports of syncope or presyncope.

Twenty-four men with ED—12 with PD and 12 with multiple system atrophy (MSA)—participated in a randomized, double-blind, placebo-controlled, crossover study of sildenafil [72]. Subjects completed the International Index of Erectile Function questionnaire [82] and a quality-of-life questionnaire; partners completed a brief questionnaire. The starting dose for the active drug was 50 mg. Dosage was titrated up to 100 mg or down to 25 mg at follow-up visits, depending on efficacy and tolerability. Of the 12 men with PD, 10 completed the study, and 9 of the 10 men reported a good response to sildenafil. Eight men titrated up to 100 mg; one man titrated down to 25 mg. Although one man reported lack of efficacy, most of the participants with PD reported significant improvement in the ability to achieve and maintain erection, along with improvement in sex life with sildenafil. Partners' questionnaire responses confirmed the patients' reports. Men with PD demonstrated minimal change in blood pressure (BP). Six men with MSA were studied before recruitment was stopped. Four men received placebo first. Three men with MSA experienced significant postural fall in BP with symptoms of orthostatic hypotension 1 h after receiving sildenafil. Patients with MSA reported improved sexual function and quality of sex life after taking sildenafil. The authors recommended the measurement of lying and standing BP as well as education about symptoms of hypotension before prescribing sildenafil for men with early parkinsonism, which may be

difficult to distinguish from MSA. In publishing a practice parameter for treatment of nonmotor symptoms of PD, the Quality Standards Subcommittee of the American Academy of Neurology concluded that sildenafil 50 mg is possibly efficacious for treating ED in male patients [73].

Apomorphine

Apomorphine is a D1/D2 receptor agonist used to treat resistant motor fluctuations in adults with PD [83]. Under experimental conditions, the parenteral administration of apomorphine produces erectile responses in humans and rats [83, 84]. Apomorphine-induced erections are likely the result of stimulation of central D2 dopamine receptors and are inhibited by the selective D2 antagonist, sulpiride [85]. Domperidone, a peripheral dopamine antagonist, does not inhibit apomorphine-induced erections or the yawning that accompanies the erection [86]. Animal studies suggest there is a link between the hypothalamic pathways involved in erection and yawning [87]. Apomorphine-induced erections in men with PD have been reported. O'Sullivan and Hughes [66] surveyed 15 men who attended a movement disorder neurology clinic and used intermittent subcutaneous injections of apomorphine to treat PD complicated by motor fluctuations. Five of the 15 men reported erection associated with apomorphine treatment. Erections coincided with apomorphine administration. Four of the men had experienced ED before beginning apomorphine treatment, and two of the men had improvement in their sexual relationship with their partner as a result of treatment. The only patient that had not experienced ED prior to beginning apomorphine treatment reported undesirable arousal associated with the erections.

In a placebo-controlled trial of men with no discernable organic etiology for ED, buccal administration of apomorphine was significantly more effective than placebo, as demonstrated by rigidity testing [88].

Other Treatment Methods

According to the First International Council on Erectile Dysfunction, second-line therapy includes vacuum constriction devices, intracavernosal injection, and transurethral therapy [68]. Third-line therapy utilizes penile prosthesis and revascularization. Reports evaluating the efficacy of these treatment modalities in men with PD were not identified in the literature review.

Levodopa and alternate current (AC)-pulsed electromagnetic field density stimulation are not recognized treatments for ED. However, their effect on sexual function has been described [89–93]. Levodopa was evaluated in a clinical trial of 21 healthy men without ED [89]. Subjects ingested 800 mg of levodopa for 7 days. Sleep-related penile tumescence was monitored. Erectile responses significantly improved from baseline, and no adverse effects were reported. The results provide support for a central dopaminergic erection-mediation pathway.

Semistructured interviews were conducted in 12 men and 7 women, treated for 3–15 months, to assess the effect of levodopa treatment on sexual behavior [90]. The interviewers assigned numerical values to interview responses. Six men and one woman (37%) reported activation of sexual behavior at some point during the therapy. There were strong negative trends between sexual activity and age of patient ($r=-0.42$) and duration of parkinsonism ($r=-0.44$). Three patterns of change in sexuality were described. In the first pattern, general improvement in overall function was accompanied by mild improvement in sexual function. This result depended on the patient's past sexual habits, age, and availability of a partner. In the second pattern, activation of sexual drive was independent of overall functional improvement. Three (16%) men demonstrated this effect, which was usually mild and did not persist despite continuation of levodopa. The third pattern was loss of sexual inhibition in patients who developed an acute brain syndrome.

Psychiatric interviews, sexual and affective rating scales, hormonal studies, and neurological assessment were used to evaluate levodopa therapy in seven men with PD, mean age 62, and mean duration of illness 4 years [91]. Four men reported increased sexual interest or activity related to treatment. One man also reported increased interest with placebo.

The effect of levodopa on mood was assessed in 20 patients followed during initiation and maintenance of therapy [92]. Six of nine men had spontaneous erections while taking 4–6.5 g of levodopa/day. Three of the men had been impotent for up to 10 years prior to levodopa therapy and were generally puzzled and embarrassed. The erections were not related to sexual objects and were not accompanied by sexual fantasies. Three of the men reported an increase in libido. One man who had been impotent was able to resume satisfactory sexual intercourse.

Sandyk [93] reported on two men with PD and ED, ages 70 and 73, respectively, who experienced sexual arousal and nocturnal erections after receiving treatment for PD with transcranial administrations of AC-pulsed electromagnetic fields (EMFs) of 7.5 pT flux density. EMF treatment was administered after the men received their usual antiparkinson medication when they were in the "on" state. The first patient received treatment for 2 consecutive days. During the first treatment, he felt relaxed and yawned. He reported a decrease in parkinsonian symptoms after the treatment. In the evening, he experienced sexual arousal and awakened during the night with several repetitive spontaneous erections that lasted 15–20 min. During the second treatment, he experienced sexual arousal and had nocturnal erections during the subsequent three nights. The second patient had Hoehn and Yahr stage IV PD. He had two successive EMF treatments for 4 days and reported sexual arousal associated with nocturnal erection.

Diagnosis and Treatment of Women with PD and Impaired Sexual Function

Factors that affect sexual function in women include depression, anxiety, relationship issues, history of abuse, gynecological issues, menopausal status, medical illness, and medication adverse effects. Female sexual dysfunction can be assessed in relation to the female sexual response cycle of desire, arousal, orgasm, and resolution [79]. Female sexual dysfunction may involve lack of sexual desire, impaired arousal, inability to achieve orgasm, or pain with sexual activity. Usually, several phases are affected. A sexual problem must be persistent or recurrent and cause personal distress or interpersonal difficulty for diagnosis utilizing the American Psychiatric Association (APA) guideline for sexual disorders.

A comprehensive approach to the evaluation of sexual function in women should include complete sexual history, medical history, physical examination, pelvic examination, hormonal profile, and physiologic testing, as indicated [78]. An individualized treatment plan is developed based on the woman's goals. Nonpharmacological therapies as well as physical therapy and pharmacological therapies have been described. Therapeutic interventions for the treatment of impaired sexual function in women with PD were not identified in this literature review.

Conclusion

The incidence of impaired sexual function in adults with PD is greater than the general population. Psychological factors, hormonal abnormalities, autonomic nervous system disorders, vascular disease, and medication adverse effects should be considered when evaluating impaired sexual function in adults with PD. Depression, physical disability, and ANS dysfunction may contribute to the increased incidence of ED in men with PD. Further clinical and basic science research are needed to study therapeutic interventions for impaired sexual function in adults with PD.

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Urological Dysfunction

12

Henry Moore and Carlos Singer

Abstract

Symptoms of urinary dysfunction occur frequently in patients with Parkinson's disease (PD), particularly men. Irritative symptoms, such as frequency, urgency, and urge incontinence, are reported in 57–83% of patients with PD. Obstructive symptoms, such as hesitancy and weak urinary stream, may be present in 17–36% of individuals. The appearance of urinary symptoms may follow the appearance of motor symptoms by a few years. Several mechanisms, such as detrusor hyperreflexia, detrusor areflexia, coexistent obstructive uropathies, and dysfunction of infravesical mechanisms, can be responsible for the urinary dysfunction in patients with PD. Detrusor hyperreflexia is the urodynamic correlate of irritative urinary symptoms. Detrusor areflexia is uncommon in PD and, when present, is usually secondary to the use of anticholinergic medications. Coexistent obstructive uropathies may complicate the clinical picture in patients with PD and produce both obstructive and irritative symptoms. Urinary dysfunction in PD also may be the result of dysfunctional infravesical mechanisms such as sphincter bradykinesia. In terms of pathogenesis, voiding dysfunction in PD is primarily due to the loss of the inhibitory effect that the basal ganglia exert on the pontine micturition center. This inhibitory effect likely is mediated by D1 dopamine receptors and results in a "quiet bladder" during the filling phase. In terms of treatment, the irritative symptoms often can be treated successfully with anticholinergic drugs; however, for refractory overactive bladder, intravesical botulinum toxin injections or deep brain stimulation surgery may be required. If the symptoms are obstructive in nature, bladder catheterization and sometimes urological surgery may be necessary.

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Introduction

Parkinson's disease (PD) is a synucleinopathy characterized by motor manifestations that include tremor, bradykinesia, rigidity, gait impairment, and postural instability. A variety of nonmotor manifestations also are associated with PD. Patients with PD frequently present with urinary dysfunction. The treating neurologist should have a basic knowledge of the most frequent patterns of presentation to provide advice on their significance and guide the patient regarding available treatments. This chapter has been organized in sections to summarize key issues of this subject.

Prevalence of Urological Symptoms

Urinary dysfunction affects between 27% and 39% of patients with PD [1, 2]. Urinary dysfunction may be the initial symptom of PD in 3.9% of the cases. The relative risk of bladder symptoms in persons with PD is twofold [3]. Two series have investigated the prevalence of specific urological symptoms in patients with PD and compared them with controls [4, 5]. Significantly higher prevalence figures in PD were found for urinary urgency [4, 5], sensation of incomplete bladder emptying [4], nocturia [5], daytime frequency, and urge incontinence. The estimates for obstructive symptoms (hesitancy and weak stream) exhibit the most discrepancy between men and women, perhaps reflecting overlap with prostatic disease (see Table 12.1).

Sammour et al. [6] prospectively evaluated lower urinary tract symptoms (LUTS), using the International Continence Society questionnaire, in 110 patients (84 men) with PD. Sixty-three patients (57.2%) were symptomatic. Quality of life was affected by the severity of LUTS; the symptoms with the worst impact were nocturia (80.9%) and intermittency (44.5%). Other symptoms of less impact were incomplete emptying in 40%, hesitancy in 37.3%, urgency in 36.3%,

Table 12.1 Prevalence of urological symptoms in two populations of patients with PD

Urinary symptoms	Singer et al. [4]	Sakakibara et al. [5]
Urinary urgency	46% (men)	54% (men) 42% (women)
Sensation of incomplete bladder emptying	42% (men)	
Nocturia		63% (men) 53% (women)
Daytime frequency		16% (men) 28% (women)
Urge incontinence		70% (men) 28% (women)

[a]Determined to be significantly higher than a control population

increased urinary frequency in 35.4%, and urge incontinence in 20.9%.

Irritative Versus Obstructive Symptoms

Urinary symptoms are usually grouped either as irritative (frequency, urgency, and urge incontinence) or obstructive (hesitancy and weak urinary stream). Irritative symptoms invariably predominate by a large margin. Proportions for irritative compared with obstructive symptomatology range from 73% versus 27% to 83% versus 17%, respectively [7–9]. Pavlakis et al. [10] reported a distribution of 57% irritative, 23% obstructive, and 20% mixed symptomatology in a group of 30 patients with PD.

Obstructive symptoms are not consistently reported, as illustrated by at least three reports [11–13]. Alternatively, more careful attention to nonmotor symptoms during the "off" state may uncover a higher prevalence of urinary symptomatology [14] and possibly a different proportion of irritative versus obstructive symptoms.

Appearance and Progression of Urological Symptoms

There is limited information regarding the time of appearance of urinary symptoms in PD in relation to the motor symptoms. Both the severity and duration of disease may be influential. Chandiramani et al. [13] reported an average lapse of 5.75 years between the onset of motor symptoms and the onset of urological symptoms. Araki et al. [15] studied 70 urologically symptomatic patients with PD and noted that the symptoms index scores of the patients increased with disease severity.

Sammour et al. [6] reported that voiding dysfunction increased with the neurological impairment, but not with the patient's age or disease duration. In their series, the use of levodopa, anticholinergics, and dopamine agonists had no impact in the lower urinary tract symptoms. The authors concluded that the severity of neurological disease is the only predictive factor for the occurrence of voiding dysfunction.

Sakakibara et al. [16] studied ^{123}I-β-CIT SPECT scans of seven PD patients with urinary dysfunction and compared them with four PD patients free of urinary symptoms. The uptake was significantly reduced in the former group, suggesting a link between severity of the nigrostriatal dopaminergic deficit and presence of urinary symptomatology.

Urodynamic Correlation of Detrusor Hyperreflexia

Detrusor hyperreflexia is a cystometric finding characterized by the presence of involuntary detrusor contractions in response to bladder filling that the patient is unable to inhibit. These contractions generate pressure values of 15 cm of water [10, 17, 18].

Some authors have reported a very close clinical correlation between irritative symptoms and detrusor hyperreflexia in PD [8, 15]. The prevalence of detrusor hyperreflexia found among urologically symptomatic patients with PD ranges from 45% to 100% [7–11, 15, 17, 19, 20]. This prevalence is similar to the one reported for irritative symptoms in PD (see section "Irritative Versus Obstructive Symptoms"). The information on factors predisposing to detrusor hyperreflexia in PD also seems to parallel the information on irritative symptoms (see section

"Appearance and Progression of Urological Symptoms"). Detrusor hyperreflexia may also be found in urologically asymptomatic PD patients [7].

There is limited information regarding conditions that predispose to the development of detrusor hyperreflexia. Stocchi et al. [21] reported that, of their 30 PD patients, those with a normal urodynamic pattern (36.6%) had significantly less severe disease and shorter duration of disease than those with abnormal patterns. Araki et al. [15] studied 70 PD patients who had been referred for urological evaluation and were free of obstructive etiologies. Sixty-seven percent (47/70) had pure detrusor hyperreflexia, with the majority (42/47) being Hoehn and Yahr stage 3 or higher.

Detrusor Areflexia

Detrusor areflexia is a cystometrographic finding with decreased sensation during filling and increased bladder capacity [8, 11] (>600 cc), along with a desire to void first experienced at a high-filling volume [22]. The postvoid residual volume is higher than 100 cc [22]. This results in hesitancy and weak urinary stream.

Detrusor areflexia is uncommon in PD. Incidence figures in series of urologically symptomatic patients have ranged from 0% to 27% [8, 15, 20]. Stocchi et al. [21] did not find detrusor areflexia in any of their 30 patients who had PD (symptomatic or asymptomatic) who were studied with urodynamics after anticholinergics had been withheld.

Medication Effects and Other Etiologies

Anticholinergic drugs are the most common cause of detrusor areflexia in patients with PD according to some authors [18]. In fact, the concurrent use of anticholinergics is frequently mentioned in reported findings of detrusor areflexia in PD [7, 9–11].

However, in some instances, detrusor areflexia may be found in patients with PD in the absence of anticholinergic medication. One example is the study by Raz of urologically symptomatic patients with PD, in which the confounding effect of anticholinergic drugs was eliminated by withdrawing them 1 week prior to the urodynamic investigations [8]. In those cases, the clinician must consider other alternative possibilities to the diagnosis of PD such as multiple system atrophy (see section "Diagnosis of Multiple System Atrophy"), coexistent obstructive uropathy (see section "Impact of Coexistent Obstructive Uropathies"), and "myogenic" areflexia.

Myogenic areflexia was originally described as the result of muscle fiber injury caused by an overdistended bladder secondary to obstruction [23]. Recently, a myopathic process of the bladder wall has been proposed to be present in the absence of obstruction. Araki et al. [15] have invoked this theory to explain the findings in 6 of their 70 patients referred for urological evaluation. These patients, all stage 4 in the Hoehn and Yahr scale, had detrusor hyperreflexia that was associated with impaired contractile function in the absence of obstructive etiologies. A similar process has been reported in the elderly [24].

Impact of Coexistent Obstructive Uropathies

Obstructive uropathies (i.e., benign prostatic hypertrophy in the man, stenosis of the bladder neck in the woman) have been recognized as causes in their own right of both irritative and obstructive symptoms in the general population [23]. Such irritative symptoms associated with obstructive uropathies are equally the product of a detrusor hyperreflexia and indistinguishable from the purely neurogenic type. Certain investigations have pointed to the presence of obstructive uropathies as contributing causes of urinary symptoms in some PD patients [9, 10, 20, 25]. The prevalence figures vary from 17% to 33%. However, correlation with specific obstructive symptoms is at times not outlined with sufficient clarity [9, 10, 20].

Dysfunction of Infravesical Mechanisms

PD also may course with dysfunctional infravesical mechanisms (DIVMs). A full urodynamic evaluation includes measurement of infravesical mechanisms, such as urethral pressure profile, urinary flow, and sphincter EMG recording during bladder filling and bladder emptying. DIVMs encompass dysfunction of the striated urethral sphincter and the pelvic floor, either occurring alone or in combination.

Although different kinds of DIVMs have been described in patients with PD (see Table 12.2), they have been inconsistently reported and in variable numbers [7, 10, 21, 25]; sometimes they are not found at all [20]. The descriptions are sometimes poorly characterized and may not be confirmed again in other reports. Correlation with clinical symptomatology is frequently inadequate or lacking [7, 10, 25]; therefore, the clinical significance of DIVMs is unclear.

Table 12.2 List of dysfunctional infravesical mechanisms reported in the literature

Dysfunction	References
Elevated urethral pressure profile	[7, 8]
Decreased urinary flow	[9, 26]
Sphincter bradykinesia	[10, 17, 19, 25]
Pseudodyssynergia	[10]
Sphincter "tremor"	[19]
Vesicosphincter dyssynergia	[15, 17, 25]
Involuntary asymptomatic sphincteric activity	[9, 26]

Sphincter Bradykinesia, Pseudodyssynergia, and Vesicosphincter Dyssynergia

The most frequent DIVM is known as sphincter bradykinesia, consisting of delayed relaxation of the striated urethral sphincter and pelvic floor musculature. There is a normal guarding reflex with an increase in striated muscle activity during bladder filling before the onset of detrusor contraction. Sphincter bradykinesia is an abnormality in which involuntary EMG activity persists through at least the initial part of the expulsive phase of the cystometrogram (CMG) [10].

In one series [10], 11% (3/28) of patients with PD had sphincter bradykinesia. In another study, Galloway [19] reported that 42% (5/12) of his urologically symptomatic patients were unable to relax the external urethral sphincter with voiding, which was associated with low flow rates. Andersen et al. [25] studied 24 urologically symptomatic patients with parkinsonism (the term "Parkinson's disease" is not used). The same authors revised their data in a subsequent article [17] and reported electromyographic findings in these 24 patients with PD. The authors did not specify whether all 24 patients were symptomatic. Of these patients, 21% (5/24) had impaired sphincter control, defined as poor ability to contract or relax the sphincter on command.

Pseudodyssynergia has been reported less frequently than sphincter bradykinesia. Pseudodyssynergia has been defined as "an attempt at continence by voluntary contraction of the pelvic musculature during an involuntary detrusor contraction" [23]. Pavlakis et al. [10] reported pseudodyssynergia in two patients, part of a group of ten in whom the maximum flow rate was decreased. The clinical role of this phenomenon could not be defined because of coexistent prostatic obstruction. Sphincter "tremor" was described in 11 of 12 patients in another series [19]. Neither pseudodyssynergia nor sphincter "tremor" has been confirmed in subsequent reports.

Vesicosphincter dyssynergia is a DIVM also reported less frequently than sphincter bradykinesia. Whereas Pavlakis et al. [10] called attention to the absence of vesicosphincter dyssynergia, Andersen et al. [17, 25] reported two patients with an abnormality they initially called "dyssynergia" [25] but later labeled "spasticity" [17]. In a series of 70 PD patients referred for urological evaluation who were free of obstructive etiologies, Araki et al. [15] found two patients (3%) who had both hyperreflexia and detrusor-sphincter dyssynergia (2/70).

Berger et al. [9, 26] studied 29 patients with PD (24 men and 5 women) who were urologically symptomatic. In 61% (14/23) of patients tested, they documented sporadic involuntary electromyographic activity of the external sphincter during *involuntary* detrusor contractions, but in none did this phenomenon cause obstruction. They labeled this phenomenon "involuntary sphincteric activity." Because this phenomenon was not associated with radiographic or manometric evidence of obstruction at the level of the membranous urethra, the authors concluded that it did not meet criteria for the definition of detrusor-sphincter dyssynergia. This activity is reminiscent of pseudodyssynergia in that both occur in response to involuntary detrusor contractions, but pseudodyssynergia is seen as a *voluntary* act.

Dopaminergic Medication

Dopaminergic medication likely improves voiding by facilitating relaxation of the striated sphincter and increasing bladder contractility. Raz [8] demonstrated a decrease in the urethral pressure profile (UPP) after treatment with levodopa in ten patients who had PD with urological symptoms. An increase in the UPP occurred in patients whose treatment with levodopa was interrupted for 1 week (number of patients not specified).

In a series of 30 patients with PD, 11 displayed delayed or incomplete perineal floor relaxation [21]. All experienced greatly improved perineal muscle control after subcutaneous injection of apomorphine (4 mg), a dopamine agonist. There was no effect on detrusor hyperactivity. In another series of ten patients who had PD with urinary symptoms [27], urodynamic studies were performed before and after the subcutaneous administration of apomorphine. Voiding efficiency improved after apomorphine injection with an overall decrease in bladder outflow obstruction. There was an increase in the mean and maximum flow rates in nine patients and reduction in postmicturition residual volume in six. This was accompanied by fluoroscopic evidence of widening of the urethra at the level of the distal sphincter mechanism. Three patients were unable to void during the "off" state as a consequence of decreased detrusor contractility, despite considerable discomfort and a feeling of bladder fullness [27]. After apomorphine injection, voiding detrusor pressure in these three patients increased and calculated bladder outflow resistance fell, resulting in considerable improvement in voiding. No information was provided whether these patients were on anticholinergic drugs. Because all of the patients were premedicated with domperidone, a peripheral dopamine antagonist, the investigators concluded that the effects of apomorphine on both smooth and striated musculature of the lower urinary tract must be mediated by changes in central dopaminergic transmission [27].

Uchiyama et al. [28] reported the effects of a single dose of 100 mg levodopa on urinary function in 18 patients who had PD with severe end-of-dose wearing off. Patients were on levodopa and dopamine agonists, but not on anticholinergics. There was an increase in detrusor contractility; alternatively, there was an increase in urethral obstruction. However, the net effect favored the increase in bladder contractility. The result was a decrease in residual volume, that is, an improvement in voiding efficiency.

Effects of Dopaminergic Medication on Detrusor Activity

Fitzmaurice et al. [20] reported on nine urologically symptomatic patients who had PD with detrusor hyperreflexia. The effects of levodopa were variable. Six patients had less severe detrusor hyperreflexia when "off" (including one patient whose hyperreflexia disappeared); three were better when on levodopa. A description of the impact of treatment on the actual symptoms was not provided. Detrusor function during the filling (storage) phase was not consistently altered by apomorphine in another study [27], in which detrusor hyperreflexia improved in some cases and deteriorated in others. In their study of 18 patients with PD who had severe wearing off, Uchiyama et al. [28] showed an unpredictable

effect on bladder function during filling. Urinary urgency (with or without detrusor hyperreflexia or low-compliance bladder) was aggravated in nine patients (50%), alleviated in three (17%), and unchanged in six (33%).

Diagnosis of Multiple System Atrophy

Early and prominent urinary symptoms and "obstructive" symptoms (in the absence of obstruction) are clues to the diagnosis of multiple system atrophy (MSA). Chandiramani et al. [13] performed a retrospective study of 52 patients with MSA and 41 patients with PD. Of MSA patients, 60% (31/52) had urinary symptoms preceding or coinciding with diagnosis of the disease. Sixteen patients reported frequency, urgency, or incontinence before the onset of parkinsonism; 15 patients developed urinary symptoms at the same time as parkinsonism. In contrast, in 94% of patients with PD, the urogenital symptoms clearly followed the neurological diagnosis by a few years. Two other series, identified in a review by Fowler [29], also confirm a 60% prevalence of *early* urinary symptoms in MSA. In one series [13], patients with MSA were more likely to suffer from troublesome incontinence (73%); elevated postvoid residuals were also more likely compared with PD patients (66% versus 16%, respectively). Among males with MSA, 93% had erectile dysfunction (ED), including 48% in whom ED preceded the MSA diagnosis. Although ED also may develop in PD, the proportion of early ED is less [30]. In the series of Chandiramani et al. [13], all 11 men with MSA who underwent transurethral prostatectomy (TURP) were incontinent postoperatively (see section "Urological Surgery for Prostate Obstruction").

Fowler [29] has proposed the following five urogenital criteria as implied in the diagnosis of MSA: (1) urinary symptoms preceding or presenting with parkinsonism, (2) ED preceding or presenting with parkinsonism, (3) urinary incontinence, (4) significant postmicturition residual (>100 mL), and (5) worsening bladder control after urological surgery. However, none of these criteria are specific, and the clinician has to view their presence in context with the remaining clinical features.

Sphincter EMG

Patients with MSA have cell loss in Onuf's nucleus, which has been associated with electromyographic changes that include denervation (fibrillations and positive sharp waves) and reinnervation (abnormal and prolonged polyphasic potentials). Such urethral sphincter abnormalities are also reflected in the anal sphincter, a more easily accessible structure [31].

Stocchi et al. [21] reported that EMG provides important differentiating data between MSA and PD. The main feature that differentiated 32 MSA patients from 30 patients with PD was abnormal sphincter EMG in 75% (24/32) of the MSA patients, compared with none of the PD patients. Vodusek conducted a comprehensive review of the subject [32]. He concluded that anal sphincter EMG abnormalities could distinguish MSA from PD during the first 5 years after the onset of symptoms and signs if other causes for sphincter denervation (e.g., surgery) had been ruled out. However, with such criteria, as Vodusek readily admits, sphincter EMG offers a low sensitivity.

Voiding Dysfunction in PD

Voiding is a function of the autonomic nervous system with a core segmental representation in the spinal cord. As the bladder fills, afferent stimuli are conducted to the S2–S4 segments. During bladder filling, the efferent sympathetic nervous system, via hypogastric nerves originating in the lumbar spinal cord, is active. This allows distension of the bladder to accommodate the urine, closure of the internal urethral sphincter [33], and inhibition of parasympathetic excitatory effect on the detrusor muscle [34]. During this phase, the external and internal urethral sphincters are tonically contracted, and there is increased tone in the striated musculature of the pelvic floor. At a certain level of bladder distention, a reflex efferent

response is triggered by activated motor neurons, which stimulate the detrusor muscle via the pelvic nerve (parasympathetic) and relax the internal urethral sphincter via parasympathetic inhibition of sympathetic terminals that innervate the bladder neck. At the same time, inhibition of Onuf's nucleus and pudendal motor nuclei causes relaxation of the striated urethral sphincter and the perineal floor, respectively.

This segmentally organized function is subject to facilitatory and inhibitory impulses from higher neurological centers that allow for voluntary control of the detrusor reflex. Specifically, impulses from the cortical micturition center in the mesial frontal lobes [21] connect to the pontine-mesencephalic reticular formation. Two micturition centers exist in the pons: the pontine micturition center and pontine storage center [35, 36]. The former is the most important and facilitates the urinary reflex. The pontine storage center is less well understood, but it has connections with the somatic nerves that cause closure of the external urethral sphincter [37]. This pathway is influenced further by the basal ganglia, the thalamic nuclei, and the anterior vermis of the cerebellum [10, 17]. Micturition is also influenced by the anterior cingulate gyrus, the locus ceruleus, the nucleus tegmento lateralis dorsalis [10, 17], and the periaqueductal gray area [35, 36, 38]. The periaqueductal gray area receives afferent information from the bladder regarding bladder fullness, as well as from the hypothalamus and other higher cortical centers. It may act as a relay center facilitating voiding through connections with the pontine micturition center [39]. Input from higher cortical centers ensures that voiding takes place at a time and place that is socially acceptable [40].

Based on a series of experiments and subsequent experience with basal ganglia surgery, the basal ganglia appear to exert an inhibitory effect on the pontomesencephalic micturition center. Lewin et al. performed pivotal experimental studies in cats that are still being cited as the backbone for current theory on pathophysiology [41, 42]. Lewin et al. stimulated the thalamus and different sites of the basal ganglia and found that the stimulation was inhibitory of detrusor contractions. Stimulation of the red nucleus, the subthalamic nucleus, and the substantia nigra was even more inhibitory than that of the thalamus. This may suggest that current deep brain stimulation procedures may be more effective in improving voiding dysfunction if STN rather than the thalamus is the target. Stereotaxic thalamotomy in parkinsonian patients, on the other hand, demonstrated an increase in detrusor activity [11].

Recent positron emission tomography (PET) studies in young, healthy individuals have demonstrated that specific sites in the brainstem and higher brain may play crucial roles in micturition control. Brain regions activated by bladder distention included the periaqueductal gray area, pons, anterior cingulate area, anterior insula, putamen, thalamus, and cerebellum [35, 36, 38, 43]. In comparison, brain PET of PD patients with detrusor overactivity showed bladder filling associated with activation of the periaqueductal gray area, supplementary motor area, insula, putamen, thalamus, and—most prominently—of the cerebellar vermis; the pons was not activated during detrusor overactivity. The authors concluded that these alterations in brain activation sites in response to bladder filling may be related to the pathophysiology of detrusor overactivity in PD [44].

In terms of stimulation of dopamine receptors, stimulation of D1 receptors is inhibitory; D2 stimulation is facilitatory. This combination of effects would result in a D_1 effect during bladder filling and a D_2 effect during bladder emptying.

Treatment of Irritative Symptoms

Irritative symptoms, a manifestation of detrusor hyperreflexia, are responsive to anticholinergic drugs. However, exclusion of obstructive uropathy prior to symptomatic treatment is advisable. Oxybutynin, tolterodine, solifenacin, darifenacin, and trospium are some of the most commonly used drugs [45]. Other agents include propantheline, hyoscyamine, and flavoxate. The oxybutynin dose ranges from 2.5 mg at bedtime to 5 mg TID.

Potential adverse effects include hesitancy, weak urinary stream, dry mouth, difficulty with visual accommodation, constipation, and aggravation of glaucoma.

Some experts have suggested using extended-release forms of anticholinergics to prevent high serum levels during therapy, with the notion that this may reduce the likelihood of cognitive dysfunction [46]. Examples include tolterodine LA at doses of 2–4 mg once daily and oxybutynin LA at doses of 5–30 mg once daily [47]. More recently, oxybutynin transdermal has been released [47]. This route avoids first-pass metabolism, resulting in a lower concentration of its active metabolite. Because this metabolite has a higher affinity in vitro for parotid cells than for bladder cells, it may explain the lower incidence of dry mouth reported with transdermal oxybutynin [47]. If therapy with a single anticholinergic agent proves to be suboptimal, the tricyclic antidepressant, imipramine, can be used in combination, since it has a different receptor site profile [23].

Solifenacin and darifenacin have emerged as alternatives to traditional anticholinergic drugs. They act specifically on the M3 receptors present on the bladder, avoiding stimulation of the muscarinic receptors present in the heart, CNS, and salivary glands, which is responsible for the adverse effects of these medications [40]. These drugs have the same efficacy as the older agents, but superior tolerability with fewer side effects [48].

If anticholinergic CNS side effects are of concern, one can choose trospium, which is a nonselective antimuscarinic agent that, due to its low lipid solubility, does not cross the blood-brain barrier. It also is not metabolized by cytochrome P450 and, thus, is less likely to produce drug interactions. It is excreted mainly unchanged in the urine, which accounts for its rapid onset of clinical effect and prolonged efficacy. Placebo-controlled trials document the efficacy of trospium in the treatment of overactive bladder, but comparative trials with other anticholinergics are scarce [49]. An extended-release formulation has been effective and well tolerated for the treatment of overactive bladder in two randomized phase III trials [50].

Botulinum toxin has emerged as a promising therapy for patients with refractory symptoms. Several studies have been performed using botulinum toxin type A in the treatment of idiopathic overactive bladder and neurogenic bladder secondary to spinal cord injuries; in these studies, the efficacy appears to be high in terms of clinical and urodynamic improvements and beneficial effects on quality of life. Information on the management of detrusor overactivity in PD has been scarce. Giannantoni et al. [51] investigated the effectiveness and safety of botulinum toxin type A injected into the detrusor muscle in four patients with PD and two with MSA. All the patients received 200 U botulinum toxin type A injected into the detrusor muscle at 20 sites under cystoscopic guidance at a single session on an inpatient basis. One and 3 months after botulinum toxin type A injection, all the patients reported a decrease in daytime and nighttime urinary frequency and improvement in quality of life scores. No patient had further episodes of urgency or urge incontinence during the 5-month follow-up. Urodynamic studies showed improvement in all urinary function variables tested. No systemic adverse effects were recorded during or after treatment. In all patients, postvoid urinary residual volume increased, but intermittent catheterization was required only in those with MSA. The authors of this small series concluded that botulinum toxin type A is a potentially effective alternative in the treatment of refractory overactive bladder. However, larger trials must be performed to confirm these promising findings [52].

Treatment of Obstructive Symptoms

The successful treatment of obstructive symptoms of hesitancy and weak urinary stream begins with a careful drug history, searching for medications with an anticholinergic effect. Urodynamic studies should follow that investigate for the presence of detrusor areflexia, DIVM, or an obstructive uropathy. The treatment of obstructive

symptoms is based on ruling out structural causes of obstruction first, followed by ensuring bladder emptying by either intermittent or permanent catheterization. Combination treatment with anticholinergic drugs and optimization of dopaminergic treatment are also recommended.

A frequent clinical setting for the development of detrusor areflexia in PD occurs when symptomatic detrusor instability (hyperreflexia) is treated with anticholinergic drugs. This may produce the urodynamic findings of involuntary bladder contractions associated with incomplete emptying, secondary to unsustained detrusor contractions [23]. In that case, management consists of combining anticholinergic drugs with clean, intermittent catheterization by oneself or others. Successful management also helps in preventing recurrent urinary tract infections.

Another possible cause of obstructive symptoms is DIVM. In cases of external urethral sphincter bradykinesia or pseudodyssynergia with high-voiding pressures (>90-cm H_2O), some investigators recommend both anticholinergic drugs and intermittent catheterization (similar to treatment employed for mixed detrusor hyperreflexia with incomplete bladder emptying) because persistent high pressures are certain to result in damage to the bladder and, ultimately, to the upper urinary tract [23]. Sphincter bradykinesia also is responsive to dopaminergic treatment [8, 21, 27], whereas pseudodyssynergia may be correctable with biofeedback [10].

Patients with MSA are also more likely to have poor bladder compliance and sphincter insufficiency [26]. This could result in episodes of incontinence, including both overflow and stress incontinence (in addition to hesitancy and weak stream). Intermittent catheterization, with or without anticholinergic drugs (e.g., oxybutynin), may be the initial treatment [13, 26]. In some cases, desmopressin spray may be used [13]. Because of motor dysfunction, treatment may evolve to permanent indwelling catheterization or suprapubic cystostomy [26, 46]. Stress incontinence in females can be treated with urethral suspension or a sling procedure, but if there is concurrent detrusor hyperreflexia, the consequence may be suboptimal [46].

Urological Surgery for Prostate Obstruction

Surgical relief of prostatic obstruction (or other obstructive uropathies) is advisable, but the resolution of urinary symptoms following surgery is unpredictable. Resolution of detrusor instability can be expected in 60–70% of patients postoperatively if the instability is the result of prostatic obstruction [23]. The patient should be advised that such operations (i.e., prostatectomy) are primarily indicated for relief of obstruction and to avoid the need of catheterization [9], but they may not eliminate the often coexistent irritative symptoms.

Berger et al. [9] reported persistence of urge incontinence in eight men with PD who had undergone prostatic surgery with evidence of detrusor hyperreflexia in seven patients. They could not find any urodynamic parameters that would predict preoperatively whether a hyperreflexic bladder will stabilize after successful relief of the obstruction [9]. If urge incontinence persists after surgery, anticholinergic therapy can be added. If it still persists, condom catheter drainage may be necessary. There are no urodynamic parameters capable of estimating preoperatively which hyperreflexic bladder will stabilize after successful obstruction relief.

Urologists should be aware of the necessity to rule out MSA prior to surgery. In the series of Chandiramani et al. [13], postoperative results were very different for PD and MSA patients. Three of the five PD patients who underwent transurethral prostatectomy (TURP) reported a good result. Despite oral oxybutynin, one patient with an adequate flow rate had persistent urgency but improved considerably after intravesical oxybutynin. Another patient had a large postvoid residual after TURP due to an atonic bladder of unknown etiology. All 11 men with MSA who underwent TURP were incontinent postoperatively. Nine (82%) had problems immediately, and two (18%) became incontinent within 1 year. Similarly, five anti-incontinence procedures in three women were unsuccessful.

Basal Ganglia Surgery

It is reasonable to expect improvement of urological symptoms in those patients undergoing deep brain stimulation surgery, but more studies are necessary. Murnaghan [7] reported results of basal ganglia surgery on urological symptoms and findings in 29 patients with PD. In the analysis, 8 patients complained of bladder disturbances, and 11 had abnormal CMGs. There were 11 patients who had CMGs performed pre- and postoperatively; only five were unchanged postoperatively. Normal bladder function was converted into hyperreflexic bladder in two of four patients examined before and after stereotaxic lesions of the thalamic nuclei, whereas stereotactic lesions of the posterior limb of the internal capsule normalized three of four uninhibited bladders. Murnaghan concluded that thalamotomy may be associated with increased bladder tonus and pallidotomy with decreased bladder tonus. Capsulotomy may reduce tonus, but bladder sensation may be affected [7].

In 1971, Porter and Bors [11] also reviewed the effects of thalamotomy on bladder function. They studied the impact of uni- and bilateral thalamotomy on 49 patients with PD (11 of whom had normal function). They found that neurogenic bladder dysfunction occurred more frequently in clinically bilateral cases. It was only after bilateral stereotaxic surgery that improvement of bladder function could be consistently documented. The same authors followed up on the status of 40 patients over a long term (4–8 months after their last operation, unilateral or bilateral). These patients had somatic manifestations that had been "significantly improved" after the surgery (no quantification provided). These results indicated that the neurogenic bladder of the parkinsonian patient was responsive to surgical therapy, although the response was not as prompt or successful as treatment of somatic manifestations. Furthermore, the subjective response of the individual was often more pronounced than the objective evidence of improvement. The authors postulated that thalamotomy improved the postvoid residual volume by relaxing the bladder floor and—especially in the "hypoactive bladder"—by increasing the activity of the detrusor muscle [11]. This analysis is consistent with the findings of Murnaghan [7]. It would have been of interest to learn if the use of anticholinergic drugs had decreased postoperatively as a possible alternative explanation to the decline in postvoid residual. Andersen et al. [25] examined 44 patients with parkinsonism, including eight who had undergone thalamotomy. None of the eight patients had normal bladder function. The authors concluded that stereotactic operations on the thalamus could produce uninhibited bladder contractions with a subsequent risk of urological disturbances.

To date, there are some reports of the beneficial effects of deep brain stimulation in the management of refractory irritative urological symptoms. One of the first reports regarding the beneficial effects of basal ganglia surgery on parkinsonian voiding dysfunction was by Finazzi-Agrò et al. [53]. The authors studied five patients who had undergone bilateral implantation of subthalamic nucleus (STN) electrodes. These patients had not been assessed urologically preoperatively. Instead, they were studied urodynamically 4–9 months after surgery with comparisons made between the stimulator-on and stimulator-off states (no mention made as to being on or off levodopa during the procedures). The authors found consistent improvement in bladder capacity and reflex volume (bladder volume at first hyperreflexic detrusor contraction). Seif et al. [54] reported a series of 16 patients with PD and detrusor hyperreflexia who underwent STN-DBS and demonstrated that STN-DBS has a significant and urodynamically recordable effect leading to normalization of pathologically increased bladder sensibility. Shimizu et al. [55] conducted an International Prostate Symptom Score (IPSS) analysis and pressure flow study (PFS) on six patients before and after a chronic stimulating electrode was placed in the STN and evaluated how subjective symptoms and bladder function changed. The IPSS total value, involuntary detrusor contraction threshold volume, and the maximum bladder capacity all improved ($p \leq 0.05$), which suggested that STN-DBS positively

contributes to improvement in urinary function. Winge et al. [56] performed a prospective study of 16 patients with PD investigating LUTS by questionnaires (ISPS, symptoms only) and Danish Prostate Symptom Score (DanPSS, symptoms, and bother of symptoms), and bladder control assessed by urodynamics, before and after the implantation of electrodes in the STN. Symptoms of overactive bladder (IPSS) decreased along with the troublesome symptoms of overactive bladder (DanPSS), $p \leq 0.01$ for both. Urodynamic parameters before and after implantation of electrodes in the STN, evaluated with and without the stimulation on, did not change significantly. Herzog et al. [57] studied 11 PD patients with bilateral STN-DBS during urodynamic bladder filling in STN-DBS ON and OFF condition. A filled bladder led to a significant increase in regional cerebral blood flow (rCBF) by brain PET in the anterior cingulate cortex, which was further enhanced during STN-DBS OFF. A significant interaction between bladder state and STN-DBS was observed in the lateral frontal cortex, with increased rCBF when the bladder was filled during STN-DBS OFF. The data suggest that STN-DBS ameliorates bladder dysfunction and this modulation may result from facilitated processing of afferent bladder information, normalizing the perception of urinary bladder filling in patients with PD.

Other Therapeutic Alternatives

Repetitive transcranial magnetic stimulation (rTMS) and percutaneous posterior tibial nerve stimulation (PTNS) are additional therapeutic alternatives for PD patients with detrusor overactivity.

The effects of inhibitory rTMS on several of the motor and nonmotor symptoms of PD are being studied [58]. Brusa et al. studied the effects of a 2-week course of low-frequency (1 Hz) inhibitory rTMS on bladder function of eight advanced PD patients [59]. The IPSS was used to measure the subjective LUTS, and a urodynamic evaluation was performed. rTMS was able to improve temporarily LUTS in PD patients, increasing bladder capacity and the first sensation of filling phase. Reduction of IPSS score also was noted, due to improvement in filling phase symptoms. The beneficial effects assessed with the IPSS lasted for up to 2 weeks after the end of stimulation. The mechanism of action of rTMS is unknown. It is possible that inhibitory rTMS induces an opposite modulation of the descending corticospinal tract output targeting the detrusor muscle, resulting in a reduced bladder overactivity. As an alternative mechanism, the authors proposed that rTMS may modulate the pontine micturition center, site of descending excitatory projections to parasympathetic sacral centers and/or periaqueductal gray (PAG), where afferent proprioceptive projections of the bladder terminate. Further studies directly measuring pelvic floor/detrusor muscle EMG activity before and after rTMS might improve our knowledge regarding the mechanism of action of this therapy.

Several different electrical stimulation techniques have been used to treat urinary disorders. Acute perineal nerve stimulation decreases detrusor overactivity in patients with spinal cord injury. Chronic nerve stimulation of perineal skin/sacral dermatomes has been used to manage urge incontinence. Sacral neuromodulation, with implantation of an S3 stimulator, has been proposed to treat refractory urge incontinence due to detrusor overactivity. The mechanism of action of these techniques is still unknown but may involve a rebalancing of inhibitory and excitatory impulses that control bladder function in the CNS [60]. PTNS inhibits bladder activity by depolarizing somatic sacral and lumbar afferent fibers [61]. Afferent stimulation provides central inhibition of the preganglionic bladder motor neurons through a direct route in the sacral cord [62]. Krivoborodov et al. [63] evaluated the effects of tibial neuromodulation in 29 patients with detrusor overactivity due to PD. They observed a decrease in the average voiding frequency and number of leakage episodes after 12 sessions and 6 months of tibial neuromodulation. Symptomatic improvement greater than 50% was achieved in 26 of 29 patients, including six patients who were refractory to anticholinergic agents and nine men

with benign prostatic hypertrophy. Kabay et al. [60] evaluated the effects of tibial neuromodulation in 32 patients with PD and detrusor overactivity associated with urodynamic findings. The urodynamic evaluations were performed before and during PTNS. The mean and first involuntary detrusor contraction (IDC) and the mean maximum cystometric capacity (MCC) were significantly improved during PTNS. The authors concluded that these results demonstrate the objective acute effect of PTNS on urodynamic parameters.

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Cardiovascular Autonomic Dysfunction in Parkinson's Disease

13

David S. Goldstein

Abstract

Patients with Parkinson's disease (PD) often have signs or symptoms of impaired reflexive regulation of the circulation, including orthostatic intolerance from orthostatic hypotension (OH). Regardless of levodopa treatment, patients with PD + OH have abnormal blood pressure responses to the Valsalva maneuver and markedly decreased baroreflex–cardiovagal gain. In contrast, only a minority of patients without OH have abnormal Valsalva responses, and baroreflex–cardiovagal gain is often within normal limits. All patients with PD + OH have reduced sympathetic noradrenergic innervation of the left ventricular myocardium, and most of those without OH also have diffuse or localized loss of cardiac sympathetic innervation. In PD patients with localized denervation, denervation is earlier or more prominent in the inferolateral wall or apex than in the anterobasal septum, consistent with a retrograde, centripetal pathogenetic process. Plasma levels of the sympathetic neurotransmitter, norepinephrine and its main neuronal metabolite, dihydroxyphenylglycol, are lower in PD + OH than in PD without OH, indicating a smaller complement of sympathetic nerves in PD + OH; however, patients with pure autonomic failure (PAF) have even lower norepinephrine and dihydroxyphenylglycol levels, suggesting more extensive noradrenergic denervation in PAF than in PD + OH. These findings contrast with those in multiple system atrophy (MSA), which can be difficult to distinguish clinically from PD + OH, because most MSA patients have intact cardiac and overall noradrenergic innervation. Therefore, PD involves not only loss of nigrostriatal dopaminergic neurons

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but also a peripheral catecholaminergic lesion with loss of postganglionic sympathetic noradrenergic neurons. Recent studies have reported a lack of association of cardiac noradrenergic with striatal dopaminergic denervation across individual patients and a closer association of loss of sense of smell with the peripheral noradrenergic than nigrostriatal dopaminergic lesions. Bases for cardioselectivity of sympathetic denervation in PD and for the seeming independence of central dopaminergic and peripheral noradrenergic denervation are subjects of current research.

Keywords
Autonomic nervous system • Norepinephrine • Sympathetic nervous system • Orthostatic hypotension

Introduction

Patients with Parkinson's disease (PD) frequently have symptoms or signs consistent with autonomic failure. Symptoms include constipation, urinary urgency and frequency, drooling, altered sweating, heat or cold intolerance, erectile dysfunction, and orthostatic or postprandial lightheadedness; corresponding signs include decreased bowel sounds, urinary incontinence, hypophonic speech, decreased swallowing of saliva, and orthostatic hypotension (OH).

Orthostatic Hypotension in PD

OH occurs commonly in PD [1]. Because of increased susceptibility to falls and other accidental trauma, OH in PD can be disabling or even life threatening, and effective treatments are available. Along with loss of sense of smell (anosmia), rapid eye movement behavior disorder, dementia, and depression, disturbed autonomic regulation of the cardiovascular system in PD is gaining recognition as a nonmotor manifestation of PD. As discussed in detail later, across patients with PD the severity of cardiovascular autonomic dysfunction seems independent of the severity of the movement disorder but is related strongly to OH and anosmia.

According to a long-held notion, OH in PD results from treatment with levodopa [2]; however, OH can occur in patients with PD who have never taken levodopa or discontinued levodopa treatment in the remote past [3]. Moreover, OH can be an early manifestation or can precede the movement disorder, the disease diagnosed initially as multiple system atrophy (MSA) or pure autonomic failure (PAF).

Even in the setting of carbidopa treatment that inhibits conversion of levodopa to dopamine outside the central nervous system, levodopa increases plasma levels of both dopamine and its deaminated metabolite, dihydroxyphenylacetic acid [4]. Increases in plasma dihydroxyphenylacetic acid levels are especially prominent when an inhibitor of catechol-O-methyltransferase is given along with levodopa and carbidopa [5]. Exogenously administered dopamine at relatively low doses is well known to produce vasodilation by stimulating dopamine receptors on vascular smooth muscle cells and possibly by inhibiting norepinephrine release from sympathetic nerves. Dopamine also augments natriuresis and diuresis, which promotes depletion of extracellular fluid and tends to decrease blood volume. Accordingly, in the setting of decreased cardiovascular sympathetic innervation and baroreflex failure, vasodilation and hypovolemia elicited by dopamine produced from levodopa might decrease the blood pressure, both during supine rest and when standing, in patients with PD. Therefore, orthostatic intolerance and OH may occur in patients with PD while taking levodopa/carbidopa or dopamine receptor agonists, not directly from

effects of these drugs alone but from interactions with baroreflex and sympathoneural denervation occurring as part of the disease process.

Early, prominent OH in patients with parkinsonism has been considered to exclude PD and to support another diagnosis, such as the parkinsonian form of MSA [6], which is characterized by OH [7]. Among patients with PD + OH, in a substantial proportion OH comes on before, at the time of, or within 1 year of onset of the movement disorder [3], and idiopathic OH initially diagnosed as PAF can evolve into PD + OH [8]. Symptomatic OH can come on late in the course of PD [9] or can already be prominent in early, untreated PD [3, 10, 11]. Considering that PD is far more prevalent than MSA or PAF, one should consider PD in the differential diagnosis of neurogenic OH [12].

At least four factors related to cardiovascular autonomic regulation distinguish PD + OH from PD without OH. PD + OH patients have failure of both the cardiovagal and sympathoneural limbs of the baroreflex, whereas PD patients without OH have normal or near normal baroreflex gains [13–15]. The baroreflex abnormalities may be related to decreased numbers of catecholaminergic neurons in the nucleus of the solitary tract [16], which is the site of the initial synapse of baroreflexes. Second, PD + OH patients all have loss of cardiac sympathetic noradrenergic innervation that is diffuse throughout the left ventricular myocardium, whereas about half of PD patients without OH have intact or locally decreased innervation [17]. Third, PD + OH patients have neuroimaging evidence for decreased renal sympathetic innervation [18], which may promote natriuresis and diuresis and increase susceptibility to blood volume depletion. Finally, PD + OH entails neuropharmacologic, neurochemical, and neuroimaging evidence for decreased noradrenergic innervation in the body as a whole, whereas PD without OH does not [19, 20].

In PD, as in other forms of primary chronic autonomic failure, OH is associated with supine hypertension [15, 21], which sometimes is severe. Review of the NIH experience to date shows that the magnitude of supine hypertension in PD is directly related to the magnitude of OH ($r = 0.57$, $p < 0.0001$) and inversely related to the log of baroreflex–cardiovagal gain ($r = -0.39$, $p = 0.01$).

Baroreflex Failure in PD + OH

A particular pattern of beat-to-beat blood pressure responses to the Valsalva maneuver can identify sympathetic neurocirculatory failure as a cause of OH [22]. Because of deficient reflexive, sympathetically mediated cardiovascular stimulation in response to decreased cardiac filling during Phase II of the maneuver, the blood pressure decreases progressively, and during Phase IV, the pressure returns slowly to and fails to exceed the baseline value (Fig. 13.1). With the advent of noninvasive means to measure blood pressure continuously, one can now relatively easily identify sympathetic neurocirculatory failure as the cause of OH in patients with parkinsonism. In our series extending over 15 years, all patients with unequivocal PD + OH who have been able to perform a technically adequate Valsalva maneuver have had this abnormal pattern, regardless of levodopa/carbidopa treatment. In contrast, only about one-fifth of patients with unequivocal PD and no OH have shown the abnormal pattern.

Failure of reflexive sympathetically mediated cardiovascular stimulation in response to acutely decreased venous return to the heart therefore seems to characterize OH in PD. It should be noted, however, that the same pattern of abnormal beat-to-beat blood pressure responses to the Valsalva maneuver is seen in PAF and in MSA. Therefore, while this pattern is a sensitive index of neurogenic OH, it has no specificity in distinguishing PD + OH from other forms of primary chronic autonomic failure.

Plasma norepinephrine levels normally approximately double within 5 min of standing from the supine position [23]. The finding of failure to increase norepinephrine levels appropriately during orthostasis is consistent with decreased baroreflex–sympathoneural function. Indices of baroreflex–cardiovagal and baroreflex–sympathoneural gain have consistently been

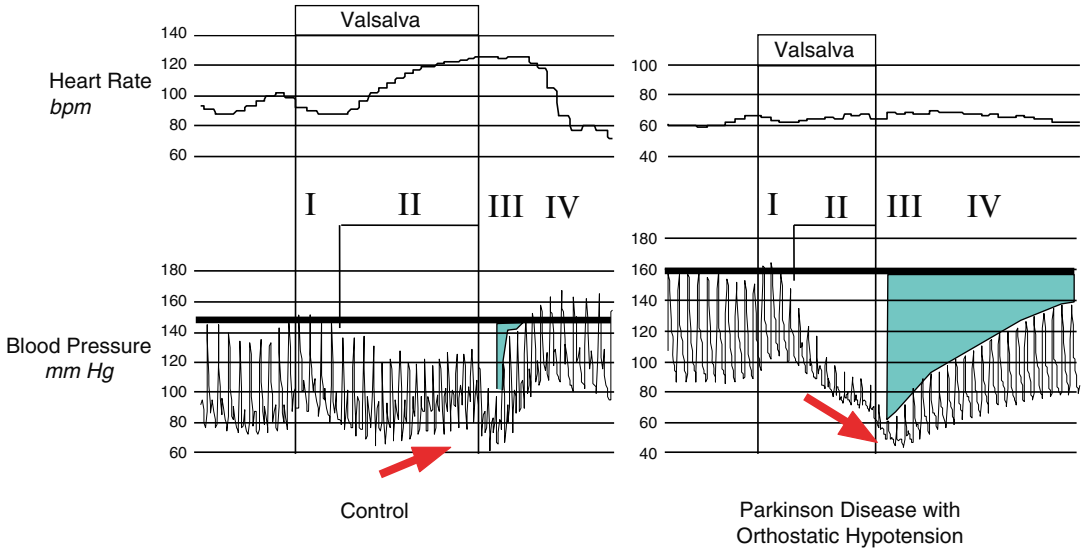

Fig. 13.1 Continuous blood pressure and heart rate responses to the Valsalva maneuver in a control subject and in a patient with Parkinson's disease and orthostatic hypotension (PD + OH). Note progressive fall in blood pressure in Phase II and absence of overshoot in Phase IV in the PD + OH patient

lower in PD + OH patients than in age-matched PD patients without OH. We have estimated baroreflex–cardiovagal gain from the slope of the relationship between interbeat interval and systolic blood pressure during Phase II of the Valsalva maneuver. Nearly all patients with PD + OH have had a baroreflex–cardiovagal gain less than 2 ms/mmHg. In age-matched subgroups averaging 67 years old, mean baroreflex–cardiovagal gain in PD + OH ($N = 30$) was 1.0 ± 0.2 ms/mmHg and in PD without OH ($N = 24$) 3.4 ± 0.8 ms/mmHg ($p = 0.002$).

As measures of baroreflex–sympathoneural function, we have used the fractional increment in plasma norepinephrine levels during orthostasis and the magnitude of fall in systolic blood pressure during Phase II of the Valsalva maneuver. By both indices, PD + OH patients have had attenuated baroreflex–sympathoneural gain, compared with age-matched patients without OH (0.34 ± 0.09 vs. 0.73 ± 0.11, $p = 0.01$; 80 ± 6 vs. 50 ± 6 mmHg, $p = 0.001$).

In our experience, PD + OH patients average about a decade older than PD patients without OH. Studies have disagreed about whether baroreflex–sympathoneural gain changes as a function of aging [24]. Some of this inconsistency seems to have resulted from the different types of measures used—direct indices (e.g., peroneal muscle sympathetic activity) or indirect (e.g., limb vascular resistance). When both direct and indirect measurements have been applied in the same subjects, cardiopulmonary baroreflex control of sympathetic outflow has been found not to be impaired with aging in healthy aged humans [25]. Regulation of sympathetic outflow by arterial baroreceptors, measured by sympathetic microneurography after injection of vasoactive drugs, also remains approximately unchanged [26]. In contrast, many studies have consistently found that baroreflex–cardiovagal gain decreases with normal human aging [27, 28].

Thus, baroreflex–cardiovagal and baroreflex–sympathoneural failure distinguish PD + OH from PD without OH. Although baroreflex failure can manifest as hypertensive crisis, volatile hypertension, orthostatic tachycardia, or malignant vagotonia [29], baroreflex failure does not of itself produce OH.

Cardiac Sympathetic Denervation in PD

At least 50 studies have agreed on the remarkable finding that most patients with PD have at least some loss of sympathetic innervation of the heart, as indicated by low myocardial concentrations of radioactivity after injection of the sympathoneural imaging agents, ^{123}I-MIBG 6-[^{18}F]fluorodopamine, or ^{11}C-hydroxyephedrine [30–32]. Postmortem neuropathologic studies have confirmed almost total absence of tyrosine hydroxylase immunoreactivity, an index of noradrenergic innervation, in epicardial nerve tissue of patients with PD [33].

In patients with PD and no OH, about half have neuroimaging evidence for loss of sympathetic innervation diffusely in the left ventricular myocardium [17], and slightly less than half have loss localized to the lateral or inferior walls (Fig. 13.2), with relative preservation in the septum or anterior wall [34]. Only a small minority have normal cardiac sympathetic innervation. Since cardiac sympathetic denervation occurs commonly in PD patients who lack OH, such denervation does not, of itself produce OH just as baroreflex failure does not of itself produce OH.

Results of follow-up cardiac sympathetic neuroimaging in PD patients without OH seem to fit with a "dying back" phenomenon, in which the more distal noradrenergic nerves degenerate first [35]. Until recently, there was no evidence for such a progression from initially normal innervation to diffuse denervation in any individual PD patient. Figure 13.3 provides such evidence in a patient with typical levodopa-responsive PD and sequential cardiac sympathetic neuroimaging over more than 10 years. For 6 years, left ventricular 6-[^{18}F]fluorodopamine-derived radioactivity both in the interventricular septum and free wall remained within two standard deviations of the normal mean. Lateral wall radioactivity then decreased, followed after about 2 years by decreased septal radioactivity.

These findings seem to fit with postmortem neuropathologic studies of patients with incidental Lewy body disease, in whom cardiac tyrosine

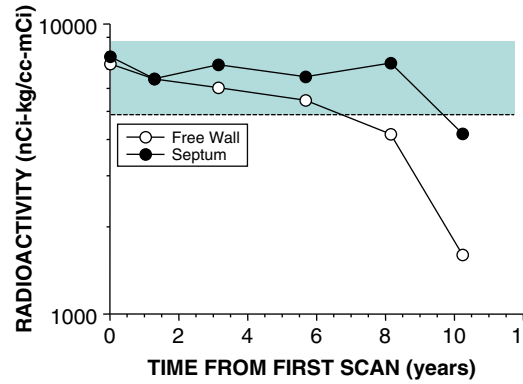

Fig. 13.3 Cardiac septal and free wall 6-[^{18}F]fluorodopamine-derived radioactivity as a function of years of follow-up in a patient with Parkinson's disease who did not have orthostatic hypotension

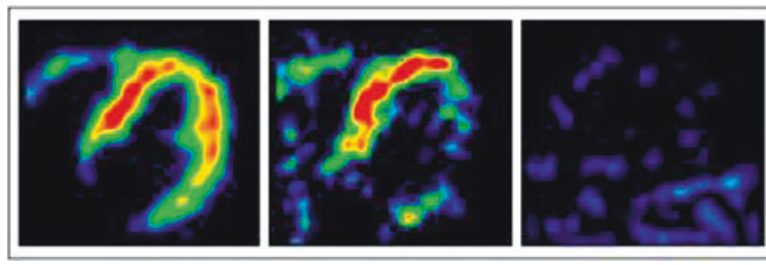

Fig. 13.2 Typical 6-[^{18}F]fluorodopamine positron emission tomographic (PET) scans in a control subject, a PD patient without orthostatic hypotension (OH), and a PD + OH patient. Not decreased 6-[^{18}F]fluorodopamine-derived radioactivity in the lateral wall in the PD patient without OH and diffusely decreased radioactivity in the PD + OH patient

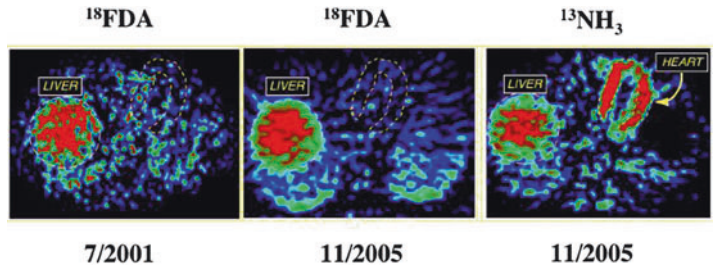

Fig. 13.4 Thoracic transaxial 6-[^{18}F]fluorodopamine sympathoneural and ^{13}N-ammonia perfusion scans in a patient who developed motor signs of Parkinson's disease (PD) in the summer of 2005. Note neuroimaging evidence for cardiac sympathetic denervation 4 years before onset of motor signs of PD

hydroxylase immunoreactivity recedes in a centripetal, retrograde manner correlated with deposition of alpha-synuclein [36, 37]. Loss of tyrosine hydroxylase immunoreactivity and deposition of alpha-synuclein in sympathetic ganglia appear to be relatively late manifestations of the disease process [38, 39]. Findings indicating loss of catecholaminergic terminals prior to loss of cell bodies have potentially important implications for the pathogenetic sequence in the nigrostriatal system.

As shown in Fig. 13.4, neuroimaging evidence of cardiac sympathetic denervation can precede motor signs of PD by several years [40]. The stark contrast from the trends in Fig. 13.3 suggests a degree of independence of cardiac noradrenergic from striatal dopaminergic denervation among PD patients. Results of nigrostriatal and cardiac scanning in the same patients have supported such independence. Across individual PD patients, the extent of putamen dopaminergic denervation as measured by the putamen:occipital cortex ratio of 6-[^{18}F]fluorodopa-derived radioactivity is unrelated to the extent of cardiac noradrenergic denervation as measured by septal myocardial 6-[^{18}F]fluorodopamine-derived radioactivity [35]. Analogously, individual values for striatal dopaminergic innervation assessed by ^{11}C-dihydrotetrabenazine-derived radioactivity are not correlated with values for cardiac noradrenergic denervation assessed by ^{11}C-hydroxyephedrine-derived radioactivity [32].

The relationship between cardiac sympathetic denervation and signs of autonomic failure in PD has been somewhat controversial. Studies based on heart:mediastinum ratios of ^{123}I-MIBG-derived radioactivity have disagreed about whether or not cardiac denervation is related to OH in PD [41, 42]. Our results using cardiac 6-[^{18}F]fluorodopamine-derived radioactivity have been clear. Mean radioactivity in the septum and free wall is substantially lower in PD + OH than in PD without OH (2,573 ± 180 vs. 5,030 ± 403 nCi-kg/cc-mCi, $p = 0.0000006$; 2,456 ± 149 vs. 4,957 ± 491 nCi-kg/cc-mCi, $p = 0.00009$).

The loss of sympathetic innervation in PD seems more prominent in the heart than in any other organ [34]. As noted below, neuroimaging evidence for extracardiac noradrenergic denervation has been reported in PD + OH but not in PD without OH.

Extracardiac Noradrenergic Denervation in PD + OH

No convincing evidence has accrued for extracardiac noradrenergic denervation in PD without OH. A neuroimaging study that noted decreased ^{123}I-MIBG-derived radioactivity in the thyroid in PD did not separate PD + OH from PD without OH [43]. In our series so far, PD patients without OH have not differed from control subjects in terms of 6-[^{18}F]fluorodopamine-derived radioac-

tivity in the thyroid, liver, spleen, renal cortex, nasopharyngeal area, or salivary glands. PD patients without OH also have had normal skeletal muscle microdialysate concentrations of norepinephrine and dihydroxyphenylglycol, indicating normal local sympathetic innervation. In contrast, accumulating evidence supports the occurrence of extracardiac noradrenergic denervation in PD+OH. PD+OH patients have neuroimaging evidence for sympathetic denervation in the thyroid gland and renal cortex [18, 34] and neurochemical evidence for denervation in skeletal muscle [20].

Because of the ready accessibility of skin biopsy tissues, it would seem important to determine if PD features cutaneous noradrenergic denervation. Several studies of cutaneous sympathetic function in PD have relied on measurements of skin humidity or electrical conductance as indices of sweat production; results have been variable [44–47]. Thermoregulatory, gustatory, and emotional sweating, however, depend on sympathetic cholinergic innervation, not sympathetic noradrenergic innervation. A case report noted markedly decreased cutaneous vasoconstrictor responses as indicated by laser Doppler flowmetry in a patient with autonomic failure and uncomplicated PD [48]. Patients with PD+OH have intact sympathetic cholinergic innervation, measured by the quantitative sudomotor axon reflex test, despite sympathetic neurocirculatory failure [20, 49]. No studies to date have assessed noradrenergic innervation specifically in PD by skin tissue contents of norepinephrine or tyrosine hydroxylase.

Concentrations of norepinephrine and dihydroxyphenylglycol in antecubital venous plasma provide a means to detect overall sympathetic denervation [50]. Thus, patients with OH from PAF have low plasma levels of both catechols during supine rest [51]. Patients with PD+OH have lower plasma norepinephrine concentrations than do patients without OH [22, 50]. In patients with PD+OH, plasma norepinephrine levels, while significantly lower than in patients without OH, are not particularly low for healthy people of similar age and are clearly higher than in patients with PAF (Fig. 13.5). The loss of noradrenergic

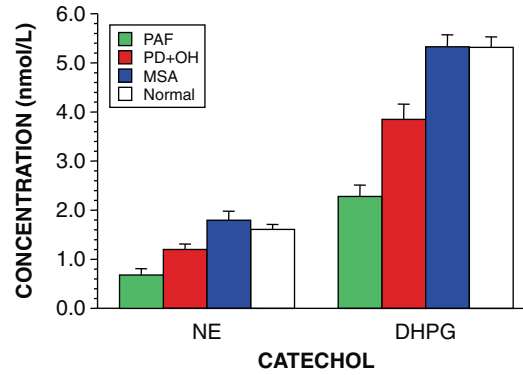

Fig. 13.5 Mean (±SEM) plasma levels of norepinephrine (NE) and dihydroxyphenylglycol (DHPG) in pure autonomic failure (PAF), Parkinson's disease with orthostatic hypotension (PD+OH), multiple system atrophy (MSA), and normal control subjects. Note decreased plasma NE and DHPG in PD+OH compared to MSA and normal control subjects but even more decreased NE and DHPG in PAF than in PD+OH

innervation in the body as a whole in PD+OH therefore seems less extensive than in PAF [52].

Partial loss of sympathetic fibers might lead to augmented traffic in the remaining fibers, resulting in increased proportionate release of norepinephrine from the reduced vesicular stores. Because denervation would produce concurrent decreases in both release and reuptake of norepinephrine, plasma norepinephrine levels might fail to detect a real decrease in norepinephrine release.

Absence of Postganglionic Lesion in MSA

Whereas all patients with PD+OH have cardiac sympathetic denervation [53], most (but not all) patients with MSA have intact cardiac sympathetic innervation, as indicated by sympathetic neuroimaging [54–58] and normal or even increased rates of entry of norepinephrine and other catechols into coronary sinus plasma [30]. Postmortem neuropathologic studies have confirmed this distinction [37, 59, 60].

A small minority of MSA patients have neuroimaging [32] and postmortem neuropathologic [61] evidence of cardiac sympathetic denervation.

Such patients may have alpha-synuclein deposition or Lewy body formation in sympathetic nerves or ganglia. That is, in addition to glial cytoplasmic inclusions that contain alpha-synuclein, now considered a characteristic pathologic feature of MSA [62, 63], some MSA patients have neuronal Lewy body pathology [64]. Clinical correlates of this "hybrid" form of alpha-synucleinopathy remain poorly understood.

In terms of differential diagnosis of PD + OH vs. MSA, whereas the finding of neuroimaging evidence of intact cardiac sympathetic innervation excludes PD + OH, the finding of cardiac sympathetic denervation does not exclude MSA.

Denervation Supersensitivity in PD

Clinical and preclinical studies of chronic autonomic failure have consistently noted increased blood pressure or vasoconstrictor responses to exogenously administered adrenoceptor agonists in PD with orthostatic hypotension. This type of finding would be consistent with "denervation supersensitivity," as described classically by Cannon [65]. Some of this supersensitivity may result from increased expression of α- or β-adrenoceptors or altered intracellular signaling after receptor occupation [66–70]. Sympathetic denervation supersensitivity in the heart might predispose to development of arrhythmias [71].

Augmented cardiovascular responsiveness to adrenoceptor agonists can have other explanations, such as decreased baroreflex buffering of sympathetic outflows, which, as noted above, seems to characterize PD + OH. Structural adaptations of vascular walls with increases in wall:lumen ratios occur commonly in hypertension, and supine hypertension often attends OH in patients with autonomic failure [15, 21]. Hence, although studies of patients with PD have noted augmented pressor responses to exogenously administered norepinephrine, and the augmentation is seen mainly or exclusively in patients with PD + OH [72, 73] as opposed to PD without OH, the results do not necessarily lead to the conclusion that in PD, OH features denervation supersensitivity.

Clinical consequences of cardiac sympathetic denervation and associated denervation supersensitivity in PD remain incompletely understood. We measured responses of pre-ejection period (PEP) and heart rate-corrected PEP (PEPI), inverse indices of myocardial contractility, to intravenous tyramine in patients with cardiac sympathetic denervation, as indicated by low 6-[^{18}F]fluorodopamine-derived radioactivity, and in control subjects with normal radioactivity. By 10 min after initiation of tyramine infusion, PEP and PEPI were decreased in the innervated controls compared with baseline, whereas PEP and PEPI remained unchanged in the denervated patients [74]. Therefore, one of the functional consequences of cardiac sympathetic denervation is failure to increase contractility in response to stimuli that depend on endogenous norepinephrine release. In a related study, we found that among patients with OH, those with cardiac sympathetic denervation had exaggerated responses to isoproterenol. This pattern suggests that cardiac denervation is associated with supersensitivity of cardiac beta-adrenoceptors [75].

Relationship of Anosmia with Autonomic Failure in PD

Virtually all PD patients have at least some loss of sense of smell [35]. Since olfactory dysfunction, OH, and neuroimaging evidence of cardiac sympathetic denervation can precede onset of the movement disorder [8, 40, 76], all three might provide biomarkers of the pathogenetic process. Recent findings suggest a degree of independence of olfactory dysfunction from nigrostriatal dopamine depletion in PD. Olfactory dysfunction is unrelated to the duration or severity of parkinsonism [77], and studies have disagreed about whether olfactory dysfunction is related to neuroimaging evidence for loss of striatal dopaminergic terminals [35, 78].

In contrast with weak or absent relationships of severity of parkinsonism with olfactory dysfunction or autonomic failure, recent reports have noted an association between loss of sense of smell and loss of noradrenergic innervation in the heart [35, 79]. We assessed whether PD patients

categorized as anosmic by the University of Pennsylvania Smell Identification Test (UPSIT) have dysregulation of autonomic outflows, indicated by baroreflex–cardiovagal or baroreflex–sympathoneural failure, or have neuroimaging or neurochemical evidence of loss of postganglionic sympathetic noradrenergic nerves. Compared PD patients with normal to moderately decreased sense of smell, anosmic PD patients had lower mean baroreflex–cardiovagal gain, larger falls in systolic pressure during the Valsalva maneuver and orthostasis, smaller orthostatic increments in plasma norepinephrine and dihydroxyphenylglycol levels, lower cardiac septal:hepatic and renal cortical:hepatic ratios of 6-[^{18}F]fluorodopamine-derived radioactivity, and lower microdialysate norepinephrine and dihydroxyphenylglycol levels [80]. Neither clinical severity of parkinsonism nor the putamen:occipital cortex ratio of 6-[^{18}F]fluorodopa-derived radioactivity was related to the UPSIT category. Therefore, in PD, anosmia appears to be associated with baroreflex failure and cardiac and organ-selective extracardiac noradrenergic denervation, but not associated with severity of parkinsonism or striatal dopaminergic denervation.

Conclusions and Future Trends

A combination of baroreflex failure and loss of sympathetic nerves in the heart and elsewhere can explain OH in PD and the worsening of orthostatic symptoms during treatment with levodopa/carbidopa or dopamine receptor agonists. Baroreflex failure also appears to contribute to the association between OH and supine hypertension in PD. Cardiac sympathetic denervation characterizes most patients with PD and all patients with PD + OH. This evidence contrasts with normal cardiac sympathetic innervation in most patients with MSA. Functional consequences of cardiac sympathetic denervation in PD probably reflect decreased ability to release norepinephrine in response to stressors and denervation supersensitivity of adrenoceptors. Whereas severities of central dopaminergic and peripheral noradrenergic lesions are unrelated across individual PD patients, anosmia and autonomic failure are related to each other. Bases for cardioselectivity of sympathetic denervation in PD and for the seeming independence of central dopaminergic and peripheral noradrenergic denervation are subjects for future research.

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Thermoregulatory Dysfunction in Parkinson's Disease

14

Mark S. LeDoux

Abstract

Homeotherms, such as humans with Parkinson's disease, must maintain core body temperature in a narrow range in the face of fluctuating environmental surroundings and endogenous heat production. A complex and highly integrated collection of autonomic, endocrine, and behavioral responses are involved in the maintenance of core temperature. Dopaminergic innervation of the preoptic and anterior hypothalamus plays an important role in the central nervous system's control of body temperature. Due to a combination of central dopamine deficiency and peripheral autonomic dysfunction, individuals with Parkinson's disease may experience heat and/or cold intolerance and paroxysmal hyperhidrosis. Sudomotor dysfunction in Parkinson's disease can be documented with the sympathetic skin response and quantitative sudomotor axon reflex and thermoregulatory sweat tests.

Keywords

Parkinson's disease • Thermoregulatory • Sweat • Sympathetic • Hypothalamus • Autonomic • Dopamine • Sudomotor

Normal Thermoregulatory Mechanisms

Patients with Parkinson's disease (PD) are made of cells that need energy to do their work. Energy exists in forms such as light, heat, and chemical bonds. Most forms of energy can be classified as either kinetic or potential. Thermal (heat) and radiant (light) are two major forms of kinetic energy. The first law of thermodynamics states that the various types of energy can be changed from one form to another. The process of photosynthesis, for example, converts the kinetic energy of light into the potential energy of covalent bonds. Concentration and charge gradients are other forms of potential energy critical to biological systems.

Biological systems continuously require energy for the performance of mechanical work,

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the active transport of molecules and ions, and the synthesis of macromolecules. Chemotrophs (e.g., humans) obtain free energy by the oxidation of foods, a process in which adenosine diphosphate (ADP) is converted to adenosine triphosphate (ATP). ATP serves as the principal carrier of free energy in biological systems. ATP contains two energy-rich phosphoanhydride bonds, and a large amount of energy is liberated when ATP is hydrolyzed to ADP.

The sequences of reactions required for the production of ATP are exothermic. In exothermic reactions, the products contain less bond energy than the reactants, and the excess energy is usually liberated as heat. On average, one-third of the potential energy contained in foods is converted to heat during the process of ATP generation. Heat is also generated in the body during the turnover of cellular macromolecules such as proteins. Heat production by the body is normally expressed in terms of metabolic rate. The metabolic rate is governed by basal cellular metabolism, muscular activity, thyroid hormones, and levels of circulating epinephrine and norepinephrine. Metabolic rate can be quantified by direct calorimetry, which measures the total quantity of heat liberated from the body during a fixed period of time.

In addition to endogenous production, heat may also be gained from exogenous sources via mechanisms such as radiation and conduction. Radiation is the transfer of heat by electromagnetic radiation. When environmental temperatures are greater than body temperatures, a thermal gradient is present, and heat can be transferred to humans by radiation. Conduction is heat exchange between objects that are in contact with one another. For instance, a person can gain heat by conduction while sitting on asphalt pavement on a scorching summer day.

Homeotherms, like humans, must maintain core body temperature in a narrow range despite fluctuations in environmental conditions and endogenous heat production. Humans have a variety of mechanisms for heat loss that can be used to prevent core temperature elevations. In humans, the vast majority of heat is generated by deep tissues such as the brain, liver, heart, and skeletal muscles. For effective elimination, this heat must first be transferred to the skin and then from the skin to the surroundings. A robust microvascular network is present in the dermis and subdermal connective tissues. Draining veins from skin capillaries are directly connected to a venous plexus located in the lower dermis and subdermal connective tissue. In the hands, feet, and ears, muscular arteriovenous anastomoses directly connect small arteries to this venous plexus. When necessary, blood flow to the skin venous plexus can increase to a quarter of cardiac output.

At an ambient temperature of 22°C, most heat is lost from the skin surface by radiation and conduction. Conduction of heat to the air layer surrounding the body is greatly augmented by convection. Heat from the skin that is conducted to the surrounding air is carried away by convection air currents. Evaporation is the final major mechanism for heat loss and becomes critical when environmental temperatures exceed body temperature. Evaporation of 1 g of water removes 0.58 kilocalorie of heat from the body. Most of this water is derived from sweat, but insensible losses from the lungs, upper airways, and skin average 50 ml/h. During strenuous physical activity in a hot environment, sweat secretion can exceed 1,600 ml/h. Urination, defecation, and respiration only account for 2–3% of heat loss in normal circumstances.

Neuroanatomical Substrates of Thermoregulation

An array of autonomic, behavioral, endocrine, and somatic thermoregulatory responses is involved in the maintenance of core temperature within a narrow range. Mechanisms activated by heat include sweating, cutaneous vasodilatation, and movement to a cooler environment. Mechanisms activated by cold include vasoconstriction, piloerection, movement to a warmer environment, shivering, and, possibly, increased output of thyroxine. The hypothalamus plays a central role in these thermoregulatory responses.

The anterior/preoptic hypothalamus contains both warm- and cold-sensitive neurons. Warm-sensitive neurons outnumber cold-sensitive neurons by a 3:1 ratio. Increased core temperatures are associated with increased firing rates of warm-sensitive neurons; cold-sensitive neurons increase their firing rates when core temperatures fall [1]. Although much less significant in the maintenance of core temperature, temperature sensors are also present in the skin and deep visceral tissues. In the skin, there are ten times more cold receptors than heat receptors. Afferent pathways for thermal receptors in the skin begin in the dorsal roots and ascend predominantly in the spinothalamic tracts. Thermal receptors in deep tissues such as the abdominal viscera may course through the vagus and splanchnic nerves before entering the central nervous system. Both skin and deep thermal receptor pathways terminate in the preoptic/anterior and posterior hypothalamic areas. The posterior hypothalamus integrates signals from the skin, deep tissues, and preoptic/anterior hypothalamus. Integrated signals are compared with the set point for core temperature. The posterior hypothalamus then triggers autonomic responses appropriate for temperature correction. Lesion and stimulation studies highlight the complex interrelated roles of the preoptic/anterior and posterior hypothalamus. Stimulation of the preoptic/anterior hypothalamic area produces cutaneous vasodilatation and sweating; stimulation of the posterior hypothalamus causes vasoconstriction and shivering. In comparison, lesions of the preoptic/anterior hypothalamus result in hyperthermia and impair the normal responses to environmental heat, such as sweating and cutaneous vasodilatation. Lesions of the posterior hypothalamus lead to hypothermia in cold environments because heat conservation and generation mechanisms are impaired.

The intermediolateral and intermediomedial cell columns of spinal segments T1 to L3 of the spinal cord are the origin of preganglionic sympathetic outflow. These preganglionic neurons receive first- and higher-order control from cell groups in the hypothalamus and brainstem, including the rostral ventrolateral medulla, rostral ventromedial medulla, caudal raphe nuclei, A5 noradrenergic cell group, lateral and posterior hypothalamus, periaqueductal gray, and preoptic area [2]. The axons of preganglionic neurons form the white rami communicantes that pass to the sympathetic trunk. Preganglionic axons may synapse with postganglionic neurons in the sympathetic ganglia and rejoin the spinal nerves as gray rami communicantes. Preganglionic axons may also ascend or descend the sympathetic trunk before making synapses on postganglionic neurons. Other preganglionic fibers course through the sympathetic ganglia and form the splanchnic nerves that synapse in the prevertebral ganglia. Acetylcholine is the neurotransmitter released at preganglionic synapses on postganglionic neurons. Acetylcholine is also released by the postganglionic sympathetic innervation of sweat glands; norepinephrine is released by the vast majority of postganglionic nerves that innervate blood vessels. Other neurotransmitters, particularly peptides, may be released in combination with either acetylcholine or norepinephrine.

Dopamine Effects on Thermoregulation

The potential role of dopamine in the modulation of neuronal activity in the preoptic/anterior hypothalamus has been studied in a variety of model systems. When directly injected into the preoptic/anterior hypothalamus of rats, the dopamine agonist apomorphine causes hypothermia. In contrast, local injections of dopaminergic antagonists like haloperidol cause hyperthermia [3]. An in vitro study by Scott and Boulant [4] detailed the effects of dopamine on individual hypothalamic neurons; single-unit activity was recorded from the preoptic/anterior hypothalamic area in rat tissue slices. Dopamine excited 41% of warm-sensitive neurons and inhibited 100% of the cold-sensitive neurons. Dopamine also decreased the thermosensitivity of the cold-sensitive neurons. Hasegawa et al. [5] used in vivo microdialysis to monitor the levels of dopamine and its metabolites in the preoptic/anterior hypothalamus of exercising rats. The levels of the dopamine metabolites 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) increased

during exercise. In aggregate, these experimental findings indicate that dopaminergic innervation of the preoptic/anterior hypothalamus is involved in heat loss mechanisms. More recent work suggests that dopamine D1/D5 and D2 receptors may play independent roles in thermoregulatory mechanisms [6, 7].

Testing Thermoregulatory Mechanisms

Core and Skin Temperature

Human core temperatures undergo circadian fluctuations of up to 0.6°C. Core temperature is lowest during sleep and, in most people, reaches its nadir at about 6:00 AM. Core temperature is highest in the evenings and rises with physical activity. In women, core temperature rises during ovulation. Esophageal and bladder temperature-sensing devices may be superior to rectal probes for highly accurate measures of core temperature [8]. However, rectal temperatures are reliable enough for most routine clinical applications and more easily acquired in the outpatient setting. Oral temperatures are typically 0.5°C below rectal temperatures and are relatively unstable during long-term recordings. Axillary temperatures are undependable, and tympanic membrane temperature measurements may be compromised by cerumen, narrow external auditory canals, and tympanic membrane defects from previous trauma [9].

In contrast to core temperature, skin temperature may vary greatly from one body surface area to another and is highly dependent on environmental temperature and the body's need to dissipate heat. Skin temperature patterns can be analyzed in two ways. One method is infrared pyrometry. Pyrometry is the measurement of radiation emitted from an object. Pyrometers work without making contact with the object of interest. An infrared pyrometer can be used to document skin temperatures at several standard sites (e.g., forearm, thenar pad, hypothenar pad, distal pads of each finger, thigh, anterior leg, dorsum of the foot, and each toe pad) on each half of the body. Infrared telethermography provides a more sophisticated color-coded digital representation of body-surface temperatures; high-resolution digital images of the trunk, face, extremities, palmar surfaces of the hands, and plantar surfaces of the feet can be obtained in minutes. Side-to-side differences of >1°C are considered clinically significant.

Sudomotor Function

Sympathetic Skin Response

The sympathetic skin response (SSR) has also been called the somatosympathetic response because the afferent component of its neural pathway is mediated predominantly by type II and III myelinated fibers. Although a variety of stimuli can be used to elicit the SSR, many laboratories provide a shock stimulus to the supraorbital or sural nerves. The efferent component of the SSR is mediated by the type B and C sympathetic innervations of sweat glands. Using the standard electrophysiological equipment typically employed in nerve conduction studies, potentials are acquired from all four palmar–plantar surfaces. On the hand, the cathode is placed over the second palmar interspace and anode over the pulp of the middle finger. On the foot, the cathode is placed over the second plantar interspace and the anode on the pulp of the second toe. Since the SSR is sensitive to a variety of environmental factors, the patient should be relaxed, the room should be very quiet and dimly lit, and the test should be performed before other potentially painful neurophysiological studies such as needle electromyography. Voltage is recorded for 10 s. In a study by Knevzevic and Bajada [10], the average latency to onset of the palmar and plantar responses was 1.5 ms and 2.1 ms, respectively. In normal subjects, an early negative potential is followed by positive and then late long-duration negative potentials.

The SSR diminishes with age, and the plantar SSR may be absent in elderly subjects. The SSR also habituates, and repeat studies should be performed at intervals of at least 30 s. The SSR is widely used in clinical neurology, and SSR

abnormalities have been described in numerous diseases of both the central and peripheral nervous systems. Unfortunately, this test suffers from poor sensitivity and specificity in routine clinical application.

Quantitative Sudomotor Axon Reflex Testing

The quantitative sudomotor axon reflex testing (QSART) depends on the integrity of postganglionic sympathetic sudomotor axons and sweat glands. The stimulus for the QSART is iontophoretically applied acetylcholine [11]. Acetylcholine activates the terminals of postganglionic sympathetic axons. The impulse is transmitted antidromically to a branch point and then orthodromically to activate sweat glands. The QSART requires a multicompartment sweat cell; one compartment serves as the stimulus compartment for delivery of acetylcholine and another for evaporation of sweat by nitrogen gas. An intervening compartment blocks diffusion of sweat between the stimulus and evaporation compartments. Recordings are typically performed from multiple sites such as the medial forearm, proximal leg, distal leg, and dorsum of the foot. The latency, duration, and amplitude of the response are recorded. The QSART is both sensitive and reproducible. Some clinicians simply measure sweating with an evaporimeter without iontophoretic application of acetylcholine.

The QSART is usually normal in purely central and preganglionic disorders. The QSART is frequently abnormal in axonal neuropathies such as those seen in diabetes and other metabolic disorders. In early diabetic axonal neuropathy, only distal sites such as the dorsum of the foot may show QSART abnormalities. As distal axonal neuropathies progress in severity, postganglionic failure may be detected at more proximal sites.

Thermoregulatory Sweat Test

The thermoregulatory sweat test (TST) provides a global assessment of the entire sympathetic sudomotor pathway [12, 13]. A normal TST requires the integrity of high-order centers in the hypothalamus and brainstem, the intermediolateral cell columns, the white rami communicantes, sympathetic ganglia, postganglionic neurons, and sweat glands. To perform the TST, an indicator powder (one part alizarin red, two parts corn starch, one part sodium carbonate) is first applied to the unclothed body surface. The powder is light orange when dry and purple when wet. The subject is then enclosed in a chamber at 45–50°C with a relative humidity of 35–40%. Oral temperature is continuously monitored throughout the procedure and should not exceed 38.5°C. Under these conditions, a heating time of 30–45 min is required to elicit a maximal sweat response. A digital camera is used to photograph the body and provide a permanent record of sweating patterns. An image analysis program can then be used to determine the percentage of anterior body surface anhidrosis (%TST).

When used in combination with the QSART, the TST can, in most circumstances, determine whether an abnormality is preganglionic or postganglionic. It is important to note, however, that the transsynaptic effects of long-standing preganglionic lesions can impair postganglionic sympathetic sudomotor function [12, 14]. The TST may be used to evaluate sudomotor dysfunction in a variety of neurological diseases, including hypothalamic structural lesions, spinal cord pathology (e.g., vitamin B12 deficiency, syrinx, traumatic myelopathy, multiple sclerosis), neurodegenerative disorders such as multiple system atrophy (MSA), and disorders of the peripheral nervous system (e.g., diabetes, amyloidosis, other small-fiber neuropathies). In patients with compensatory regional hyperhidrosis, the TST can be used to demonstrate anhidrosis in other body regions.

Silastic Sweat Imprint Test

This test directly measures the sweat gland response to a muscarinic agent, pilocarpine. Denervated glands fail to respond. In many labs, acetylcholine is used in place of pilocarpine, although sweating in response to the former reflects stimulation of both muscarinic and nicotinic receptors. After intradermal injection of pilocarpine, sweat imprints are formed by the secretion of active sweat glands into a plastic (Silastic) imprint. After removal, the indentations in the Silastic material can be examined with a

microscope, photographed in either digital or analog format, and analyzed with a variety of morphometric software packages. The test can determine sweat gland density, a histogram of sweat droplet size, and sweat volume per area. Denervated sweat glands lose their sudomotor response to pilocarpine.

The Silastic sweat imprint test is sensitive, is reproducible, and complements the QSART. The QSART detects postganglionic sudomotor dysfunction among a population of sympathetic axons and sweat glands. In distinction, the Silastic sweat imprint method provides quantitative information about individual sweat glands. The QSART may be more sensitive than the Silastic sweat imprint method for detection of early autonomic neuropathy.

Quantitative Thermoregulatory Sweat Test

Subjects are acclimatized to a room with stable temperature (40°C) and humidity (40%) for 30 min [15]. Local sweat rates are measured using the ventilated capsule method. Plastic capsules are attached to two skin recording areas (forearm, thigh) and connected to plastic tubing. Low-humidity air is passed at a constant flow rate through the capsule, and changes in relative humidity are measured using capacitance hygrometry. Resting sweat rates and the frequency of sweat expulsions are measured for 10 min from the two recording sites. Thyrotropin-releasing hormone (TRH) is then infused, while resting sweat rates and the frequency of sweat expulsions are measured for another 10 min. Control subjects show significant increases in sweat rates and the frequency of sweat expulsions during infusion of TRH.

Skin Blood Flow

Laser Doppler flow meters can be used to measure skin blood flow before, during, and after autonomic maneuvers [16]. Modern laser Doppler flow meters provide real-time assessment of perfusion in very small volumes of tissue (1 mm^3). Changes in blood flow are measured in response to perturbations intended to increase or decrease sympathetic innervation of the cutaneous vasculature. Measurements are frequently acquired from the finger and toe pads because sympathetic activity in these areas is limited to vasoconstriction. Simultaneous continuous noninvasive measurements of blood pressure and laser Doppler perfusion from the forearm allow for calculation of cutaneous vascular resistance in response to both sympathetic vasoconstrictor (deep inspiration, foot immersion in cold water) and vasodilator (postischemic reactive hyperemia, heating of the body) responses [17].

Clinical Manifestations of Thermoregulatory Dysfunction in PD

Heat and Cold Intolerance

Both heat intolerance and cold intolerance are difficult to define and fairly common in the elderly population. A person with heat intolerance may feel unusually hot and dizzy after vigorous activity or on a torrid summer day. Other manifestations of heat intolerance may include flushing, malaise, and generalized weakness. Cold intolerance is, seemingly, a more common complaint noted on review of systems. However, cold intolerance is usually interpreted by patients to mean an inability to keep their hands and feet warm, particularly in cold weather. More significant manifestations of cold intolerance would be difficulty maintaining core temperature with associated weakness and dulling of consciousness in chilly environments. One report suggests that parkinsonian patients may have an increased susceptibility to hypothermia [18]. A comprehensive autonomic symptom survey in PD analyzed the relative frequency (1–7 days/week) of subjective heat and cold intolerance in PD patients in comparison with age-matched controls [19]. On average, cold intolerance was more common in the PD group, although this result did not reach statistical significance. In contrast, there were no differences between PD patients and age-matched controls in heat intolerance.

Paroxysmal Hyperhidrosis and Other Sweating Abnormalities

Sweating (i.e., sudomotor) abnormalities were included in early descriptions of PD prior to the availability of levodopa [20, 21]. In more recent times, some patients have reported that sweating abnormalities antedated their initial diagnosis of PD. Ray Kennedy, for example, a renowned soccer player in England during the 1970s, exhibited "unprovoked bouts of perspiration accompanying feelings of heat" before his PD was diagnosed and then treated with levodopa [22]. Most studies indicate that sweating abnormalities increase in severity with declining motor function in PD [23]. Both hypohidrosis and hyperhidrosis have been described in PD. Hypohidrosis is most common in the lower extremities. Hyperhidrosis, if present, tends to occur in the upper trunk, neck, and face. Head and neck hyperhidrosis could be a compensatory response to impaired sweating in other body regions [24]. However, in some patients with PD, profuse sweating may seemingly involve the entire body surface.

Hyperhidrosis may occur on a paroxysmal basis with the paroxysms being triggered by "off" periods. Sage and Mark [25] described copious sweating during "off" periods in four patients with advanced PD. Plasma levodopa concentration was measured in one of their patients and correlated with clinical signs; drenching sweats started just before the noted decline in plasma levodopa levels and continued into the motor "off" period for about 1 h.

Levodopa and/or Dopamine Agonist-Withdrawal Neuroleptic Malignant-Like Syndrome

The neuroleptic malignant syndrome (NMS) most commonly occurs 4–14 days after initiation of therapy with a neuroleptic and approximately 90% of NMS cases occur within 10 days of neuroleptic initiation. Although the clinical spectrum of NMS is broad, certain features are necessary to make a diagnosis: hyperthermia (>38°C), muscular rigidity, delirium, and autonomic dysfunction. Autonomic features may include hypertension, hypotension, tachycardia, diaphoresis, sialorrhea, and incontinence. Rhabdomyolysis with elevated creatinine kinase is present in many cases; renal failure may result. An NMS-like syndrome may occur after withdrawal of levodopa and/or dopamine agonists. Concomitant use of either lithium or anticholinergics increases the risk of both NMS and NMS-like syndromes.

In patients with PD, an NMS-like syndrome may occur during "off" periods [26], after reduction in levodopa or dopamine agonist therapy [27, 28], and even during the premenstrual period despite lack of levodopa withdrawal [29]. Average age was 72 years, and mean disease duration was 9.5 years in a recent series of 11 PD patients who developed an NMS-like syndrome after sudden discontinuation of levodopa therapy [30]. In this series, the NMS-like syndrome appeared at a mean latency of 93 h after stopping levodopa.

The first and most important component of treating the NMS-like syndrome in PD patients is immediate reinstitution of therapy with levodopa and/or a dopamine agonist. Patients with an NMS-like syndrome must be closely monitored in an intensive care unit. A nasogastric feeding tube should be placed if the patient is delirious and unable to take medications by mouth. If available, apomorphine can be used until a feeding tube can be placed or in patients with upper gastrointestinal dysfunction (e.g., anatomical obstruction, recent laparotomy). Serum creatinine kinase and urine myoglobin should be checked for evidence of muscle necrosis. Urine output should be monitored with an indwelling catheter. It is important to correct volume depletion and hypotension with intravenous fluids. Methods to reduce body temperature include cooling blankets and oral or rectal acetaminophen. Benzodiazepines can be used to calm the agitated patient. Dantrolene has been used in patients with NMS to reduced rigidity and lessen the severity of rhabdomyolysis. Forced diuresis with a mannitol drip can prevent renal failure in patients with laboratory evidence

of rhabdomyolysis. Clinical outcomes are good in the majority of patients receiving proper intensive medical management.

Thermoregulatory Test Abnormalities in Parkinson's Disease

Sudomotor and other thermoregulatory test abnormalities are present in many patients with PD (see Table 14.1). In early PD, test abnormalities are most consistent with central and preganglionic autonomic dysfunction. In more advanced PD, an increasing percentage of patients will, in addition, show evidence of postganglionic sympathetic abnormalities. As in most other neuropathies, the postganglionic sympathetic neuropathy in PD first becomes manifest in the longest axons (i.e., those to the distal lower extremities). Given that primary PD is most appropriately classified as a neurodegenerative syndrome with variable and broad expressivity, it is not surprising that even within a particular Hoehn and Yahr (H&Y) stage, sudomotor testing will be normal in some patients and yet strikingly abnormal in others. Therefore, thermoregulatory testing may not be particularly useful for diagnosing "Parkinson's disease" in an individual patient but may supply information important for the clinical management of a patient already diagnosed with PD based on standard clinical criteria.

The TST was used in two early studies of autonomic dysfunction in PD. Appenzeller and Goss [24] reported a normal TST in 8 out of 18 patients with PD; the remaining patients had almost complete anhidrosis on the trunk and limbs with hyperhidrosis on the face. Appenzeller and Goss suggested that the facial hyperhidrosis was a compensatory response to anhidrosis elsewhere on the body. In the same year, Aminoff and Wilcox described patchy impairment of the TST in 4 out of 11 PD patients [31].

In 1986, Goetz et al. published their studies of autonomic function in 31 patients with PD [32]. Average patient age, disease duration, and H&Y stage were 61 years, 123 months, and 3.1, respectively. Findings were compared with those of 10 age-matched controls. Off-medication skin temperature after heat stress was lower in the PD group than in controls. Off-medication head and neck sweating, as measured with TST, was significantly greater in the PD group. In contrast, there were no differences in skin temperature and sweating between the control group and PD patients on medication, indicating a substantial role for dopaminergic neurotransmission in thermoregulation. A study of 35 carefully selected PD patients at the Mayo Clinic with the TST revealed mean anterior hypohidrosis of about 40% [33]. Of these 35 patients, 50% had H&Y stage III disease, about 30% had stage IV disease, none had stage V disease, and the remainder had stage I or II disease.

Quantitative measures of sweating using instrumentation that generates continuous dependent variables (evaporimetry, capacitance hygrometry) also show that PD patients sweat more in the head and neck region than age-matched normal subjects. PD patients tend to exhibit lower extremity hypohidrosis, particularly as their disease progresses. Also consistent with distal sympathetic dysfunction, foot temperature may be colder in PD patients than in controls [34]. Turkka and Myllylä [35] showed that sweating in the upper parts of the body was greater in PD patients than in controls both before and after heating. Upper body relative hyperhidrosis also increased with increasing disease severity. After a 5-min heating stimulus, PD patients sweated less in the foot than the control subjects.

In comparison with advanced disease, sweating abnormalities are both less frequent and less severe in early PD. For example, Kihara et al. [36] measured local sweat rates on the forearm and thigh in ten patients with early primary PD (H&Y stages I and II) and found that forearm sweat rates were virtually identical to control values. In distinction, the control group had a higher average thigh sweat rate than the PD group, although this difference did not reach statistical significance. In a quantitative thermoregulatory sweat test (QTST) included in the same study, early PD patients failed to increase local sweat rates with TRH infusion. This result is intriguing and suggests the need for additional testing with

Table 14.1 Tests of sudomotor function in PD

Name	Technique	Pathway(s) analyzed	Findings in Parkinson's disease	References
Sympathetic skin response (SSR)	Record palmar and plantar current change in response to shock stimulus	Type II and III mechanoreceptor afferents and sympathetic efferents	Incidence of absent or diminished responses increase with increasing disease severity	[34, 37, 38]
Quantitative sudomotor axon reflex test (QSART)	Measure sweat volume and latency of response to iontophoresis of acetylcholine	Postganglionic sympathetic innervation of sweat glands	Mildly abnormal, in general, and degree of abnormality increases with disease severity	[33, 53]
Thermoregulatory sweat test (TST)	Apply indicator powder to whole body prior to whole body heating	Central and peripheral sudomotor pathways	Patchy or mainly lower extremity anhidrosis or hypohidrosis in the majority of patients	[24, 31–33, 39]
Silastic sweat imprint	Obtain imprints of sweat droplets after iontophoresis of pilocarpine or acetylcholine	Postganglionic sympathetic innervation of sweat glands	Mean total volume and sweat droplet density lower in PD	[37, 38]
Quantitative thermoregulatory sweat test (QTST)	Measure resting sweat rate and frequency of sweat expulsions before and after infusion of TRH	Central and peripheral sudomotor pathways including hypothalamic control centers	Absent response to TRH in early PD	[36]
Evaporimetry	Measure temporal and spatial differences in sweat production	Central and peripheral sudomotor pathways	Sweating fluctuates in conjunction with motor wearing off	[23]

a larger cohort of patients to establish the reproducibility, sensitivity, and specificity of the QTST as a marker for early PD.

Several groups have demonstrated SSR abnormalities in PD [34, 37, 38]. Since the SSR is mediated by both central and peripheral autonomic pathways, it can be loosely interpreted as a general measure of sudomotor integrity. The incidence of abnormal SSRs increases, and response amplitudes decrease with rising H&Y stages and United Parkinson's Disease Rating Scale (UPDRS) scores. In PD, therapy with levodopa or dopamine agonists has no significant effect on the SSR [34, 38]. SSR abnormalities are more pronounced on limbs affected by greater motor dysfunction (e.g., tremor, rigidity) than contralaterally [34].

Asymmetrical thermoregulatory test abnormalities in patients with asymmetrical motor signs have been reported by some [34, 38] but not all investigators [32, 35]. De Marinis et al. [39] reported both asymmetrical sweating and facial telethermography in PD patients. In their study, facial cutaneous dilatation was induced by sublingual administration of nitroglycerin. Facial telethermography was performed at baseline, 15 and 30 min after administration of nitroglycerin. Both sweating and cutaneous facial dilatation were reduced in PD patients. Decreased heat elimination and sweating were more pronounced on the hemi-body (arms, legs) with greater motor dysfunction. As initially described by Gowers [20], excessive head and neck sweating in PD patients may only involve the parkinsonian side of the body. Therefore, asymmetrical head and neck sweating in PD may be a compensatory response to asymmetrical hypohidrosis elsewhere. Asymmetric autonomic dysfunction also has been described in patients with strokes and other focal structural abnormalities of the central nervous system [40–42]. Lesions of the hypothalamus are associated with contralateral hyperhidrosis [41, 42]. It is possible that dopaminergic projections to the preoptic/anterior hypothalamus and/or the posterior hypothalamus are defective ipsilateral to the side of the brain with greater dopaminergic cell loss. Alternatively, the activities of cortical–hypothalamic projections that contribute to thermoregulation may be distorted by defective signaling within cortical–basal ganglia loops.

Postganglionic sympathetic innervation of sweat glands, as measured by the QSART and Silastic sweat imprints, may show abnormalities in PD, particularly in more advanced stages of the disease. In the study of 35 PD patients from the Mayo Clinic cited above, the QSART was 37% abnormal at the forearm and 40% abnormal at the foot [33]. However, the QSART abnormalities were mild in most PD patients. In two studies, Silastic sweat imprints were used to show decreased total sweat volume and sweat droplet density in PD patients in comparison with age-matched controls [37, 38]. For example, in the report by Mano et al., the average sweat volume per gland was 0.0143 mm^3 in PD patients (1, H&Y stage I; 11, H&Y stage II; 11, H&Y stage III; 11, H&Y stage IV; 0, H&Y stage V) and 0.0327 mm^3 in controls [37]. Mean total sweat volume was 3.6 mm^3/cm^2 in PD patients and 11.9 mm^3/cm^2 in controls.

Pathological Bases for Thermoregulatory Dysfunction in Parkinson's Disease

The thermoregulatory test abnormalities and clinical manifestations of thermoregulatory dysfunction in PD suggest the presence of widespread neural pathology encompassing both preganglionic neurons and sympathetic ganglion cells in addition to higher-order autonomic centers in the brainstem and hypothalamus. Postmortem pathological findings provide the anatomical basis for specific sudomotor and other thermoregulatory findings in PD. Because neuronal loss occurs at sites where Lewy bodies are numerous, the presence of Lewy bodies has been used as a marker for neuronal degeneration in PD. All comprehensive pathological studies have shown that Lewy bodies are not limited to the substantia nigra pars compacta. Clearly, PD is not a disease restricted to midbrain dopamine neurons. In fact, the earliest pathological descriptions of PD noted the presence of Lewy bodies within an important component of the central

autonomic nervous system, the dorsal motor nucleus of the vagus nerve [43]. Den Hartog Jager and Bethlem [44] emphasized the widespread distribution of Lewy bodies in their seminal pathological study of PD. Lewy bodies were detected in the sympathetic ganglia in five out of six PD cases. In the central nervous system, Lewy bodies were numerous in the locus ceruleus, hypothalamus, and brainstem. In four cases, Lewy bodies were found in the lateral horns of the spinal cord. Den Hartog Jager and Bethlem stated, "…we believe that every investigation into the pathogenesis of idiopathic paralysis agitans will have to make allowance for this widespread neuronal degeneration."

Subsequent postmortem pathological studies corroborated and expanded upon previous findings in PD. Rajput and Rozdilsky [45] examined the brains from six patients with PD, one with MSA, and one control. Lewy bodies in sympathetic ganglia were seen in five of the PD cases; using nonstereological methods, associated ganglion cell loss was present in three of these cases. Intermediolateral cell column Lewy bodies were prominent in the MSA case but were detected in only one of the six PD cases. Lewy bodies in sympathetic ganglia from PD cases are surely a symbol of neurodegeneration and not a trivial consequence of aging. Forno and Norville [46] examined the stellate ganglia from nine patients with primary PD, nine patients with parkinsonism without nigral Lewy bodies, and 17 controls. Stellate ganglia Lewy bodies were limited to the primary PD cases. In a more recent study, Lewy bodies in the paravertebral sympathetic ganglia were found in 28 of 30 PD cases but in only 5 of 60 non-parkinsonian controls over 60 years of age [47].

Although less severe than that noted in cases of MSA [48], neuronal loss within the intermediolateral cell column of the spinal cord has been well documented in PD despite a relative paucity of Lewy bodies [49]. In a study of 25 PD and 25 control cases, there was a 31% relative reduction of neurons within the intermediolateral cell column at the second thoracic segment in the PD cases. A more striking 63% reduction in neurons was seen at the ninth thoracic segment.

In addition to the substantia nigra, locus ceruleus, and dorsal motor nucleus of the vagus [45], a report by Langston and Forno [50] indicated that Lewy bodies are also consistently found in the hypothalamus. In their study of 30 PD brains, at least 2 Lewy bodies were identified in each hypothalamus. More than 60 Lewy bodies were detected in six of the brains. Lewy bodies were concentrated in the tuberomammillary, lateral, and posterior hypothalamic nuclei. Degeneration in the posterior hypothalamus could explain some of the thermoregulatory abnormalities in PD. It is noteworthy that shivering, which is controlled by the posterior hypothalamus, was shown to be severely impaired in one PD patient exposed to experimental lowering of body temperature [18].

Morphology of the PD postganglionic autonomic nervous system has been evaluated with punch skin biopsies. Even in subjects with relatively early PD, immunohistochemistry for PGP-9.5 showed reduced innervation of sweat glands and erector pili muscles [51]. In another study, staining for vasoactive intestinal polypeptide (VIP) in skin was also diminished in PD [52].

Use of Thermoregulatory Testing to Differentiate PD from Other Neurodegenerative Disorders

In an individual patient, testing of thermoregulatory function or even autonomic function, in general, may not distinguish PD patients from those with other neurodegenerative disorders such as MSA [53], progressive supranuclear palsy (PSP), dementia with Lewy bodies (DLB), the Guamanian parkinsonism–amyotrophic lateral sclerosis (ALS)–dementia complex and cortical–basal ganglionic degeneration. Nevertheless, when coupled with a careful history and physical examination, magnetic resonance imaging, and additional neurophysiological studies (e.g., electronystagmography, electromyography), tests of thermoregulatory function, particularly sudomotor function, can assist in the diagnosis of PD and, in a very high percentage of cases, allow for confident differentiation of PD from other, less common, disease processes [54, 55].

Delineation of MSA from PD is a major diagnostic dilemma for both general neurologists and specialists in movement disorders. Because first-rate facilities for testing autonomic function are not available at many medical centers, neurologists at these sites rely heavily upon clinical clues to differentiate PD with autonomic dysfunction from MSA: (1) good response to carbidopa/levodopa, (2) presence of a resting tremor, (3) asymmetry of motor signs, (4) absence of significant anterocollis, (5) absence of upper motor neuron signs, and (6) absence of the "cold hands sign [56]." Unfortunately, even highly skilled clinicians will have difficulty distinguishing some cases of PD from MSA. When available, thermoregulatory testing may provide additional bits of evidence supporting one diagnosis or the other. These tests range from simple bedside tests to difficult overnight studies. Index finger temperature can be measured in the clinic with a routine digital thermometer. In one study, mean (± standard deviation) index finger skin temperatures were 29.5 ± 3.9°C in nine MSA patients, 32.6 ± 0.9°C in ten PD patients, and 32.2 ± 1.1°C in ten age-matched control subjects. Values from five of the MSA patients were within the range of the PD patients and controls. On average, patients with MSA are more likely than those with PD to exhibit severe abnormalities on thermoregulatory tests (e.g., QSART and TST) that are commonly performed in specialized autonomic function laboratories [33, 57, 58]. In one study, mean anterior anhidrosis was nearly 90% in a group of 75 patients with MSA undergoing the TST [33]. The SSR can be performed in most neurology clinics with standard electromyography equipment and is also more likely to be absent or markedly diminished in MSA than in PD [58, 59]. In contrast to PD, TRH may enhance sweating in MSA [15, 36]. Finally, long-term measurement of core temperature with a rectal probe has shown that the normal nocturnal fall in core temperature is blunted in MSA patients [60]. Certainly, a patient not being treated with levodopa or a dopamine agonist and with minimal or absent resting tremor, mild symmetric rigidity, cold digits, absent SSRs, and marked anhidrosis as documented with a QSART is unlikely to have primary PD. In aggregate, autonomic sudomotor studies suggest that the primary lesion in PD is ganglionic and postganglionic, whereas MSA is preganglionic [55]. Moreover, sudomotor dysfunction appears to progress more rapidly in MSA than PD.

To prevent potential diagnostic confusion, it is important to recognize that thermoregulatory testing may also be abnormal in other, less common, neurodegenerative disorders such as PSP and the Guamanian parkinsonism–ALS–dementia complex. Low et al. examined autonomic function in 16 Guamanian parkinsonism–ALS–dementia complex patients [61]. Deficits in postganglionic sudomotor function (i.e., QSART) were greater in the Guamanian parkinsonism–ALS–dementia complex patients than in non-Guamanian PD but less severe than those evident in MSA. In a series of 12 PSP patients with moderate to advanced disease, average anterior anhidrosis on the TST and % abnormality on the QSART were a bit greater than that found in a group of 35 PD patients of H&Y stages I to IV [37]. It is doubtful that thermoregulatory testing would be very useful in distinguishing early PSP from early PD.

Treatment of Thermoregulatory Dysfunction in Parkinson's Disease

Cold Intolerance

Patients who report cold intolerance should be informed of several common-sense approaches to deal with cold weather conditions. Most importantly, they must wear warm socks, mittens, or gloves and cover their head with a wool hat or cap. In windy conditions, the head, neck, and upper chest should be protected with a hood and scarf, windbreaker jacket, or other suitable apparel. If walking through snow, it is important to wear waterproof shoes so that the feet are kept dry. Cigarette smoking should be avoided since it can impair circulation in the hands and feet. Finally, patients should be encouraged to wear several layers of clothing; one or more layers can be easily peeled off indoors.

Heat Intolerance

Anticholinergics (e.g., benztropine, trihexyphenidyl) and other medications with anticholinergic effects (e.g., diphenhydramine, tricyclic antidepressants) should be avoided in patients with heat intolerance. These patients should be instructed to limit physical activity in hot/humid environments and make a special effort to keep well hydrated during warmer months. They should not mow their lawn during the early afternoon of a hot summer's day, for example. Outdoor activities should be limited to the early morning and late afternoon. A wide-brimmed hat will limit exposure to direct sunlight and loose, lightweight clothing will allow convection to occur. Patients taking diuretics should be particularly cautious in hot/humid environments.

Hyperhidrosis

Since head and neck hyperhidrosis may be an appropriate thermoregulatory compensatory response to appendicular sudomotor dysfunction, it should not be specifically treated. However, patients can carry a handkerchief to wipe sweat from their foreheads and avoid wearing shirts with a tight collar. Episodic hyperhidrosis occurring at the onset of motor "off" periods may improve with adjustments in dopaminergic therapy such as addition of a dopamine agonist [25], closer spacing of levodopa dosing, and combining levodopa with catechol-O-methyltransferase and monoamine oxidase type B inhibitors. Hyperhidrosis may also be alleviated by stimulation of the subthalamic nucleus and/or contiguous caudal ventral thalamus/zona incerta [62].

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Respiratory Dysfunction in Parkinson's Disease

15

Holly Shill

Abstract

Pulmonary complications remain the leading cause of morbidity and mortality in Parkinson's disease (PD). Obstructive and restrictive airway disease is related to disordered motor control of the respiratory musculature. While this may lead to overt symptoms such as stridor and respiratory failure, it more commonly results in silent aspiration and atelectasis, predisposing patients to pneumonia. PD medications may produce pulmonary side effects themselves, as seen with pleuropulmonary fibrosis related to dopamine agonists. Finally, motor fluctuations in advanced PD may trigger respiratory symptoms. Recognizing these pulmonary complications will assist the clinician in appropriately managing the disease and potentially reducing the impact of the abnormal respiratory system on overall PD patient health.

Keywords

Pulmonary • Hypophonia • Dyskinesia • Pneumonia • Pleuropulmonary fibrosis • Stridor • Exercise

Introduction

In 1817, James Parkinson described a man who spoke "with such a low voice and indistinct articulation, as hardly to be understood but by those who were constantly with him. He fetched his breath rather hard" [1]. Thus, involvement of the airway and respiratory apparatus has been appreciated since the original description of the shaking palsy. In the early reports on morbidity and mortality in Parkinson's disease (PD), pneumonia was a common cause of early death [2]. More recent reports indicate that, although patient lifespan is improving with optimal medical management, pulmonary complications are still the most frequent cause of death [3–7]. Clinician attention to these prevalent complications is paramount. Although many of the clinical aspects discussed in this chapter are related to the

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underlying motor dysfunction in some manner, they are often evaluated and treated by nonneurologists and thus are appropriate for discussion as aspects of nonmotor dysfunction in PD.

Hypophonia

Bradykinesia and rigidity of the vocal cords, leading to dysarthria and hypophonia [7], is common and can be considered a cardinal sign of PD. Its severity is often graded in terms of subjective perception of difficulties by the patient as well as by objective findings on clinical examination. Greater than 70% of patients experience problems with speech and 30% judge the difficulty the most debilitating aspect of their disease [8, 9]. Patients often are reluctant to speak in front of others, speak on the telephone, or go out socially because they fear difficulty in making themselves understood.

Strategies for improving vocal quality have been quite broad. Neurologists will generally approach the problem by manipulating dopaminergic medications and speech typically responds to this to a certain degree. Simple speech therapy has been used, as well as more specific therapies designed to circumvent the abnormal basal ganglia circuitry in PD. A therapy termed the Lee Silverman Voice Treatment focuses on "think loud, think shout" and may change neural control of speech to a more "reflex" production of speech [10, 11]. A second method, termed Pitch Limiting Voice Treatment, may improve speech without the straining associated with the previous method [12]. Otolaryngologists have used permanent therapies to augment voice, such as laryngoplasty and alloplastic or autologous vocal cord injections; evidence for efficacy in PD is limited. Percutaneous collagen injection into the vocal cords may offer a better tolerated, albeit nonpermanent option, for patients [13, 14]. Neurosurgical approaches, such as pallidotomy and deep brain stimulation of the thalamus and subthalamic nucleus, although beneficial for many PD symptoms and signs, typically are less helpful for hypophonia. In fact, bilateral therapies and unilateral gamma knife therapy may have an unacceptable adverse effect on speech [15–18]. Patients should be counseled appropriately with respect to expectations with these surgical therapies and their potential effect on voice.

Obstructive Complications

When first studied, a lower airway obstructive defect similar to chronic obstructive pulmonary disease was considered to be the predominant ventilatory abnormality in PD [19, 20]. If symptomatic, this is manifest clinically as wheezing and decreased expiratory flow rate. However, due to the combination of improved medical therapies, better patient characterization, and control for obstructive risk factors such as smoking, this entity now is recognized to be less common than previously thought. Attention, instead, has shifted to upper airway obstruction (UAO), manifest clinically as stridor. There are two typical obstructive patterns of the upper airway associated with PD [21]. Type A, termed "respiratory flutter", shows an oscillatory pattern on a flow-volume loop with a frequency similar to tremor. This pattern is due to vibration of the vocal cords and supraglottic structures, rather than diaphragmatic oscillations. Type B has irregular and abrupt changes in airflow, sometimes with intermittent complete obstructions. This type may be due to both UAO and poor control of the ventilatory pump. Both patterns are thought to be due to poor basal ganglia control of the striated muscles of the ventilatory system. In an early study of 21 PD patients, 12 had a type A pattern and 6 a type B pattern. One-third of patients met respiratory criteria for UAO. Only four patients had respiratory symptoms. Patients with airway obstruction had more advanced PD, as characterized by Hoehn and Yahr staging. Many of the patients in this study were smokers and PD medications were not controlled, which leads to some caution in interpreting this study. A second, similarly performed, study of 31 nonsmoking, asymptomatic, but advanced PD patients documented 4 with a type A pattern, 16 with type B, and 9 with UAO [22]. Patients in this study were on levodopa treatment. This suggests that even asymptomatic,

medically managed patients may have subclinical evidence for UAO.

Based on these early studies, UAO was considered to be relatively asymptomatic and present primarily in more advanced, sedentary PD patients; consequently, it has received little clinical attention. It may, however, have significant relevance in patient management. Stridor may be a presenting symptom of PD and respond to levodopa [23]. Stridor and respiratory failure may result from stopping dopaminergic medication abruptly [24–26]. Reports such as these have fueled further study into the effects of medication on respiratory function. Both levodopa and dopamine agonists may improve ventilatory parameters, particularly UAO [27–29]. Studying patients with spirometry while off levodopa therapy showed a much higher prevalence of UAO, than while on therapy [30, 31]. When combining poor upper airway control with sensitivity to dopaminergic medications, one might speculate that withdrawal of oral medications around the time of surgery might contribute to the higher frequency of aspiration pneumonia and longer hospital stays characteristic of surgical patients with PD [32]. Thus, this "asymptomatic" abnormality, coupled with impaired cough reflex [33], might be more important clinically than previously thought. Careful attention to manipulation of PD medications is important with respect to the upper airway. Every attempt should be made to continue PD medications through any type of procedure or surgery [34]. In the outpatient setting, doses should be changed gradually in an effort to reduce these types of respiratory complications.

The relationship between idiopathic PD and obstructive sleep apnea is poorly understood. Complaints by patients of daytime sleepiness, nocturia and cognitive impairment may prompt a sleep study. However, recent studies suggest that even if obstructive sleep apnea is found, it tends not to be as significant in PD patients as in those individuals with typical risk factors (i.e., increased body mass index and larger neck size) and is rarely the primary cause of those complaints [35–37]. It is unclear whether there may be a higher prevalence of sleep apnea in PD; some study suggests there may be [38]. Based on this, the following recommendation is made: appropriate symptoms in those PD patients with typical risk factors, such as obesity and/or advancing disease and nocturnal off symptoms, should raise suspicion of the possibility of sleep apnea. Sleep evaluation should be performed in patients with appropriate symptoms.

Finally, upper airway obstruction and central hypoventilation are associated with the parkinsonian variant, multiple system atrophy (MSA) [39, 40]. MSA is characterized by poor response to typical PD medications and autonomic insufficiency, clinically manifest as impotence, incontinence and orthostatic hypotension. Stridor occurring in this setting is generally not responsive to typical PD medications and is a poor prognostic sign [41]. Tracheostomy should be considered. MSA patients should be counseled appropriately if they develop stridor because of its poor prognosis.

Restrictive Abnormalities

Restrictive abnormalities of the pulmonary apparatus in PD also are recognized. The chest wall muscles may develop bradykinesia and cocontraction, leading to an increase in chest wall compliance [30]. The intercostal and scalene muscles may develop a tremor pattern, which contributes to decreased coordinated activity of the respiratory pump [42]. Furthermore, repetitive activities show early fatiguing in PD [43]. This may lead to apparent weakness of the chest wall muscles during normal respiration, similar to that seen in primary neuromuscular disorders, which manifests in pulmonary function testing as a restrictive abnormality [44, 45]. Postural and arthritic changes due to longstanding disease may mechanically restrict ventilation [31, 46]. Restrictive changes may adversely affect the clinical state by reducing vital capacity, leading to symptoms of fatigue. Poor expansion of the lungs may lead to atelectasis, which predisposes to pneumonia. Restrictive abnormalities are less responsive to dopaminergic therapy but may respond to pulmonary rehabilitation (see below under "Exercise and Ventilation").

Medical therapy for PD also may produce restrictive abnormalities in the lung tissue itself. All of the ergot dopamine agonists have been reported to cause pleuropulmonary fibrosis [47, 48]. This appears to be specific to the ergot dopamine agonists and does not occur with agents such as pramipexole, rotigotine, and ropinirole. Clinical symptoms include dyspnea, pleuritic pain, and nonproductive cough with pulmonary infiltrates and pleural effusions present on chest radiograph. Sedimentation rate may be elevated and the pleural fluid may show inflammatory cells with a predominance of eosinophils. Although initially believed to be present in 2–5% of patients on these agents, this condition is now considered to be exceedingly rare [49, 50]. Discontinuing the offending dopamine agonist usually reverses the abnormalities. The pathophysiology for this entity is poorly understood but may reflect serotonergic activation triggering an inflammatory response [51]. A link between this response and prior exposure to asbestos has been postulated [52].

Motor Fluctuations and Respiration

Although levodopa therapy improves respiratory and motor function, development of dyskinesias (abnormal involuntary movements well recognized in advancing PD) may affect ventilation. Patients with respiratory dyskinesias may experience dyspnea and chest pain shortly after levodopa administration [53]. Serial pulmonary function testing demonstrates the appearance of rapid shallow breathing and a decline in pulmonary function in conjunction with the clinical onset of limb and orofacial dyskinesias that are typical of peak-dose levodopa-induced dyskinesias [54]. Since complaints of acute chest pain and shortness of breath in this older population might result in an extensive evaluation for cardiac and pulmonary disorders, this adverse effect of treatment should be considered early in the differential diagnosis. The dyskinesias generally subside with reduced dopaminergic medication.

In more advanced patients, end-of-dose wearing off of levodopa efficacy may induce acute pulmonary symptoms, including dystonia of the laryngeal muscles causing stridor [55, 56]. Chest wall tightness with shortness of breath and anxiety may occur and superficially resemble a panic attack; this may be due in part to a psychological reaction to the sudden appearance of chest wall rigidity causing an acute restrictive condition [57]. These types of wearing-off phenomena are treated similarly to other motor fluctuations. Generally, the strategy is to smooth the levodopa response by providing appropriate dose overlap or by initiating longer acting therapies that reduce abrupt withdrawal symptoms [58].

Although it might be anticipated that these types of nonmotor symptoms are rare complications of long-term therapy, it is becoming apparent that they are more common and debilitating than previously recognized. In a survey of a group of patients with motor fluctuations, 40% complained of dyspnea, 21% experienced stridor as a wearing-off symptom, and 8% had intermittent coughing [59]. All of these respiratory symptoms were tied to the patient's motor state, suggesting a correlation with PD fluctuations, and therefore part of the primary pathophysiology of PD.

Exercise and Ventilation

Defective motor control of ventilatory muscles is the primary contributor to the obstructive and restrictive changes seen in PD. However, PD patients also may have trouble regulating breathing when walking. They are not able to effectively synchronize breathing with locomotion [60]. PD patients may expend up to 10% more energy walking than people without PD due to alteration in gait and respiratory coordination [61]. This may lead to decreased exercise tolerance and also may contribute to the fatigue that many patients experience [59]. Patients who exercise regularly seem to maintain good respiratory status [60]. Those patients undergoing a formal pulmonary rehabilitation program may achieve improvement in ventilatory function [62–64]. Patients with fatigue and poor exercise tolerance should be considered for these nonpharmacological interventions. Further study of

the effect of regular aerobic exercise on pulmonary status is needed, particularly whether it reduces pulmonary complications.

Summary

PD affects the ventilatory system at all levels. Laryngeal involvement leads to hypophonia, which may respond to medical treatment, as well as nonpharmacological therapies. Upper airway involvement in general may present as stridor or subclincally as silent aspiration. It responds well to dopaminergic therapy, at least initially. Restrictive disease may manifest as fatigue and predisposes to atelectasis and pneumonia. Motor fluctuations in PD also may produce pulmonary symptoms; they are addressed by appropriate adjustment of dopaminergic medications. Ergotamine dopamine agonists may induce pleuropulmonary fibrosis. Finally, attention to the respiratory tract may improve exercise capacity and reduce fatigue. Awareness of all the pulmonary complications may help to reduce morbidity and mortality in PD.

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Dermatological Disorders in Parkinson's Disease

16

Robert B. Skinner Jr. and Mark S. LeDoux

Abstract

The first suggestion of an increased risk of melanoma in Parkinson disease (PD) patients was reported by Skibba et al. (Arch Pathol 93:556–561, 1972) in 1972. They reported a 55-year-old male with PD who developed a local recurrence of a primary melanoma and multiple primary melanomas 4 years after primary excision and 4 months after starting levodopa. Since levodopa is a metabolite in the biosynthesis of dopamine and melanin involving the enzyme tyrosinase, and increased tyrosinase activity is found in melanoma, they speculated that levodopa "could enhance and stimulate growth on any residual melanoma tissue".

Keywords

Parkinson's disease • Dermatological disorders • Melanoma • Seborrhea • Seborrheic dermatitis

Melanoma

The first suggestion of an increased risk of melanoma in Parkinson disease (PD) patients was reported by Skibba et al. [1] in 1972. They reported a 55-year-old male with PD who developed a local recurrence of a primary melanoma and multiple primary melanomas 4 years after primary excision and 4 months after starting levodopa. Since levodopa is a metabolite in the biosynthesis of dopamine and melanin involving the enzyme tyrosinase, and increased tyrosinase activity is found in melanoma, they speculated that levodopa "could enhance and stimulate growth on any residual melanoma tissue" [1].

Robinson et al. [2] in 1973 reported a 50-year-old male who developed a melanoma in a congenital nevus. The clinical change in the congenital nevus started prior to levodopa therapy, which was given for 21 days. The patient developed metastatic disease 6 months

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later and died of metastatic melanoma 4 months later. They speculated that "it is difficult to resist the impression that levodopa, having an undoubted importance in production of skin melanin, might stimulate the growth of malignant melanoma" [2].

These first two reports of PD patients with melanoma emphasized the possible role of levodopa and not an increased prevalence of melanoma in PD. Leiberman and Shapock [3] in 1974 reported two PD patients with initiation of levodopa and melanoma growth and one PD patient with melanoma 5 years prior to PD and 7 years prior to levodopa. Fermaglich and Delaney [4] in 1977 reported a 71-year-old male who developed a melanoma 7 years prior to diagnosis of PD and reported a rate of 3 melanomas per 100,000 PD patients compared with 1 per 100,000 in the general population. Sober and Wick [5] found over a 5-year period that only one patient had taken levodopa in 1,099 patients with primary cutaneous melanoma. They concluded that levodopa was rarely associated with primary melanoma. Kochar [6] reported a single patient developing melanoma in a benign nevus 4 months after starting levodopa for PD. He reviewed the literature and concluded that "it seems prudent to clinically monitor pigmentary lesions in patients receiving levodopa therapy" [6]. Weiner et al. [7] critically reviewed the literature and noted there was only anecdotal evidence supporting a link between levodopa and melanoma, and that levodopa has antitumor effects on melanoma. Dizdar et al. [8] reported that levodopa increases 5-S-cysteinyldopa levels but does not cause progression of melanoma.

Rampen [9] reported three patients who developed melanoma while on levodopa for PD. His review of the literature summarized "it can be safely stated that the available literature data do not endorse the supposition that levodopa intake has an effect on malignant transformation of melanocytes" and "there is no substantial evidence from the reported cases that levodopa therapy enhances melanoma growth" [9]. Pfutzner and Przybilla [10] reported two patients who developed melanoma during levodopa treatment. They reviewed the 28 total reported patients who developed melanoma while on levodopa. They concluded it was "difficult to decide whether there is a relation between the administration of levodopa and the development of malignant melanoma" and stated "we advise that changes in the appearance of pigmented lesions in patients treated with levodopa should be carefully evaluated" [10].

Siple et al. [11] in 2000 conducted a MEDLINE search with the key terms levodopa, melanoma, and PD and found 34 case reports. They concluded that an analysis of the literature revealed an "unlikely association between levodopa and induction or exacerbation of malignant melanoma." Fiala et al. [12] reviewed the clinical characteristics of 54 patients with melanoma and PD (43 from literature search and 11 from Scott and White Clinic and Memorial Hospital). They concluded the occurrence of PD and melanoma was coincidental and not causal. Levodopa did not predispose PD patients to melanoma nor "exaggerate" melanoma if already present. Olsen et al. [13] found 14,088 PD patients in the Danish National Registry of Patients and in these PD patients noted 1,282 cancers in the Danish Cancer Registry compared with an expected 1,464 cancers. However, they found an increased risk for melanoma with a standardized incidence rate of 1.95. Thus, PD patients had an almost twofold higher incidence of melanoma than the general population.

In a subsequent report, Olsen et al. [14] documented an increased prevalence of melanoma prior to the first hospital contact for PD and, thus, before the diagnosis of PD. They concluded this suggested melanoma is not caused by the treatment of PD. Zanetti et al. [15] investigated the relationship of levodopa and risk of melanoma in PD patients using a computerized bibliographic database. They found no evidence of an increased risk of melanoma incidence or progression due to levodopa, but good evidence of an increased risk of melanoma in PD patients. They found a positive correlation between melanoma risk and social class, and speculated that PD and melanoma risk may be due to common genetics or possibly due to social class associated with melanoma and PD. Constantinescu et al. [16] located all melanomas in the DATATOP clinical trial

cohort and compared them to published expected values. They found a higher than expected incidence of melanoma in PD and no association between levodopa treatment and melanoma incidence.

Hernandez [17] postulated that the genes that regulate pigmentation are the link between PD and melanoma, and that individuals with fair phenotypes are at increased risk for both PD and melanoma. Further, Hernandez hypothesized a central role for tyrosinases in both melanoma and PD. She noted that a copper-dependent tyrosinase is centrally involved in melanin production in peripheral tissues including skin. Neuromelanin is believed to be produced via a different mechanism involving a tyrosine hydroxylase. However, tyrosinase has been noted in the substantia nigra of various vertebrates, including humans, and the neurodegeneration in PD primarily occurs in highly pigmented neurons of the substantia nigra pars compacta. It seems entirely plausible that related pathways involving tyrosinases in melanin and neuromelanin production may provide a key to understanding the relationship between PD and melanoma.

Inzelberg and Israeli-Korn [18] and Vermeijetal [19] reviewed previously published studies and concluded that the increased risk of melanoma precedes the diagnosis of PD and that the increased risk of melanoma in PD is not due to levodopa therapy. Gao et al. [20] investigated the association between family history of PD and melanoma in 157,036 men and women without PD at the start of the study. With 14–20-year follow-up, they identified a family history of melanoma in a first-degree relative as associated with risk of PD. Therefore, PD and melanoma may share common genetic components.

Bertoni et al. [21] reported the results of a multicenter study of PD patients that included 31 centers. A total-body examination by a dermatologist was performed in 2,106 patients, and all lesions suspicious of melanoma were biopsied. The four discovered invasive melanomas were compared with the United States Surveillance Epidemiology and End Results (SEER) cancer database and the American Academy of Dermatology (AAD) skin cancer screening programs. The prevalence of invasive melanoma in the US patients with PD was 2.24-fold higher than expected in the SEER cancer database. The risk of melanoma for US PD patients was greater than seven times expected compared with the AAD skin cancer screening programs. The most robust risk factors for melanoma in PD were fair skin, blue eyes, and severe or blistering sunburns in childhood. Ferreira et al. [22] reported a meta-analysis of the association of PD and melanoma. They concluded there were consistent data for a relationship between PD and melanoma. They found insufficient data for an association between melanoma and levodopa or any other antiparkinson drug.

Seborrhea and Seborrheic Dermatitis

Seborrhea and seborrheic dermatitis (SD) both are more common in PD than in age-matched controls [23]. Seborrhea is an oily appearance of the scalp and face without erythema and scaling. Seborrheic dermatitis is a common papulosquamous skin disease that is diagnosed clinically by location of scaly erythema. Patients usually complain of pruritus of involved areas. Most patients have scalp pruritus with white scale (dandruff). Affected areas of seborrheic dermatitis may include the scalp, hairline, eyebrows, nasolabial folds, retroauricular areas, external ear canals, central chest, axillae, submammary areas, umbilicus, and inguinal folds. Blepharitis and pruritic dermatitis of the ear canal can be single site involvement of seborrheic dermatitis.

Seborrheic dermatitis has been associated with several neurological disorders. These disorders include epilepsy, primary PD, neuroleptic-induced parkinsonism, postencephalitic parkinsonism, supraorbital injury, facial paralysis, unilateral injury to the trigeminal ganglion, poliomyelitis, syringomyelia, and quadriplegia [23]. Drugs reported to produce seborrheic dermatitis include methyldopa, neuroleptics, gold, arsenic, and cimetidine [23]. Patients positive for human immunodeficiency virus, AIDS-related complex, or AIDS have a high incidence of severe seborrheic dermatitis [24].

The cause of seborrheic dermatitis is unknown [23]. It is, therefore, difficult to speculate why its incidence in PD is increased. Seborrhea and seborrheic dermatitis are associated with oily appearing skin. Areas of involvement—scalp, face, ears, and upper trunk have a dense concentration of sebaceous glands. Sebaceous glands secrete sebum, which is increased in PD or at least there is an increased static pool due to immobility in PD [25]. However, Burton and Pye found no increased sebum output in seborrheic dermatitis [26]. Levodopa does seem to improve SD in PD, possibly by decreasing sebum production [27, 28]. Martignoni et al. found a high sebum excretion rate (SER) in males with PD, but concluded this elevated SER was not due to an abnormality of the autonomic nervous system [29]. Fischer et al. [30] studied 70 PD patients and reported that 18.6% had seborrhea, 51.4% had normal sebum values, and 30% had sebostasis. They concluded there was no relationship between seborrhea and treatment of PD and that the cause of increased seborrhea in PD is "unclear."

The lipophilic yeast, *Malassezia furfur* (*Pityrosporum orbiculare*), is considered by some [31] but not by others [32] to be the cause of SD. Heng [33] found decreased numbers of *Malassezia* organisms were associated with improvement of SD. Anti-*Malassezia* therapy has been shown to improve SD in multiple studies [34]. In an extensive review of the literature, Ashbee and Evans concluded that simple overgrowth of *Malassezia* is not the cause of SD but that the "balance of evidence suggests that the organism is very important in their (seborrhea and SD) etiology and not merely an opportunistic colonizing the increased skin surface area" [34]. O'Neill et al. [35] postulated a preclinical condition for PD in spouses of PD patients and a pathogenic condition in the home environment. They found scaly inflammation of the head and neck was greater in PD spouses than controls. They speculated that *Malassezia* may be the home environment agent and could be the causal agent for PD.

The treatment of SD begins with a shampoo containing ketoconazole, zinc pyrithione, or selenium sulfide, which have activity against *Malassezia*. The shampoo is used three times a week and left on for 10 min. Shampoo is used to eliminate *Malassezia* from the scalp (*Malassezia* headquarters) and not to wash off dandruff. A pyrithione zinc 2% soap (ZNP Bar; Stiefel Laboratories, Inc.) is used to wash the face. This combination of medicated shampoo and soap controls most SD. If more treatment is needed, then addition of ketoconazole 2% cream, hydrocortisone 1%, or 2.5% lotion should control the SD. Protopic ointment 0.1% (tacrolimus; Astellas Pharma US) has anti-inflammatory properties and activity against *Malassezia* [36].

Drug Eruptions

Perhaps the best-known drug eruption in the setting of PD is livedo reticularis, characteristically caused by amantadine [37–39]. Livedo means bluish or lilaceous, and reticularis refers to the netlike pattern. Livedo reticularis may be primary (idiopathic) or secondary. The idiopathic form can be seen in young women under cold conditions and is typically benign. In contrast, secondary livedo reticularis is often associated with severe underlying conditions such as polyarteritis nodosa, rheumatoid vasculitis, lymphoma, cryoglobulinemia, syphilis, antiphospholipid antibody syndrome, and tuberculosis.

Although livedo reticularis may appear within weeks of initiating therapy with amantadine, a latency of several years is experienced by some patients [37–40]. Amantadine-induced secondary livedo reticularis frequently is associated with peripheral edema. The rash typically resolves and associated edema often improves with discontinuation of amantadine. Laboratory investigations for other secondary causes should be considered if livedo reticularis does not resolve after discontinuation of amantadine. Rimantadine, the alpha-methyl derivative of amantadine, appears to be associated with a much lower risk of peripheral adverse effects and may be considered a therapeutic alternative to amantadine in selected patients [41].

Dermatological disorders have been described with dopamine agonists, bromocriptine and apomorphine in particular [42, 43]. In a small subset of subjects treated chronically with bromocrip-

tine, a reversible erythromelalgia-like rash may appear [42]. Histopathologically, this rash is characterized by perivascular lymphocytic infiltration and edema. Apomorphine injections and infusions may produce an eosinophilic panniculitis [43]. Basically, this amounts to a local inflammatory reaction in subcutaneous fat. In some patients, however, systemic eosinophilia has been described [44].

To this day, levodopa remains the most widely prescribed medication for PD. Levodopa is typically combined with a decarboxylase inhibitor (carbidopa or benserazide) or with carbidopa and entacapone (Stalevo). In one report, entacapone was associated with a bullous skin eruption [45]. Rashes with one or more preparations of carbidopa/levodopa have been ascribed to formulations containing yellow dyes (D&C Yellow 10 and FD&C Yellow 6). Substituting formulations not containing these dyes usually permits continued treatment of the PD patient with carbidopa/levodopa [46, 47].

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Part III

Sleep-Related Dysfunction in Parkinson's Disease

Insomnia in Parkinson's Disease

17

Maria L. Moro-de-Casillas and David E. Riley

Abstract

The International Classification of Sleep Disorders (ICSD) defines insomnia simply as "difficulty in initiating and/or maintaining sleep". Other definitions exist, and there is no clear consensus in this matter. The core elements of insomnia are an inadequate quantity or quality of sleep, with both nocturnal and daytime consequences. Traditionally, insomnia has been subgrouped into sleep-onset insomnia, sleep-maintaining insomnia, and insomnia with early morning awakening; however, there is extensive overlap, and most insomniacs fit into more than one subgroup.

Sleep disorders, particularly in the elderly, are strongly associated with increased morbidity and mortality, significant limitations in activities of daily living, and impaired quality of life. Aside from the obvious complications of daytime fatigue and somnolence, insomniacs have an increased incidence of psychiatric disorders such as depression and anxiety, increased use of over-the-counter medications and alcohol, and a higher incidence of accidents and unemployment. Chronic sleep loss has multisystem consequences and may represent a risk factor for obesity, insulin resistance, and Type 2 diabetes. However, the brunt of negative effects of sleep deprivation is borne by the brain. Chronic insomnia independently predicts incident cognitive decline in older men, but it also has been suggested that some degree of apparent age-related cognitive decline may be due to treatable insomnia.

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Keywords

Nocturia • Insomnia • Melatonin • Bromocriptine • Restless legs syndrome • Unified Parkinson's Disease Rating Scale • Nighttime awakenings • Sleep fragmentation • PRIAMO • International Classification of Sleep Disorders

Introduction

The International Classification of Sleep Disorders (ICSD) defines insomnia simply as "difficulty in initiating and/or maintaining sleep" [1]. Other definitions exist, and there is no clear consensus in this matter. The core elements of insomnia are an inadequate quantity or quality of sleep [2], with both nocturnal and daytime consequences. Traditionally, insomnia has been subgrouped into sleep-onset insomnia, sleep-maintaining insomnia, and insomnia with early morning awakening; however, there is extensive overlap, and most insomniacs fit into more than one subgroup [3].

Sleep disorders, particularly in the elderly, are strongly associated with increased morbidity and mortality, significant limitations in activities of daily living, and impaired quality of life [2]. Aside from the obvious complications of daytime fatigue and somnolence, insomniacs have an increased incidence of psychiatric disorders such as depression and anxiety [4], increased use of over-the-counter medications and alcohol, and a higher incidence of accidents and unemployment [5]. Chronic sleep loss has multisystem consequences and may represent a risk factor for obesity, insulin resistance, and Type 2 diabetes [6]. However, the brunt of negative effects of sleep deprivation is borne by the brain [7]. Chronic insomnia independently predicts incident cognitive decline in older men [8], but it also has been suggested that some degree of apparent age-related cognitive decline may be due to treatable insomnia [9].

Insomnia is the most frequently reported sleep problem in the USA and in industrialized nations worldwide [10]. Bixler et al. reported an overall prevalence of insomnia of 42 % in a sample of 1,006 subjects aged 18–80 [11]. Women are 1.3 times more likely than men to report insomnia symptoms [12]. The elderly (>65 years old) have a prevalence rate of sleep difficulty 1.5 times higher than that of adults younger than 65 [13]. Schubert et al. found that almost half (49 %) of an older population (ages 53–97) reported at least one insomnia trait (difficulty getting to sleep, difficulty returning to sleep after waking up, or repeated awakenings) occurring at least five times a month [14].

The economic burden of insomnia on society is enormous [15]; the annual per person cost of untreated insomnia in the United States civilian labor force exceeds $1,000 [16]. In a Canadian study, the largest proportion of insomnia-related expenses was attributable to work absences and reduced productivity. Indirect costs included healthcare consultations, prescription and over-the-counter medications, as well as alcohol used as a sleep aid [17].

Against this background, and with the added consideration that insomnia is highly dependent on subjective reporting [18], it is difficult to determine the contribution of superimposed illness to the problem of insomnia in affected patients. Nevertheless, insomnia has been associated with many medical conditions, including neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease (PD) [19]. Nonmotor manifestations of PD, including sleep disorders, have a major impact on the quality of life of patients and their families [20]. The most important nonmotor complaints associated with poor quality of life in PD patients are depression, apathy, and insomnia [21].

Sleep Physiology

The recognition of the state of sleep is based on both behavioral and physiologic criteria [22]. The behavioral criteria include eye closure, reduced responsiveness to environmental stimuli, decreased or absent movement, and a reversibly unconscious state [23]. Physiologically, sleep normally proceeds through cycles of five stages. The first four, collectively known as nonrapid eye movement sleep (NREM sleep), are numbered consecutively and represent progressively deeper states of somnolence. They account for 75–80 % of sleep time in a healthy adult. During these phases, electroencephalography (EEG) displays varying amounts of high-voltage slow activity and delta waves (1–4 Hz), with characteristic sleep spindles (12–14 Hz) and K-complexes during stage II. Recent nomenclature has combined stages III and IV and divided NREM sleep into N1, N2, and N3 stages [24]. The fifth (fourth) stage of sleep is characterized by rapid eye movements (hence the term, REM sleep), atonia, low-voltage fast brain activity, cardiorespiratory irregularities, and dreaming [23]. Sleep cycles last 90–100 min, and a normal sleep period has four to six cycles. The duration of REM sleep increases from the first to the last cycle, and at the end of the sleep period can persist for as long as 1 h. With aging, important changes in sleep structure occur, including decreased total nocturnal sleep time, reduced delta sleep, delayed onset of sleep, reduced REM sleep, and reduced threshold for arousal [25]. Probably the most characteristic change is a phase advance of the normal circadian rhythm, which results in earlier sleep onset, accompanied by earlier awakening in the morning [26]. Interference with the initiation, orderly progression, and completion of normal cycles of sleep results in insomnia.

The sleep cycle is regulated by a variety of neurochemical/neuroendocrine systems and is the result of active and passive mechanisms, under genetic and molecular regulation [27]. Multiple monoamines, including dopamine (DA), serotonin, norepinephrine, and histamine, as well as acetylcholine and the neuropeptide, hypocretin [28], appear to be involved in the modulation of the sleep–wake cycle. Serotonin and DA both function to promote waking and to inhibit slow-wave sleep and/or rapid eye movement sleep [29]. The most prominent pathways utilizing DA include the mesostriatal, mesocortical, and mesolimbic systems. Midbrain dopaminergic neurons may have the potential to influence thalamocortical neuron excitability, and theoretically the sleep/wake state, through connections with the striatum and through extensive collaterals to the thalamus [30]. Neural mechanisms closely related to behavioral states have been associated with the modulation of "burst-firing" patterns of dopaminergic neurons [31]. REM sleep deprivation may produce a significant increase in striatal DA levels, suggesting that sleep deprivation can induce plasticity in the mesostriatal DA system [32]. DA activity is itself under the influence of a circadian rhythm [33]. The rest/activity cycle of *Drosophila* has features in common with that of mammals [34]. Kume et al. reported that a certain *Drosophila* line with a mutation in the DA transporter gene has abnormally high levels of activity and reduced sleep, providing evidence that dopaminergic signals regulate arousal [35].

Hypocretin neurons are exclusively located in the lateral and perifornical regions of the hypothalamus. They project widely through the central nervous system (CNS) including the locus ceruleus, septal nuclei, thalamus, and substantia nigra, where they have an excitatory effect on several arousal systems, including autonomic, metabolic, and neuroendocrine [36]. Studies of hypocretin levels in the cerebrospinal fluid (CSF) of patients with PD have conflicted [37–39]. In a postmortem study of 11 patients with PD and five controls, Thannickal et al. reported massive loss of hypocretin cells in the hypothalamus of PD patients; the severity of loss of hypocretin correlated with the clinical stage of PD [40]. The authors postulated that loss of hypocretin cells may be the cause of narcolepsy-like symptoms of PD. Loss of these cells occurs prior to onset of drug treatment in many PD patients. Politis et al. reported reductions of hypothalamic D2-receptor availability using positron emission tomography with (11)C-raclopride in PD patients [41].

However, the results could not determine whether this reduction was disease related, due to chronic exposure to levodopa, or both. There are distinct patterns of release of various hormones (including cortisol, growth hormone, and corticotrophin) during the sleep cycle, with the potential existence of common regulatory pathways of the sleep EEG and the nocturnal hormone secretion [42, 43].There is consensus that both abnormal sleep and impaired daytime alertness occur in the majority of PD patients [44]; clinical observations of sleepiness in PD further support the role of DA in the sleep–wake cycle [31]. The effects of levodopa and DA agonists on sleep [45] also point toward a role of dopaminergic systems in sleep. Thus it is not surprising that most PD patients experience difficulties with sleep due to the disease, its treatment, or both [46].

Insomnia in Parkinson's Disease

Sleep disorders are a common problem in patients with PD [47–49]. Their frequency appears to be higher than that expected from the effects of age alone [50]. Prevalence figures for sleep disorders in PD range from 40 to 98 % [51, 52]. Polysomnographic data in PD patients demonstrate a wide variety of findings (1) light fragmented sleep [53], (2) decreased sleep efficiencies [54], (3) increased wakefulness [54], (4) decreased amounts of REM sleep [54], (5) increased REM sleep latencies [55], (6) fragmented REM sleep [54], (7) increased frequency of arousals [54], (8) decreased amounts of sleep spindles [55, 56], (9) poorly formed K complexes [55, 56], and (10) increased muscle activity in REM sleep (REM without atonia) [54]. It is evident that both the macro- and microstructure of sleep are affected in this group of patients.

The PRIAMO study found that 98.6 % of patients with PD ($n=1{,}072$) reported nonmotor symptoms [57]. Insomnia was reported by 37 %; other commonly reported symptoms that could alter sleep patterns included fatigue, anxiety, and leg pain. Sleep disturbances can occur at any stage of PD but are more common as the disease progresses; this suggests a direct relation between impaired sleep and severity of disease [51, 58]. A prospective longitudinal cohort study of nocturnal sleeping problems in patients with PD over 8 years found that more than 50 % of patients reported insomnia [59]. Patients with insomnia had higher depression scores and were often female. Similar findings were also reported by Verbaan et al., who found higher insomnia rates in female patients and a strong relation between nighttime sleep problems and depression [60]. Porter et al. reported that 22 % of 122 PD patients had marked sleep disturbances, with the most common symptoms being sleep fragmentation and nocturia [61]. Insomnia was an important and independent predictor of poor health-related quality of life in a population-based cohort of patients with PD [62].

The most common form of insomnia in PD patients is that of frequent nocturnal awakenings, also known as sleep fragmentation [55]. Factor et al. studied sleep complaints, as well as the effect of sleep on motor symptoms, through a questionnaire survey in 78 patients with PD (median age 67 years old; average disease duration 6.7 years) and 43 elderly controls (median age 63) [50]. Sleep initiation problems occurred frequently in both groups, with no significant difference between them, but sleep fragmentation was more common in PD patients (88.5 % in PD vs. 74.4 % in the control group). In a community-based study, Tandberg et al. found that the most common sleep complaints reported by 245 patients with PD were sleep fragmentation and early awakening [52]. In this study, patients with PD reported sleep disorders significantly more frequently than patients with diabetes and healthy control subjects, with a third of the PD patients rating their overall nighttime problem as moderate to severe. Another study, comparing 90 PD patients with 71 age-matched healthy subjects, showed a high prevalence of sleep disturbances in both groups (81 % of PD patients vs. 92 % controls) [63]. There were no differences between the groups regarding the prevalence of disturbances of sleep initiation or maintenance; however, those PD patients who experienced sleep maintenance difficulties reported a significantly greater number of awakenings.

Kumar et al. reported the frequency and nature of sleep disturbances in 149 PD patients and 115

age-matched controls [51]. They found that 42 % of PD patients reported sleep problems, compared with 12 % of a healthy control population. Insomnia was reported by 39.6 % of patients but only 5 % of the control group. Within the PD group, those patients with sleep complaints had a longer duration of disease, higher Unified Parkinson's Disease Rating Scale (UPDRS) scores and were receiving higher doses of levodopa. They also had longer sleep latencies than those without sleep problems. Nighttime awakenings were significantly associated with rigidity and Hoehn and Yahr (H&Y) scores.

The frequency of sleep initiation difficulties in PD patients is not as well established as that of sleep maintenance. Most studies have not documented significant differences between PD patients and control subjects [50, 52, 63]. However, Kales et al. found sleep initiation problems to be a prominent problem in PD patients [46].

Although it has been suggested that sleep deprivation influences DA systems [64], data concerning the effects of sleep deprivation on motor symptoms in PD patients are scarce and controversial. Bertolucci et al. reported improvement in rigidity, bradykinesia, gait, and posture disturbances lasting 2 weeks after a single night of total sleep deprivation (TSD) in 12 patients with PD [65]. These results supported the positive effects of REM sleep deprivation shown in an animal model of PD [66]. However, beneficial results are not universal. Fifteen patients with PD underwent one night of TSD, one night of partial sleep deprivation (PSD), and one control night of normal sleep. Mean UPDRS motor scores and tapping velocities did not show any substantial effect of sleep deprivation [64]. Only four patients after PSD showed an improvement in their motor score of greater than 20 % compared with the score after normal sleep.

Contributing Factors

The etiology of light and fragmented sleep in PD is multifactorial [48, 67]. Treated patients with more advanced disease typically experience wearing off of antiparkinsonian medication effect at night, resulting in recurrence of tremor, rigidity, and akinesia and increased sleep latency. Rigidity and akinesia both contribute to inability to turn in bed, which has been rated as the most troublesome nocturnal symptom, affecting 65 % of 220 PD patients in one study [68]. Multiple motor symptoms persist during sleep and interfere with its normal physiology [69]. During light sleep, PD tremor can reappear [70]. The effect of sleep on involuntary movements (dyskinesia) in PD and other movement disorders was studied by Fish et al. [71]. They reported that dyskinesia in PD was most likely to occur after awakenings or in stage one sleep; this movement was very rare during the deeper phases of sleep. The movement that occurred without awakenings was usually preceded by arousal phenomena and, rarely, by sleep spindles or slow waves.

Repetitive muscle contractions can occur during NREM sleep. Askenasy et al. reported that NREM sleep transforms the waking "alternating" parkinsonian tremor into subclinical repetitive muscle contractions [72]. Their amplitude and duration decreased as NREM sleep progressed and disappeared during REM sleep. Additional motor abnormalities that contribute to sleep fragmentation include dystonia, which can lead to pain [68], blinking and blepharospasm [69, 70], painful leg cramps [68], and fragmentary myoclonus [73].

A common complaint of PD patients is frequent urination, and nocturia was the most common form of nighttime disability in a group of 220 PD patients [68]. In this study, 79 % of the patients had to "visit the lavatory" during the night, and one-third needed to urinate three or more times. When nocturnal urinary frequency is compounded with the inability to walk without assistance (as in, for example, 35 % of these 220 patients) [68], nocturia can represent a major source of stress and disability in PD. Urinary frequency in PD may be due to disease-related dysautonomia or to age-related urologic abnormalities and can increase patients' morbidity, as it exposes them to frequent falls and consequent injuries, including fractures [73], and further immobility.

Dhawan et al. explored the nature and range of sleep dysfunction in early, untreated PD (mean

H&Y 1.9), and advanced PD (mean H&Y 3.4) [74]. Logistic regression analysis showed that nocturia, cramps, dystonia, tremor, and daytime somnolence were significantly impaired in drug-naïve PD patients compared with controls.

Coexisting psychiatric and medical disorders can also affect sleep in PD patients. Depression may play an important role in modulating normal sleep architecture [47], and early-morning awakening with inability to return to sleep is a fundamental symptom of depression. The high prevalence of depression in PD patients makes it an important consideration in the differential diagnosis of insomnia. Depression is discussed in detail in an earlier chapter.

Other disturbances of sleep that can contribute to insomnia, namely REM sleep behavior disorder and sleep-related breathing disorders, are detailed elsewhere in this volume. Other PD non-motor symptoms discussed elsewhere that may affect the ability to sleep restfully include pain, anxiety, and hallucinosis.

Restless Legs Syndrome

The restless legs syndrome (RLS) is characterized by an irresistible urge to move the limbs that (1) becomes evident or is accentuated in the evening and at nighttime, (2) occurs when the legs are rested (sitting or lying down) and is relieved by moving the legs or walking, and (3) is accompanied by paresthesias or dysesthesias variously described as creeping, crawling, itching, burning, pulling, aching, restless, tingling, cramping, or other sensations [75]. The onset is unilateral in 40–50 % of cases. The legs are almost always involved, but the arms may be affected as well in 25–50 %. The majority of patients also experience periodic limb movements in sleep (PLMS), and many display similar dyskinesias while awake. Symptoms tend to increase with age. RLS may affect as much as 5 % of the population, and 10 % of those over 65. The main effect of RLS on sleep is sleep latency insomnia (i.e., delaying the onset of sleep), but RLS may also cause fragmented, nonrestorative sleep, and occasionally excessive daytime sleepiness.

Many cases are idiopathic or hereditary. However, as with insomnia in general, RLS is a common disorder that appears to be even more common when associated with a variety of chronic illnesses, including PD. Approximately 20 % of PD patients report symptoms consistent with RLS; in over 70 % of these cases, the onset of PD precedes or occurs concomitantly with the development of RLS [76]. Some PD patients clearly relate their RLS symptoms to the development of motor symptoms when the benefit from their medications wears off [77, 78]. Gunal et al. identified five such instances among 72 consecutive PD patients with motor fluctuations [79]. By contrast, Tan et al. could not find any PD patients with RLS in a survey of 125 consecutive patients [80], although the same authors reported a prevalence of RLS of only 0.6 % in their general population. Möller et al. reviewed the association between the two disorders and concluded there was an increased risk of RLS in PD, albeit slight [81].

It is important to identify RLS because of its high rate of response to treatment. Systematic survey of PD patients indicates that the majority of affected individuals will not volunteer symptoms of RLS [76]. In patients in whom the symptoms of RLS fluctuate in tandem with motor manifestations of PD, patients may assume that such symptoms are typical of “off” periods and not a distinct experience. Thus, such historical information must be actively and specifically sought in order to establish the diagnosis of RLS.

Effects of Antiparkinsonian Treatment

Pharmacological agents used in the treatment of PD may play a role as a cause of sleep disorders [45, 48, 82]. Dopaminergic medications have prominent effects on both circadian rhythms and sleep–wake modulatory systems [69]. The effects of levodopa on sleep are nonspecific, exerted through pre- and postsynaptic mechanisms, as well as through interaction with different neurotransmitters [69]. Levodopa suppresses REM sleep and delays REM sleep

latency [45, 83]; it has improved daytime vigilance in narcoleptic patients [84]. In a questionnaire study, the use and duration of levodopa therapy in patients with PD were associated with a higher frequency of sleep disruption, with sleep fragmentation being the most common sleep complaint [85].

Bromocriptine has induced changes in sleep architecture similar to levodopa, including shorter REM sleep, superficial sleep, and prolongation of REM sleep latency, in PD patients [86]. Pergolide, bromocriptine, and apomorphine produce "biphasic effects" (opposite effects at low and high doses) on sleep architecture in rats [87]. At low doses, they decrease wakefulness and increase NREM sleep. The newer nonergoline dopaminergic agonists, ropinirole and pramipexole, also affect sleep physiology. At lower doses, D3 agonists increase NREM and REM sleep and reduce locomotion in rats; with higher doses, D2/D3 agonists improve locomotion, without major sedation [88]. In one study, ropinirole was shown to improve sleep efficiency and total sleep time in five patients with chronic insomnia secondary to RLS [89]. The potential clinical effect of DA agonists and levodopa to induce "sleep attacks" is discussed in a succeeding chapter. Selegiline can suppress REM sleep [90]. Puca et al. reported an increase in sleep spindle activity in parkinsonian patients following administration of amantadine [91].

Treatment of Insomnia in Parkinson's Disease

The first step in the management of insomnia in PD is correct identification of contributing factors. A detailed history provided by the patient, and any bedmate or caregiver, is crucial. For those with complicated or varying sleep problems, the use of a symptom diary could be useful. In some instances, diagnostic testing with polysomnography might be necessary. Successful treatment of sleep disturbances in PD patients can postpone their institutionalization, allow the caregiver better sleep, and improve quality of life [73, 92].

If a specific cause for insomnia is found, it should be treated first [3]. Comorbid conditions such as nocturia, sleep apnea, RLS, anxiety, and depression should be addressed, as their treatment will likely improve sleep quality. General sleep hygiene rules should be recommended as appropriate to each individual. Some of these instructions include (1) reduce excessive time in bed; (2) increase exercise and physical activity; (3) curtail caffeine intake; (4) observe a fixed wake-up time; (5) avoid naps; (6) avoid caffeine, alcohol, or heavy meals before bedtime; (7) limit fluid intake after 17:00 h; (8) use available aids for getting in and out of bed; and (9) make medications, water, and a bathroom or commode chair easily accessible [3, 69, 73]. Sleep hygiene rules should be instituted no more than one at a time to enhance compliance. Behavioral therapy, through stimulus control, sleep restriction, and sleep hygiene education, plays an important role in the treatment of insomnia [69, 73, 93]. Other nonpharmacologic measures, such as bright light therapy or chronotherapy, may be beneficial [92, 93].

Insomnia in a parkinsonian patient should always prompt careful reassessment of dopaminergic therapy. Adjustment of dosages must be carefully individualized. In some patients, excessive dosages of dopaminergic medications should be avoided at night. Levodopa can have an arousal effect, potentiate wakefulness, and enhance sleep fragmentation [73]. On the other hand, increases in dopaminergic medications may improve sleep significantly by improving motor symptoms, and specifically tremor and akinesia. Activity and immobility during sleep were recorded by means of a wrist monitor in 84 PD patients and 83 age- and sex-matched normal controls [94]. In mild-to-moderate disease, levodopa and DA agonists were disruptive to sleep by virtue of their effects on sleep regulation. However, in individuals with more severe PD, the drugs had beneficial effects on nocturnal disability [94]. The effects on sleep of other medications, such as anticholinergics, selegiline, and amantadine, should also be considered.

Use of hypnotics usually is not indicated, as the role of these medications is primarily in the

treatment of acute insomnia, and in chronic insomnia there is a risk of dependence [69, 73]. If benzodiazepines are used, short-acting ones are preferred; those with a long half-life can produce daytime sedation, dozing, and disturbances in perceptual skills [3, 73]. Newer, nonbenzodiazepine hypnotic agents have been well accepted in the treatment of insomnia in the general population. Zolpidem and zaleplon have hypnosedative actions comparable with those of benzodiazepines, but they display specific properties. They share a short plasma half-life (zaleplon 1 h and zolpidem 5 h) and a limited duration of action and are less sedating than benzodiazepines [95]. A double-blind placebo-controlled trial of zolpidem in ten PD patients suggested that it may be helpful for parkinsonian motor symptoms as well as insomnia [96].

The role of melatonin in the treatment of insomnia in the general population is controversial [3]. Its use in PD requires further investigation.

Nocturia frequently causes sleep disruption in PD patients. Oral anticholinergic agents, such as oxybutynin and tolterodine, may provide sufficient antispasmodic effects on the urinary bladder, and both are available in sustained-release preparations for nighttime dosing. Suchowersky et al. found intranasal desmopressin to be a safe and effective tool for nocturnal polyuria in PD [97].

RLS fortunately shares with PD a responsiveness to dopaminergic medication, and DA agonists are particularly appropriate in the management of RLS because of the greater tendency of levodopa to produce augmentation [98]. Other agents effective in the treatment of RLS include gabapentin, clonazepam, and opiates.

Sleep architecture in PD may improve with subthalamic nucleus (STN) stimulation [99], with pallidotomy [100], or with combined STN–pedunculopontine nucleus stimulation [101]. In ten insomniac patients with PD on dopaminergic therapy, STN improved nighttime akinesia by 60 %, suppressed axial dystonia, and increased total sleep time by 47 % and sleep efficiency by 36 % [99]. It also decreased the duration of wakefulness after sleep. Periodic leg movements and motor behavior during REM sleep were not influenced by stimulation [99].

Conclusion

Insomnia is a common complaint, and one of the most important determinants of quality of life, in PD patients. The most common form of insomnia in PD patients is frequent nocturnal awakenings. Insomnia may be a direct complication of PD or its treatment or a by-product of other complications such as depression, nocturia, and RLS. Proper management of insomnia involves identification and treatment of contributing factors, careful assessment of the regimen of antiparkinsonian medications, institution of good sleep hygiene measures, and judicious use of hypnotic medication.

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Rapid Eye Movement Sleep Behavior Disorder

18

Suzanne Stevens and Cynthia L. Comella

Abstract

Rapid eye movement sleep behavior disorder (RBD) is a rapid eye movement (REM) parasomnia in which the normal muscle atonia of REM sleep is absent. The lack of muscle atonia may lead to motor activation and the appearance of dream enactment behaviors. Dream content during RBD is vivid and often has aggressive themes, such as being threatened, defending loved ones, being chased, or attacked. During an episode, both the patient with RBD and their bed partner are at risk for serious injuries (e.g., bruises, lacerations, and bone fractures). Polysomnography is required for RBD due to its potentially injurious behavior and to rule out the treatable condition of obstructive sleep apnea that can mimic RBD. Controlled trials are lacking; yet, clonazepam has been effective in treating symptoms in up to 90 % of patients with RBD. Other treatment approaches include melatonin, quetiapine, antiepileptic agents, adrenergic agonists, and acetylcholinesterase inhibitors. RBD is frequently associated with synucleinopathies such as multiple system atrophy, dementia with Lewy bodies, and Parkinson's disease. In these patients, RBD symptoms may precede motor symptoms by months to years. Abnormalities in central dopaminergic mechanisms have been postulated.

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REM sleep • REM sleep behavior disorder • Parasomnia • Dreams • Polysomnography • Clonazepam • Pseudo-RBD

Introduction

Rapid eye movement (REM) sleep typically comprises 15–25 % of the normal sleep cycle and is the stage in which at least 80 % of dreaming occurs. REM sleep is defined electrophysiologically by a desynchronized cortical electroencephalogram (EEG), skeletal muscle atonia, REM, autonomic instability, and pontogenicular (PGO) spikes. REM sleep behavior disorder (RBD) was initially described as a parasomnia by Schenk in 1986 [1]. RBD is an abnormal state of REM in which normal REM-associated muscle atonia is absent, enabling the activation of the motor system. Loss of REM-associated muscle atonia may lead to an enactment of dream content. Dream content during RBD episodes often involves aggressive themes of being threatened, chased, or attacked. Hence, the activities observed during RBD may include talking, yelling, clapping, punching, thrashing, kicking, sitting up, falling out of bed, and running. Because of these sometimes violent behaviors, several reports exist of injuries during sleep, including lacerations, ecchymoses, bone fractures, and subdural hematomas. These injuries have been incurred by both patients and bed partners during episodes. The bed partner may be suddenly awakened by being pummeled or choked by the spouse, who exhibits no evidence of hostility during waking hours. The bed partner often seeks refuge by sleeping in another room. Then, the patient awakens in the morning with no recollection of these behaviors, but associated dreams may be recalled.

Idiopathic RBD is diagnosed when no concurrent neurological disease is found; symptomatic or secondary RBD is associated with an underlying neurological disease. RBD is more common in the elderly population, affects men more than women, and is particularly frequent in certain neurodegenerative disorders that have common features of parkinsonism and pathological findings of synuclein pathology (e.g., idiopathic Parkinson's disease [PD], multiple system atrophy [MSA], and dementia with Lewy bodies [DLB; [2]]).

Prevalence

The prevalence of RBD in the general population is approximately 0.05 %. The male predominance is significant; up to 87 % of patients with RBD are men [3, 4]. Gender predisposition has not yet been explained. The mean age of onset with RBD symptoms is in the age range of 52–62 years, but RBD has been reported in patients from 9 to 84 years old. Cross-sectional analysis of large groups of patients with RBD shows that idiopathic RBD is less common than symptomatic RBD. In three large case series, 25–43 % of patients with RBD were designated as idiopathic, whereas 48–75 % were classified with symptomatic RBD. The most frequently associated neurological disorders in patients with RBD were neurodegenerative diseases, which comprised 48–92 % of cases [3–5]. Neurodegenerative diseases most often linked with RBD are synucleinopathies, PD, and MSA [4, 6], but rare case reports of RBD in progressive supranuclear palsy [7] and corticobasal degeneration (CBD; [8]), both tauopathies, also exist.

The presence of RBD in synucleinopathies is well established. Synucleinopathies are disorders that are alpha-synuclein positive on pathology and include Parkinson's disease (PD), dementia with Lewy bodies (DLB), pure autonomic failure (PAF), and multiple system atrophy (MSA). RBD is only rarely reported in other neurodegenerative disorders such as the tauopathy Alzheimer's disease. Boeve offers a comprehensive review on this topic [9].

In one interview study, 15 % of idiopathic patients who had PD were found to have a clinical history meeting the International Classification of Sleep Disorders (ICSD) criteria for RBD.

Among the RBD patients, one-third had caused injury to themselves or their caregivers [10]. Using polysomnography (PSG) along with clinical history, investigators have shown as many as 58 % of patients who had PD tested to have REM sleep without atonia, but 42 % of these did not have obvious behavioral abnormalities, suggesting that RBD is a common feature in PD and may be presymptomatic in many [11]. In a cohort study of patients with PD reporting sleep disturbances, the frequency of RBD with support from video-PSG was 46 % [12]. This same study showed that periodic limb movements of sleep were higher in the PD+RBD group, which the authors postulate represent motor dysfunction of NREM sleep associated with PD. In one study that compared clinical features in patients who had PD with RBD to those without, factors related to RBD occurrence in PD included longer duration of PD, more severe disease, and treatment with higher doses of dopaminergic drugs [13].

The prevalence of RBD in MSA is even greater than in PD. One study assessing 39 consecutive MSA patients showed that 69 % had clinical features consistent with RBD, and 90 % were diagnosed with RBD when evaluation included PSG [14]. Similarly, in patients with RBD and dementia, these clinical features are highly suggestive of DLB; confirmatory pathological examinations have been performed in some cases [2, 15].

One intriguing aspect of the relationship between RBD and these parkinsonian syndromes is the observation that RBD symptoms may precede the onset of parkinsonian symptoms by many years. Schenck reported that in 38 % (11/29) of 29 primary RBD male patients, a parkinsonian syndrome developed a mean of 4 years after the clinical diagnosis of RBD and a mean of 13 years after historical symptoms of RBD began [16]. This estimate has been confirmed by others [17]. In patients with DLB assessed by Boeve et al., 97 % developed RBD either before or concurrent with the onset of dementia [15]. Similarly, RBD preceded MSA onset of symptoms by at least 1 year in 44 % of individuals with MSA [14]. Based on these observations, RBD has been theorized to be a harbinger of specific neurodegenerative conditions [18].

Etiology and Pathogenesis

Anatomy

The anatomic localization and pathophysiological mechanisms underlying RBD remain to be fully elucidated. Jouvet was the first to describe the REM mechanisms in animals [19, 20]. He also showed that cats lesioned bilaterally in the dorsolateral pontine tegmental region had REM sleep without atonia, which developed into dream enactment behavior in the weeks following lesioning, a phenomenon like that seen in human RBD. In these experiments, lesions of other regions of the brainstem did not result in REM abnormalities. Furthermore, suppression of REM sleep abolished the oneiric behaviors, implying that the abnormality responsible for REM-related motor activation involved the disruption of pathways responsible for the normal components of REM sleep.

Specific anatomic areas suspected to be engaged in the pathogenesis of RBD include the pedunculopontine nucleus (PPN) and lateral dorsal tegmental nucleus (LDT). The PPN is located in the pontomesencephalic tegmentum. Both the PPN and the LDT are cholinergic nuclei with rostral projections to the gigantocellular tegmental field (FTG). Injections of cholinergic agents into the pontine reticular formation enhance the release of acetylcholine in the FTG and induce a REM-like state with EEG desynchronization and the generation of PGO spikes, which implies that the PPN and LDT may have pivotal roles in the regulation of REM [21]. The PPN also has been implicated in the akinesia and gait difficulties of parkinsonism [22]. Although limited work has been done, the PPN has been found in several studies to degenerate in PD with a loss of approximately 50 % of the cholinergic neurons [23, 24]. This finding has led to the hypothesis that a loss of PPN cholinergic neurons may be involved in selected motor findings in both parkinsonism and RBD development. The pathological findings in a small number of patients with RBD, most with features suggestive of DLB, have included significant neuronal loss in the locus ceruleus.

The locus ceruleus has important connections with the PPN and is integrally associated with the control of REM sleep [25, 26].

Lai and Siegel have developed a more detailed theory to explain the frequent coexistence of RBD and parkinsonism [18]. In their model, two juxtaposed areas of the brainstem undergo degeneration: the rostroventral midbrain (RVMD) and the ventral mesopontine junction (VMPJ). The RVMD includes the substantia nigra, among other nuclei, and projects to the basal ganglia and basal forebrain. The VMPJ consists of the caudal part of the ventral tegmental area, retrorubral nucleus, and ventral mesencephalic field (among others) and projects to the pontine inhibitory area, locus ceruleus, and nucleus magnocellularis. Lesions in the VMPJ area in animals produce increased phasic and tonic muscle activity during REM sleep. RVMD lesions in animals produce transient parkinsonism and sleep fragmentation, a sleep disturbance that affects many patients who have PD [27]. Lai and Siegel hypothesize that neuronal degeneration occurs simultaneously in both brainstem areas in parkinsonism. In those patients whose initial symptoms consist of RBD, degeneration may begin in the VMPJ and later involve the adjacent areas of the RVMD. Conversely, parkinsonism symptoms preceding RBD may implicate the onset of neurodegeneration in the RVMD with subsequent involvement of the VMPJ, thus providing evidence of an anatomic link between parkinsonism and RBD [18].

Neuroimaging and Neurophysiology

In symptomatic RBD, magnetic resonance imaging has demonstrated lacunar infarcts in the dorsal pontomesencephalic area in some patients, suggesting that abnormalities in this area may underlie RBD [28]. However, in primary RBD, MRI findings do not differ from age-matched controls, and proton magnetic resonance spectroscopy (1H-MRS) does not indicate mesopontine neuronal loss or 1H-MRS-detectable metabolic disturbances [29]. However, multiple studies have shown alterations in the dopaminergic system in patients with primary RBD. Using [^{11}C] dihydrotetrabenazine (DTBZ) positron emission tomography (PET) scans, Albin et al. showed a marked reduction in dopaminergic innervation in the caudate nucleus and the anterior and posterior putamen in patients with RBD [30]. With the same methodology and the addition of [^{123}I]iodobenzovesamicol to measure the density of thalamic cholinergic terminals, Gilman et al. demonstrated an inverse correlation between dopaminergic innervation and the severity of muscle atonia loss in patients who had MSA with RBD. Changes in thalamic cholinergic terminals did not correlate with the severity of REM atonia loss but instead correlated with the severity of sleep apnea in these patients [31]. Single-photon emission-computerized tomography (SPECT) scans using radio-labeled *N*-(3-iodopropene-2-yl)-2β-carbomethoxy-3β-(4-chlorophenyl) tropane demonstrated that in patients with subclinical RBD and clinically manifest idiopathic RBD, there is a progressive reduction in dopamine transporter binding when compared with age-matched controls; the reduction is not as profound as that seen in PD [32, 33]. Studies with DTBZ, a ligand that binds to the VMAT2 receptor and reflects the number of dopamine-producing neurons, show that patients with idiopathic RBD have a reduced density of striatal DTBZ binding, indicating loss of dopaminergic neurons in the substantia nigra, and that the degree of loss correlates with the severity of RBD symptoms [30]. Together, SPECT and PET scans support the hypothesis that dopaminergic dysfunction may be a primary factor in the pathogenesis of RBD. Diffusion tensor imaging studies visually assess microstructural brain tissue integrity. Unger et al. used this MR technique on 12 subjects with idiopathic RBD and 12 controls. Microstructural abnormalities were seen in the white matter of the brainstem, right substantia nigra, olfactory region, left temporal lobe, fornix, internal capsule, corona radiata, and right visual system of the idiopathic RBD patients. These changes include structures commonly affected by synucleinopathies [34].

REM Sleep Behavior Disorder and Hallucinations

The recent association of RBD with the occurrence of dopaminergic medication-induced hallucinations in PD suggests that the disorders may be related and that both are manifestations of disordered REM sleep. Comella et al. reported that patients who had PD with hallucinations had reduced nocturnal REM sleep when compared with a similarly treated group without hallucinations [35]. Arnulf et al. found that hallucinating patients with PD all demonstrated RBD, and that REM intrusions into delusions and hallucinations coincided with REM intrusions into wakefulness [36]. Using a similar paradigm, Nomura et al. showed that hallucinating patients had more sleep fragmentation, and 71 % had REM sleep without atonia versus only 25 % of nonhallucinating patients [37]. They also demonstrated that visual hallucinations coincided with periods of REM, and the dream content of the sleep-onset REM periods during the multiple sleep latency test closely resembled the content of their daytime hallucinations. Both hallucinations and RBD symptoms improved with administration of clonazepam, an accepted, although unproven, treatment for RBD. An 8-year longitudinal study in 80 patients who had PD showed that the presence of RBD in PD predicted the later development of hallucinations [38]. Overall, these studies suggest that REM sleep disruption may have a pivotal influence not only in the development of RBD but also in the pathophysiology of drug-induced hallucinations in PD.

Clinical Presentation

Individuals with RBD often seek medical evaluation only at the urging of their bed partner, who describes the most prominent clinical feature of RBD—acting out dreams. The history from the bed partner typically is the following: during sleep, the patient often punches, kicks, or vocalizes. Although the patient often attacks the bed partner, the patient is actually responding to dream content occurring during REM sleep, which creates an internal environment to which the patient is actually reacting. If the patient is awakened during an episode, the patient is frequently coherent and has recollection of a vivid dream, frequently involving themes of being chased or having to protect oneself against an attacker. However, the dream content may be mundane as well, such as sitting and having a conversation. This content often matches the physical activity or verbalizations made by the patient. Given that REM sleep occurs more in the latter half of the night, history often places the timing of these events to the second half of the night. Yet, they may occur at any time throughout the night.

Case Presentation

A 70-year-old man presented with violent behaviors during the night that had begun 8 years previously. He had been unaware of these behaviors, but his wife found these events to be very disturbing. As a result of these nocturnal behaviors, the patient intermittently had injured his wife, and on more than one occasion had awakened to find himself on the floor with bruises and abrasions. He provided three examples of such episodes (1) he was dreaming of a dog biting and attacking him. In defense, he kicked at the dog, but in actuality was kicking his wife. When awakened by his wife, he was immediately coherent and recalled the content of the dream. (2) He dreamed he knocked a cake platter on the floor and broke it, when he actually had knocked the lamp off of his nightstand table and broken it. (3) He dreamed he was being chased by unknown assailants and was hiding behind a door in a barn. He actually had gotten out of bed, and while running behind a closet, collided with the doorknob and incurred a contusion around his eye. (4) He dreamed he had caught a football and was running down the football field, and in actuality he had grabbed his wife around the neck and was trying to drag her out of bed. Two years after his presentation to our sleep disorders clinic, and 7 years after the onset of RBD, he developed a resting tremor, cogwheel rigidity, mild bradykinesia, and masked face, consistent with idiopathic Parkinson's disease.

Table 18.1 Criteria for diagnosing REM sleep behavior disorder in the international classification of sleep disorders

(A)	Presence of REM sleep without atonia (RSWA) on PSG
(B)	At least one of the following:
	1. Sleep-related, injurious, potentially injurious, or disruptive behaviors by history (i.e., dream enactment behavior)
	2. Abnormal REM sleep behavior documented during polysomnographic monitoring
(C)	Absence of EEG epileptiform activity during REM sleep unless RBD can be clearly distinguished from any concurrent REM sleep-related seizure disorder
(D)	The sleep disorder is not better explained by another sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder

Diagnosis

The *International Classification of Sleep Disorders*, 2nd edition [39] codifies the diagnostic criteria for RBD (Table 18.1) PSG is indicated in patients with any potentially injurious sleep-related behavior. "Pseudo-RBD" has been used to describe dream enactment behavior occurring at the termination of a respiratory event during REM sleep due to obstructive sleep apnea (OSA). The pseudo-RBD resolves once sleep apnea is treated and the respiratory events are eliminated. The OSA may also be a provocative factor for RBD in those patients otherwise predisposed to RBD. Interrater reliability for scoring REM sleep in PD has been shown to be high [40]. There are few data about the night-to-night variability of RBD, and false-negative studies certainly may be encountered, particularly with a single-night study. If there is a coexisting primary sleep disorder, such as OSA or periodic limb movement disorder (PLMD), the sleep disruption resulting from these disorders may trigger RBD episodes, necessitating treatment of these primary sleep disorders, which may improve coexistent RBD.

The differential diagnosis of a patient presenting with the history of acting out dreams includes sleepwalking and sleep terrors. These are non-REM parasomnias, which often occur during slow-wave sleep and are classified as arousal disorders by the ICSD. Additional diagnostic possibilities are seizure, rhythmic movement disorder, dissociative disorders, and malingering. As mentioned previously, movements associated with other primary sleep disorders, such as arousals associated with OSA, arm and leg movements associated with PLMD, or seizure, can be ruled out by overnight PSG. These disorders may be the primary cause of motor activity during sleep or a precipitating factor for RBD.

Eisensehr et al. conducted a retrospective analysis of PSG data while investigating the utility of specialized interviews for detecting RBD [41] and found that the specialized interviews had a low sensitivity of 33 % for RBD patients with PD but a high specificity of 90 %. In contrast, the sensitivity was 100 % and specificity was 99.6 % in non-PD subjects. They concluded that PSG was required to diagnose RBD in patients with PD, whereas interviews were sufficient for patients without PD. Gagnon et al. prospectively studied 33 subjects with PD and 16 control subjects, who each underwent a structured clinical interview followed by PSG. Of the PD patients, 11 (33 %) had RBD by PSG, but only half of these were detected by history. Only 1 of the 16 control subjects had RBD by PSG [11].

Clinical interview alone does not appear to be sufficient to diagnose RBD in patients with PD. PSG should be performed to rule out other primary sleep disorders, such as OSA and PLMD, as well as to look for epileptiform activity on the EEG. Capturing an RBD episode during PSG validates the diagnosis. Even if there is no confirmation of an RBD episode, REM without atonia may be seen, and the disorders already mentioned can be eliminated if the study is normal.

Treatment

Pharmacological Treatment

Clonazepam is effective even at low doses of 0.25–0.5 mg (with occasional higher doses needed) in up to 90 % of patients who tolerate this medication [3–5], but no controlled clinical trials have been conducted to date. However, in some patients, the long half-life and sedating adverse effects of clonazepam may result in daytime sleepiness, confusion, or falls and may worsen underlying OSA [42]. There are reports of triazolam improving RBD, but no evidence of other benzodiazepines doing so, although those with a shorter half-life than clonazepam could potentially have less troublesome daytime adverse effects. The efficacy of clonazepam may be a result of a serotonergic property not shared by other benzodiazepines. Studies in idiopathic RBD have shown that clonazepam decreases the visible motor activities of RBD occurring during sleep, but REM without atonia persists, as measured by electromyography. This may indicate the presence of two different systems—one responsible for the actual motor activity of acting out of dreams and the other responsible for REM without atonia—as opposed to these being on a continuum of disease severity. Melatonin in doses of 3–12 mg has successfully treated RBD, either by itself or administered adjunctively with clonazepam, and has produced restoration of REM without atonia [43]. Other medications listed in Table 18.2, including donepezil [44], have been reported to successfully treat RBD as well. Boeve reports success with quetiapine in some cases [43]. Clonidine may be effective through its REM suppression effect. Successful treatment of RBD with levodopa has been reported in patients who have PD. No large-scale, randomized studies comparing these various therapies currently exist that would assist in clinical decision making regarding RBD treatment.

Selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs) have been reported to precipitate or worsen RBD. It is not known whether they induce muscle movement during REM sleep or whether they unmask RBD in susceptible individuals. Avoiding SSRIs and SNRIs by using an alternative agent, such as bupropion, for treatment of depression may be considered.

Table 18.2 Medications reported to improve REM sleep behavior disorder

• Clonazepam
• Melatonin
• Quetiapine
• Triazolam
• Carbidopa/levodopa
• Carbamazepine
• Gabapentin
• Clonidine
• Donepezil

Nonpharmacological Treatment

Safety of the sleeping environment is of the utmost importance in this disorder. Given the severity of injuries that have been reported, securing the environment must be reinforced to patients with this disorder. This may include removing any potentially injurious furniture with sharp corners or other items from the area around the bed, or putting pillows or a mattress on the floor beside the bed if the patient falls out of the bed routinely. Others have placed their mattress on the floor to reduce the risk of injury.

Case Presentation

The patient was initially treated with 0.5 mg clonazepam at bedtime, which was subsequently titrated to 3 mg at bedtime without significant improvement. Carbidopa/levodopa was initiated, given his parkinsonian symptoms, but the patient discontinued this medication because of gastrointestinal upset. Melatonin was then tried and titrated up to 12 mg at bedtime, with dramatic improvement in the patient's presenting complaint of acting out his dreams.

Conclusion

RBD is present in many patients with PD and may be due to the degenerative changes occurring with PD in brainstem structures crucial for generating REM sleep. Patients who have PD with hallucinations appear to have RBD more often than those without hallucinations, offering support to the theory that hallucinations are caused by a REM abnormality. Injury risk with this disorder is high, particularly because the elderly population is at higher risk for developing RBD. PSG should be performed to rule out other causes for motor activity during sleep. When tolerated, clonazepam treatment is highly effective. Patient safety can be improved by securing the sleeping environment to minimize the risk of injury in this disorder.

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Excessive Daytime Sleepiness in Parkinson's Disease

19

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Abstract

Much has been written about sleep issues associated with Parkinson's disease (PD), including excessive daytime sleepiness (EDS). This chapter enumerates these issues related to the disease itself, whether directly or indirectly. Secondary causes of EDS, as well as recognition and management of EDS, will be addressed. We also examine some of the possible mechanisms involved and highlight some unique aspects

The term, EDS, refers to the inappropriate propensity for, as well as the actual inappropriate occurrence of, sleep during normal waking hours. EDS is a real and serious component of PD. Since the recognition of EDS years ago there have been a plethora of articles, research, and observations on sleep in patients with PD and sleep issues have been incorporated into the rubric of what constitutes PD. In the last decade, new scales have been developed (e.g., the SCOPA scale, the Pittsburgh Sleepiness Quality Index, and the Parkinson's Disease Sleep Scales 1 and 2). More telling perhaps, the revised Unified Parkinson's Disease Rating Scale (MDS-UPDRS) includes questions regarding nocturnal and daytime sleep.

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Excessive daytime sleepiness • Sleep–wake pathology • ESS • SCOPA • PDDS2 • Epworth Sleepiness Scale • Inappropriate Sleep Composite Score • Stanford Sleepiness Scale • Parkinson's Disease Sleep Scale • Pittsburgh Sleep Quality Index • SCOPA Sleep Scale

Much has been written about sleep issues associated with Parkinson's disease (PD), including excessive daytime sleepiness (EDS). This chapter enumerates these issues related to the disease itself, whether directly or indirectly. Secondary causes of EDS, as well as recognition and management of EDS, will be addressed. We also examine some of the possible mechanisms involved and highlight some unique aspects

The term, EDS, refers to the inappropriate propensity for, as well as the actual inappropriate occurrence of, sleep during normal waking hours. EDS is a real and serious component of PD. Since the recognition of EDS years ago there have been a plethora of articles, research, and observations on sleep in patients with PD and sleep issues have been incorporated into the rubric of what constitutes PD. In the last decade, new scales have been developed (e.g., the SCOPA scale, the Pittsburgh Sleepiness Quality Index, and the Parkinson's Disease Sleep Scales 1 and 2). More telling perhaps, the revised Unified Parkinson's Disease Rating Scale (MDS-UPDRS) includes questions regarding nocturnal and daytime sleep [1].

EDS is a common problem in PD. Sleep disturbances occur in approximately 75 % of patients with PD [2] and affect patients' sense of well-being and function [3]. EDS certainly impacts social functioning, particularly with driving [4, 5]. Often sleep disturbances are caused by serious conditions such as depression, dementia, sleep apnea, or stridor. It is therefore vital to understand and address sleep issues in PD patients.

EDS Mechanisms in PD

Numerous observations and studies suggest that sleep disturbances in PD are directly related to the disease itself. Petit et al. reported abnormal sleep architecture, with decreased nonrapid eye movement (NREM) sleep stages 3 and 4 and REM sleep in patients with PD [6]. Diederich et al. [7] reported that nocturnal sleep architectural abnormalities increased with disease duration (specifically total sleep time and REM sleep time), whereas sleep efficiency decreased with disease duration. In contrast, Yong et al. [8] utilized polysomnography (PSG) to find that reduced total sleep time was associated with increased age and levodopa use in individuals with PD, compared with controls. Stavitsky et al. [9] reported that hallucinations and daytime dozing were reported more frequently by PD patients with left-sided than right-sided symptom onset despite similar sleep architecture, suggesting hemispherical network differences. Both right- and left-sided onset patients had more EDS than controls. Individuals with PD and EDS have more widespread brain atrophy than those without EDS and more gray matter atrophy than either those without EDS or controls [10].

The observation that rapid eye movement sleep behavior disorder (RBD) often predates neurodegenerative diseases such as PD and MSA suggests that sleep–wake pathology is intrinsic to both disorders. Stockner et al. showed that, similar to PD, patients with idiopathic RBD have midbrain hyperechogenicity, suggesting that it may be a risk marker for PD [11]. Iranzo et al. [12] demonstrated that serial SPECT scans on

patients with idiopathic RBD demonstrate progressive decline in *striatal* tracer uptake, reflecting progressive nigrostriatal dopaminergic dysfunction. Studies and reports on deep brain stimulation (DBS) document sleep benefit from various targets, including the subthalamic nucleus (STN), globus pallidus interna (GPi), and pedunculopontine nucleus (PPN), which lend credence to the direct involvement of PD on sleep parameters. Although disorders such as restless legs syndrome (RLS) and periodic limb movement disorder (PLMD) are regarded as movement disorders, their circadian pattern of involvement begs the question whether they truly are sleep–wake disorders with kinetic manifestations. Perhaps conversely, it is fascinating that most of the motor symptoms in PD, such as tremor, dyskinesia, dystonia, and rigidity, are abolished by sleep, indicating a sleep–wake pattern as well.

Multiple nuclei, receptors, and pathways appear to be involved in the array of sleep disturbances in PD. These include dopamine, orexin/hypocretin, melatonin, and their relationship to (abnormal) circadian rhythms. Over the last decade, there have been new discoveries and proposed theories regarding the sleep/wake cycle involving multiple areas of the brainstem, hypothalamus, and striatum and numerous neurotransmitters. For instance, Saper [13] proposed the presence of a sleep-switch model with "flip-flop" mutual inhibitions among sleep-associated activities in the ventrolateral preoptic nucleus (VLPO), and wakefulness-associated activities in the tuberomammillary nucleus (TMN), dorsal raphe nucleus, and locus ceruleus (LC). In addition, the components of the ascending reticular activating system (ARAS) include dopaminergic neurons in the substantia nigra (SN), ventral tegmental area (VTA, A10 area), cholinergic neurons in the basal forebrain, the PPN, and laterodorsal tegmentum (LDT). Many of these areas have been noted to have Lewy body pathology as postulated by Braak et al., including the suprachiasmatic nucleus (SCN), PPN, LDT, LC, and the ARAS, in addition to the SN. It is plausible to assume that cell loss or dysfunction in these areas could lead to sleep disruptions in PD [14–16].

Borbely proposed two separate processes in the sleep–wake cycle: the endogenous biological clock that drives the circadian rhythm of sleep–wake cycle and a homeostatic component that influences sleep propensity [17]. It appears that REM sleep is driven by the circadian component and NREM sleep by the homeostatic component. The SCN is involved in both wakefulness and sleep processes. It is the central pacemaker for the circadian rhythm. Lewy body pathology has been found in the SCN in PD patients and certain "clock genes" such as *Baml1*, located in peripheral cells and leukocytes and involved with regulating the circadian rhythms, are reduced in PD patients during dark phase expression. Decreased expression of *Bmal1* correlated with Unified Parkinson's Disease Rating Scale (UPDRS) and Pittsburgh Sleep Quality Index Score (PSQI) [18]. Hilker et al. [19] reported an inverse relationship between REM sleep duration and mesopontine fluorodopa (F-DOPA) uptake in patients with PD. They postulated that there is an REM-inhibiting effect of increased monoaminergic transmission within the upper brainstem in early PD. Thus, at least the circadian rhythm process has been implicated in PD.

An overview of melatonin and its effects on sleep in PD can be found in a review by Srinivasan et al. [20]. Melatonin is secreted by the pineal gland in humans and diffuses into the capillary blood and cerebrospinal fluid. Melatonin production is synchronized to the light/dark cycle by the SCN. Fibers from the SCN pass via a circuitous route involving the paraventricular nucleus of the hypothalamus, medial forebrain bundle, reticular formation, lateral horn cells of the spinal cord, and superior cervical ganglion, to then innervate the pineal gland [20]. Disruptions in this pathway, including cell or receptor loss, could alter wake/sleep cycles. Melatonin exerts its physiological effects through G-protein MT1 and MT2 receptors found in various cells throughout the body. Receptors have been found in the SCN, cerebellum, hippocampus, SN, caudate, putamen, ventral tegmental areas, and nucleus accumbens. MT1 and MT2 receptors found in the human amygdala and SN have decreased expression in patients with PD [21].

Numerous studies have shown that melatonin restores the phase and amplitude of circadian rhythmicity by interactions with MT1 and MT2 receptors expressed in the SCN [20]. Bordet et al. [22] and Fertl et al. [23, 24] reported phase advances of melatonin circadian rhythm in PD patients. In 2002, Mena-Segovia et al. reported altered sleep/wake cycles in striatum-lesioned rats with increased wakefulness and reduced slow wave sleep, but little modification of the phase of circadian rhythm [25].

Melatonin itself has displayed protective properties in some animal models. Antonio et al. [26] reported that melatonin can prevent neuronal cell death in the nigrostriatal pathway in the MPTP animal model. Melatonin also reduces radical formation, including preventing excessive electron leakage at Complex I in the mitochondria. Complex I functioning in mitochondria is defective in PD patients [27]. Thus, a loss of melatonin-producing cells, its receptors, or their function may affect patients with PD in many ways, including the production of sleep abnormalities.

Melatonin has shown modest clinical benefit in PD patients. Dowling et al. found that treatment with 50 mg melatonin significantly increased night time sleep revealed by actigraphy; 5 mg of melatonin was associated with subjective improvement of sleep versus placebo [28]. Mederios et al. [29] studied 18 patients with PD and found that 3 mg of melatonin improved subjective sleep measures (e.g., the Epworth Sleepiness Scale (ESS) and the PSQI) but not objective measures, such as the PSG. In contrast, melatonin has shown benefit in REM behavior disorder (RBD) [30].

Dopamine (or the lack thereof) has been implicated in sleep disturbance in PD. Rats with a selectively damaged nigrostriatal pathway develop hypersomnolence [31]. Primates treated with the toxin, 1-methyl, 4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) developed somnolence that was reversible with levodopa and bupropion [32]. Clinically, dopamine-depleting agents, such as tetrabenazine or reserpine, are sedating, as are dopamine-blocking agents such as neuroleptics [33]. Paradoxically, low dose dopamine agonists induce sleepiness, whereas high doses cause alertness [34].

Numerous studies have demonstrated the presence of a retinal circadian clock. Melatonin and dopamine regulate this clock via opposing roles. Dopamine release produces a light adaptive physiology; melatonin produces a dark-adaptive physiology. Each one inhibits the other in this circadian rhythm [35]. Pathological changes in the retina, including cell loss and reduction of dopamine and thinning of the circumpapillary retinal nerve fiber layer, are present in PD [36, 37]. Thus, it is possible that aberrations in circadian rhythms in PD patients originate in the retina itself. This also might help explain the proposed effectiveness of bright light therapy for PD patients with disturbed sleep [38, 39]—the bright light stimulus may increase the expression of more dopamine or perhaps increase its functionality, thus compensating for the dopaminergic neuronal loss in various areas, including the SCN.

The stability of the sleep–wake cycle relies on mutual inhibition. Destroying this stability will cause disruption in the sleep–wake cycle. The neuropeptide, orexin, also known as hypocretin, appears to modulate wakefulness via monoaminergic pathways. Blocking or destroying these neurons or orexin receptors may cause quick switching from one state to the next, as occurs in narcolepsy. A lack of orexin function or a reduction of orexin levels also leads to instability of the sleep–wake cycle, as is in the elderly with sleep disorders. Low levels of orexin/hypocretin were noted in the cerebrospinal fluid (CSF) of persons with narcolepsy, thereby helping to establish its role in sleep–wake cycle disruptions. This prompted studies looking for similar findings in PD patients, fueled further by a report that PD patients display narcoleptic characteristics on PSG [40], and both Asai et al. and Fronczek et al. subsequently did demonstrate loss of orexin neurons in PD patients [41, 42]. Similarly, Lessig et al. [43] found neocortical hypocretin levels to be reduced in dementia with Lewy bodies (DLB) and correlated with hypersomnolence. However, most studies of CSF levels of orexin/hypocretin in PD patients have been normal [44–46]. Some investigators have surmised that CSF samples are not a good measure of orexin levels and that direct ventricular samples should be obtained [41]. Others have suggested that CSF orexin levels do not drop until >70 % of the neurons are lost. The problem may lie at the receptor level

itself, considering that the receptors are widely distributed throughout the brain, including areas involved with the sleep–wake cycle such as the LC, TMN, median raphe nucleus, and mesopontine reticular formation. [47]. Orexin may have other effects on the dopaminergic system. Moorman and Aston-Jones [48] reported that in recordings of anesthetized rats, orexin modulates dopamine neurons in the VTA in part by enhancing the medial prefrontal cortex control of dopamine neurons, which is involved in conditioned responses to reward-associated stimuli. They also noted this was in a diurnal pattern insofar as orexin-1 receptor antagonism decreased tonic dopamine cell activity in active but not rest period animals, suggesting a diurnal influence of orexin. However, they did not comment upon sleep behavior or upon effects on dopaminergic neurons of the SN. It would have been interesting to know what effects would have occurred in sleep behavior and architecture given the diurnal pattern and what aberrations would have been seen in a PD animal model?

These theories and studies support the notion that sleep disruptions are innately part of PD. The myriad of systems and substrates involved caution against viewing EDS in a simplistic fashion. EDS may involve multiple factors, even in an individual patient, and management needs to target these factors systematically to be most effective.

Evaluation of EDS

EDS may be due to PD itself, its treatment, or from secondary causes. The best approach is to weed out the various possibilities causing the EDS. One must start with the history to discern whether there is the presence of EDS. Thereafter one needs to uncover whether it is primary or secondary to the PD.

History

It is not sufficient to wait for patients to complain about their sleep issues. For a variety of reasons, patients often do not offer complaints regarding their sleep habits or EDS. Older PD patients and their caregivers often believe napping is part of normal aging. Many patients believe that EDS is part and parcel of the disease process and that no treatment is available. They may not realize there may be other conditions responsible and that many are treatable. Studies also have shown that general physicians often do not screen for sleep-related issues [49].

It is therefore, best to approach the subject first either with one of the various questionnaires available or with a few screening questions. Simple questions (e.g., “How is your sleep?”, “Is being tired ever a problem for you?”, “Have others noticed that you fall asleep easily?”, and “Do you fall asleep at inappropriate times?”) can open a meaningful discussion with patients and caregivers. Attempts to clarify should be made when a complaint of sleepiness or tiredness arises. It is crucial to distinguish fatigue and tiredness from true sleepiness. The former usually are due to a lack of energy or motivation and certainly may overlap with sleepiness. However, fatigue in the absence of EDS, hypersomnolence, or an increased propensity to fall asleep should lead one to explore other medical and psychiatric conditions, particularly depression. Nonetheless, these patients should be followed closely for EDS if any doubt remains. Once a diagnosis of EDS has been established, one should take measures to minimize or avoid potential hazards to the patient and society at large. Risks should be assessed and recommendations made to prevent injuries, including automobile accidents. These recommendations should be documented to reduce liability.

Focused EDS History

EDS in patients with PD can arise from a variety of causes. It is imperative to conduct a focused, organized interview regarding possible causes to achieve practical solutions. It is highly preferable to have patients, spouses, and/or caregivers present to obtain as much detail as possible.

An easy first step is with an inquiry about medications. It is not uncommon for sleepiness to occur with changes in medications or dosages, particularly with levodopa and dopamine agonists

[50–52]. Sedation as a common adverse effect of numerous medications, including antiparkinsonian agents, antidepressants, and over-the-counter medicines. Conversely, some medications, such as selegiline, amantadine, and bupropion, may cause insomnia. One should also explore nighttime caffeine use. It is imperative to establish a timeline of events with regard to when medications are administered .When a medication association is clear, it is reasonable to adjust the medication(s) accordingly as a first step, especially when time is limited. If this is not effective, a more detailed evaluation is warranted. Treating empirically with wake-promoting agents, such as modafinil or methylphenidate, without further investigation into the cause of EDS is not recommended [40]. One also should ask about alcohol use, as well as products that may contain alcohol, such as cough suppressants. Related to this line of questioning is sleep quality and hygiene in general. Physicians should inquire regarding nighttime schedules and habits, including activities that occur in the bedroom and in bed (such as reading or watching television), sleep body positioning, and hours devoted to sleep.

Medical conditions that might trigger EDS should be excluded. Depression especially should be assessed when falling asleep inappropriately is not a major problem. Depression also can be a manifestation of sleep apnea and other sleep disturbances. When depression overshadows EDS, appropriate treatment can help both conditions. Depression often manifests with trouble maintaining sleep or with early awakenings. Atypical depression can present with hypersomnolence.

Next, one should assess for serious, common, and treatable disorders of EDS. Determining if there is true hypersomnolence (unrelated to insomnia) can help direct further investigation regarding EDS. When present, hypersomnolence indicates a higher likelihood of obstructive sleep apnea (OSA), sleep disturbances, and medication effects. Physicians should ask about snoring, witnessed apneic events, and morning headaches. Obesity, hypertension, strokes, congestive heart failure, hypothyroidism, large neck size, and retrognathia are also clues to the diagnosis. It should be noted that OSA is *not uncommon* in individuals with normal body habitus.

When EDS seems to occur prominently over a short period of time without changes in medications, a search for encephalopathy should be pursued. Physicians should ask about recent behavioral changes, sick contacts, or unusual complaints from the patient. Psychosis is not pathognomonic of encephalopathies but may be present in individuals with PD with dementia, DLB, and other neurodegenerative diseases; it also may be medication induced. Patients with PD and EDS can present with a narcoleptic phenotype, which may be from the disease itself. However, the presence of cataplexy is very suggestive of narcolepsy itself. In that situation, one should ask specifically about sleep-related hallucinations, sleep paralysis upon awakening, and irresistible urges to fall asleep. In any case, a polysomnogram, and possibly a multiple sleep latency test should be obtained when hypersomnolence is not related to medications or other relevant medical conditions.

Patients and spouses should be asked directly about secondary causes of EDS and inquire about symptoms of RBD, RLS, and PLMD, as well as insomnia. All of these are common in PD. Specific symptoms related to PD itself also must be determined. These include hyperkinetic phenomena such as tremor, dyskinesia, and dystonia, as well as hypokinetic disturbances such as difficulty turning in bed. Nonmotor symptoms, such as pain, psychosis, anxiety, and nocturia, also may affect sleep.

Questionnaires

Various questionnaires are available to help screen for, and elucidate sleep disturbances, including EDS and specific conditions like sleep apnea. Some questionnaires (e.g., ESS, SCOPA, and PDDS2) have been used and validated in PD. Several will be mentioned in detail since they have been reviewed and recommended by the Movement Disorder Society task force [53]. Each has been utilized to varying degrees in the PD population and demonstrated usefulness in

assessing aspects of sleep or daytime sleepiness in PD. Each has its own advantages and limitations. Questionnaires do not replace a good history but are screening tools to help identify and rate sleep problems and guide the practitioner to a more focused line of questioning, differential, and subsequent diagnosis. Further, none of these six scales mentioned are appropriate or sufficient to diagnose specific sleep disorders in PD.

Epworth Sleepiness Scale

The ESS is a quick and useful test to ascertain if EDS is present. It is a simple set of questions that quantifies the propensity to sleep in eight situations. The rating is from 0 to 4 with 0 representing in a given situation "would never doze" and 3 representing "high chance of dozing". A cumulative score range is from 0 to 24. Normal ranges without sleep disorders are around 0–10. The ESS is simple to use, low in cost, and reliable in detecting patients with a severe propensity to fall asleep. It is often used with a cut off of 10 and above indicating pathological daytime sleepiness. Patients with narcolepsy or sleep-related breathing disorders (SRBD) have higher scores. The ESS can be used as a measure of treatment success since scores decrease with effective treatment. A disadvantage of the ESS include is that patients must recall their experiences with sleepiness, which may be inaccurate. They also must rate situations they have not necessarily experienced. Mild cases of EDS may be missed. Further, the ESS may be affected by anxiety, depression, and somatization. It is best to use it in conjunction with a good history rather than as a screening tool. It is still widely used in its original form in trials and study reports.

Inappropriate Sleep Composite Score

The Inappropriate Sleep Composite Score (ISCS) is a face-to-face questionnaire, administered by clinical staff, designed to identify patients at risk of sudden onset of sleep while driving. The time period is unspecified. The ISCS takes two questions from the ESS with four additional items regarding falling asleep in unusual situations (driving, eating, attending work, or attending to routine household activities).

This score is complementary to the ESS and geared to identify patients at risk for sleep attacks. It has not been studied outside the PD population to our knowledge. Its reliability is unknown. It would be interesting to see how patients would score with and without dopamine agonist therapy.

Stanford Sleepiness Scale

This is a one-item self-rating, seven-point Likert type scale designed to assess subjective sleepiness. High scores indicated high levels of sleepiness. The patient is asked to choose the set of descriptors that best describe his/her current feeling of sleepiness. The scale has been widely used in almost all types of sleep disorders. It does not offer information over a longer period of time however. The advantage is that it is very simple and quick.

Parkinson's Disease Sleep Scale-2

This scale was revised from the original PDDS that was designed to measure nocturnal problems, sleep disturbances, and EDS in PD over the previous week. On the revised Parkinson's Disease Sleep Scale-2 (PDSS2), 6 of the 15 questions were modified to address such issues as sleep apnea, akinesia, pain, and RLS. The visual analogue scale was transformed into a frequency measure (how many times does it occur?). PDSS2 scores range from 0 (no disturbance) to 60 (maximum disturbance). It has been validated in a study that showed it had internal consistency, construct validity, and precision [54]. The PDSS2 helps differentiate sleep problems into various factors:

1. PD-specific nocturnal motor symptoms such as akinesia, early morning dystonia, tremor during waking period at night, PLM, and restless behavior.

2. PD-specific nocturnal nonmotor symptoms such as hallucinations, confusion, pain, cramps, breathing difficulty with snoring, and immobility.
3. Sleep-specific disturbances such as insomnia, sleep maintenance, and nocturnal urination.

The study demonstrated that sleep was more severely disturbed and disrupted when noticed by the caregiver/bed partner than without such notice. The scale also identified severe PDSS scores in those with advanced disease. One possible advantage was that specific symptoms could be identified by combining similar items, thus allowing for more focused treatment. One major disadvantage is that it neglects questions regarding daytime sleepiness.

Pittsburgh Sleep Quality Index

This is a self-rating questionnaire designed to evaluate sleep quality, examine sleep habits and disturbances in the past month. There are 19 questions for the patient that are combined to form seven component scores (subjective sleep quality, latency, duration, habitual sleep efficiency, sleep disturbances, use of sleep medications, and daytime dysfunction). Five more questions are answered by the caregiver but do not contribute to the final score. There is a maximum score of 21 for the seven components.

The scale has been used to compare sleep quality in PD patients and associated disorders like RLS, depression, dementia, and patients with anxiety and hallucinations. It has been used to compare sleep quality before and after treatment in PD patients. Limits include the heaviness toward sleep habits and inadequate coverage of sleep disturbances and daytime sleepiness. It has also been criticized for some ambiguity of the items.

SCOPA Sleep Scale

This scale is self-administered and involves three subscales. The first is a five-item subscale with four response options that address nighttime disturbances occurring the previous month. These include sleep initiation, fragmentation, efficiency, duration, and early awakening. There is a maximum score of 15 with each question being three points. The second is a six-item subscale with four response options that evaluates daytime sleepiness. Patients indicate how often they fell asleep unexpectedly, in particular situations, how often they had difficulty staying awake, and whether falling asleep in the daytime was considered a problem. There is a maximum score of 18. The last subscale is a single item addressing the quality of sleep. Advantages include the fact that it gives a broader duration of time for which the EDS is explored, it encapsulates both night and day issues for a more detailed view of the possible factors involved, and it touches upon the concept of sleep attacks that can be serious. It does not necessarily address specific disorders such as RBD, OSA, or RLS.

Clinical Examination

Physical findings suggestive of EDS are scarce. Mere observation is limited often to patients falling asleep during the interview. Obesity and/or large neck circumference may suggest OSA; however, it is not uncommon for OSA patients to a have normal body habitus. Evidence of peripheral neuropathy may raise suspicion of RLS in the select patient complaining about abnormal leg movements at night. Lethargy or inattention may suggest encephalopathy. In our experience, those patients with evidence of psychosis or moderate-to-severe dementia on examination increase our suspicion for the development, or presence, of EDS. Unexplained bruises should raise suspicion for RBD. Focal neurological deficits may warrant neuroimaging to rule out structural processes such as masses, strokes, or subdural hematomas.

Ancillary testing is appropriate at times, especially if the onset of EDS is sudden or subacute. Serum electrolytes, glucose, complete cell count, erythrocyte sedimentation rate, and thyroid levels are useful when a medical condition is suspected. Likewise, liver function tests, ammonia, B12 lev-

els are useful when encephalopathy is present. Iron studies and renal function studies should be ordered in patients with RLS and PLMD. Lumbar puncture is rarely helpful except when a diagnosis of narcolepsy is considered. The absence of HLA DQBI*0602 helps exclude narcolepsy but does not rule it out completely.

Sleep Testing

Overnight PSG is the gold standard for evaluating most sleep disorders. As the patient sleeps, simultaneous recordings are obtained from EEG, submental EMG, and electrooculogram (EOG). Also, typically recorded are EKG tracings, limb movement (via anterior tibial EMG), oxygen saturation, respiratory effort, and airflow. Other devices that may be used include infrared video recorders, microphones (to capture snoring, grunting, and stridor), and esophageal pH probes.

PSG may uncover other treatable sleep disorders not evident by the history alone. It can reveal RBD, RLS, PLMD, seizures, and sleep-related breathing disorders (SRBDs) such as OSA. It also can help identify patients with hallucinations, dyskinesia, dystonia, and other "off" states. Its sensitivity varies with each condition and those that occur intermittently can be missed. Its beauty is that it is noninvasive, suitable for all ages, and gives objective evidence. Disadvantages include cost, availability, and comfort; some patients may find it difficult to sleep in a sleep laboratory facility and events may be missed if the patient is unable to sleep. Regardless, it gives valuable information to the clinician and often is critical for the diagnosis of many sleep disorders.

When to order a PSG:

1 Cases of suspected SRBDs
2 Cases of suspected RLS/PLMD/RBD, but hesitant to start empiric therapy
3 Cases of unusual behavior suspicious for seizures versus parasomnias
4 Cases of moderate–severe EDS without clear etiology despite extensive history
5 Cases of suspected nocturnal stridor should be done urgently

When sleep apnea is suspected and PSG is not available or the patient is physically unable to come to a sleep lab facility, one may employ portable pulse oximetry, though the sensitivity is lower. Any suspicion for nocturnal stridor should warrant an urgent PSG.

Actigraphy

Actigraphy is another method for home use. Placed either on the wrist or ankle, the device can capture information regarding total sleep time, latency, and immobility. It may be useful to diagnose RBD and other abnormal sleep movements. However, it does not diagnose serious conditions such as stridor or OSA. In contrast to PSG, actigraphy is comparatively inexpensive, done in a familiar setting conducive to sleep and may be worn for long periods of time if required. These last two points may allow for capturing both intermittent abnormal events, and perhaps more normative data [55].

MLST

The Multi-Sleep Latency Test (MSLT) is performed less frequently and is used primarily for the diagnosis of narcolepsy. Nonetheless, it quantifies sleep and can be useful when the history is ambiguous. The test should be done after an overnight PSG to ensure pretest sleep. During five 20-min sessions over a 2-h interval, the patient tries to fall sleep in a dark, comfortable room while monitored in the sleep lab. Results are (1) the average time to sleep onset and (2) the number of REM episodes. Short sleep latency and REM latency are suggestive for narcolepsy but not specific. Similar results can be seen with sleep deprivation and from various medications.

The Multiple Wake Latency Test (MWLT) differs from the MSLT in that one is asked to remain awake during the sessions while placed propped up on pillows in a dim lit room. The test is not usually done in clinical practice and results may not extrapolate well to real-life situations.

Causes of EDS

EDS in PD can be due to the disease itself, medication effects, associated or secondary conditions, or as a consequence of poor sleep quality and hygiene. It can be a combination of many components. It is extremely difficult to measure the contribution of each factor [40]. We find it helpful to separate causes as whether or not they are related to PD.

Common Causes of EDS in All Patients

Poor Sleep Hygiene

Poor sleep hygiene has many variables, including poor environment, poor sleep habits, insufficient time for sleep, nighttime use of caffeine and alcohol, and use of over-the-counter sleeping aids or medications. Education is key to help with compliance. Written instructions help reinforce the message. Though often time consuming and sometimes initially difficult for patients, compliance is often very rewarding with no long-term side effects and no need for expensive treatments.

Simple instructions should include:

- Allow for ample time for sleep at night.
- Do not take naps.
- Maintain the same sleep schedule nightly.
- Avoid alcohol and caffeine at night.
- Do not use the bedroom except for sleep.
- Avoid lying in bed when not sleepy.
- Have regular exercise to help maintain daytime alertness, though not before bedtime.

Circadian Rhythm Disorders

Circadian rhythm disorders are another treatable form of EDS. The diagnosis is considered when patients are adversely affected by either early or late bedtimes and respective early or late risings. This often may be seen in demented patients. These disorders should be considered in night-shift workers. Light therapy or melatonin often helps significantly [56]. Occasionally, treatment involves changing one's schedule either forward or later, depending upon the rhythm disorder involved. Difficult cases may warrant consultation with a sleep specialist.

Narcolepsy

Narcolepsy typically occurs in young adults, which makes its appearance in PD unlikely. Nonetheless, it should still be considered because patients often go for years without a diagnosis. As difficult as it is to diagnose narcolepsy in the general population, it can be more so in PD. Both disorders can be associated with hallucinations, irresistible urges to sleep and tiredness, especially PD patients on dopamine agonist therapy. Sleep paralysis, though characteristic of narcolepsy, does occur in the general population, often as an isolated symptom and is not itself enough to diagnose narcolepsy. However, cataplexy—the loss of muscle tone suddenly with emotion—is highly suggestive of narcolepsy and has not been reported in PD. In such patients, blood should be sent for HLA typing. HLA-DQB1*0602 is present in >85 % of narcolepsy patients with cataplexy, so a negative result argues against narcolepsy with cataplexy; however, only half of individuals with mild or atypical narcolepsy or without cataplexy have HLADQB1*0602 [57] and 12–38 % of the normal population have the same allele [58]. In addition to EDS and characteristic PSG/MLST findings, low hypocretin levels in the CSF (less than 110 pg/mL) also are indicative of narcolepsy [59]. In contrast, hypocretin levels are not always low in the CSF of PD patients with EDS, whether on dopamine agonist therapy [44], or in those with in advanced disease with dementia [46].

PSG and MLST testing are very helpful to diagnose narcolepsy but short sleep latency and early onset REM sleep also have been documented in PD patients [40]. Treatment for these patients often warrants a sleep specialist consultation. Wake-promoting agents such as modafinil, armodafinil, and methylphenidate may be helpful. Cataplexy is treated with norepinephrine reuptake inhibitors such as venlafaxine, or with gamma-hydroxybutyrate. Gamma-hydroxybutyrate, marketed as sodium oxybate, also has been shown to help with sleep disruption and EDS in a double-blinded trial [60].

PD-Related EDS

We divide this further into direct disease involvement, complications of the disease, and EDS caused by medications. Often there is a mixture of these factors.

Direct PD Involvement

As previously mentioned, PD patients are more likely to be somnolent than healthy elders and this risk increases as the disease progresses [52]. Dopamine deficiency may directly cause sleepiness in PD patients, which will improve with dopaminergic treatment. Abnormalities involving other extranigral nuclei, such as the LC, dorsal raphe nucleus, and the PPN, may be responsible [33].

When an extensive work up for EDS has not uncovered a specific cause, empiric treatment with wake-promoting agents, such as modafinil, may be helpful. Two small placebo-controlled studies [61, 62] showed promising results with modafinil in PD, but this was not evident in a larger double-blind trial conducted by Ondo et al. [63]. In a more limited scope, modest improvement with modafinil 100 mg was noted on the ESS in an open study of elderly, institutionalized PD patients—where it may be more difficult to ascertain the cause of EDS [64]. This finding must be weighed in light of the study having no objective measures and no placebo group for comparison. Further, it was not known whether these patients also had dementia, which has been shown to improve with modafinil.

Depression

This diagnosis is important because it is common in PD and is treatable [65, 66]. In our experience, treating depression in PD patients is very successful and often helps the parkinsonian condition itself. Treating depression often improves EDS as well. EDS in depression may result from insomnia and early morning awakening is typical. Hypersomnolence may be evident in atypical depression and may respond well to monamine oxidase inhibitors when selective serotonin reuptake inhibitors (SSRIs) are ineffective. Caution should be used with bupropion because it can cause insomnia and occasionally worsen parkinsonian features.

Dementia

Dementia is quite common in PD, with a reported prevalence ranging from 30 to 90 % [67]. PD and AD can coexist and DLB has features of parkinsonism and dementia, which may cause it to be confused with either PD or AD. Individuals with DLB often experience delusions and/or hallucinations early on, in proximity to the onset of parkinsonian features, and with usage of even low doses of levodopa or other dopaminergic agents, which may help distinguish it from PD [68]. EDS may occur in demented patients, making it difficult to ascertain the correct etiology of EDS in PD patients. Demented patients have decreased slow–wave sleep, increased sleep latency, and sleep fragmentation that contribute to EDS. They also have disorientation, sundowning, and psychosis that contribute to the development of EDS.

Pharmacological treatments for sleep disturbances in demented patients include benzodiazepines, but they may cause sedation, daytime sleepiness, and rebound insomnia. Zolpidem, zaleplon, and eszopiclone have shorter half-lives but still may cause similar adverse effects. Others have used antidepressants such as SSRIs, tricyclics, and trazodone, but many of these can cause sedation, dizziness, and weight gain. Ramelteon, a melatonin agonist, increases sleep efficiency and total sleep time and has not been associated with cognitive impairment, rebound insomnia, or abuse potential [69].

Nonpharmacological treatments showing benefit include light therapy and physical activity, though many of the studies have involved nursing home residents and may not be as applicable to patients in the home setting [70]. Nonetheless, these therapies are relatively easy, inexpensive, and may have significant benefits beyond improving EDS.

PD Treatment Related

Motor Fluctuations (Dystonia and Dyskinesia) Immobility

Treatment of PD can cause EDS in various ways. Dopamine agonists and levodopa can cause vivid dreaming, hallucinations, and paranoia, particularly at night. These often lead to insomnia, sleep disruption, and fragmentation. When psychosis occurs after an escalation of prodopaminergic agents, the dose should be lowered first; antipsychotic medications then may be added or increased if necessary and the prodopaminergic agent subsequently slowly increased if needed. Quetiapine and clozapine are usually effective antipsychotics and do not worsen parkinsonian features or cause tardive syndromes. Typically, our patients require about 100 mg of quetiapine, but doses range from 25 to 250 mg; caregivers should be warned that quetiapine can be sedating, even at low doses, but most adapt with longer use. We try to reserve clozapine for patients refractory to quetiapine because its use requires indefinite blood draws to minimize the risk of irreversible agranulocytosis.

Amantadine is notorious for causing confusion, especially in the elderly. This often occurs at night. We try to limit the total amount of amantadine in a day or give the bulk of it in the daytime. However, amantadine is often useful at night to help nocturnal or early morning dystonia. One solution is to use controlled release carbidopa/levodopa 50/200, 1–2 pills at bedtime, to alleviate early morning dystonia. We also find that this also reduces nighttime immobility without inducing significant hallucinations. Monoamine oxidase type B (MAO-B) inhibitors, such as selegiline and rasagiline, may cause insomnia and should be administered only in the morning and early afternoon.

Levodopa and dopamine agonists may cause dyskinesia. When severe, dyskinesia can prevent patients from sleeping. Dyskinesia often occurs late in the day, as the effect of repeated doses accumulates. This is especially true if one uses much controlled release carbidopa/levodopa throughout the morning and afternoon. One often needs to lower the dose of dopamine therapy to lessen the dyskinesia. We therefore try to avoid nighttime doses of levodopa or dopamine agonists to prevent nocturnal dyskinesia and psychosis. This point is extremely relevant in hospitals, rehabilitation centers, and nursing homes when medications are often given as "Q8 hours" or "Q6 hours". We advise our colleagues to write specific times such as 8 am–12 noon–4 pm–8 pm to avoid inappropriate late night doses and poorly spaced out intervals, which contributes to iatrogenic sleep disruption.

PD patients may have motor, sensory, psychiatric or autonomic symptoms when the antiparkinson medicines are not working. They may have motor phenomena such as tremor, immobility, and dystonia that may cause insomnia or sleep disruption. Patients may also have autonomic symptoms such as nocturia. As mentioned above, using controlled release carbidopa/levodopa at bedtime often alleviates these "off" phenomena. Long-acting dopamine agonists such as ropinirole, pramipexole, and transdermal rotigotine may be useful to prevent wearing off at night. On rare occasions, we have instructed patients to take these long-acting preparations in the afternoon for a more robust effect at night to prevent wearing off. For insomnia, eszopiclone showed subjective benefit in sleep quality and sleep maintenance, though not total sleep time, versus placebo in a small study of PD patients [71]. Sodium oxybate has also shown benefit in EDS in PD patients in an open-label study [72].

Secondary Causes of EDS

These conditions often cause EDS as a consequence of insomnia that disrupts either the initiation or maintenance of sleep. Maintenance of sleep can be disrupted by microarousals, sleep fragmentation, changes in sleep-arousal states, or early morning awakenings.

SRBDs/OSA

OSA, central sleep apnea, and upper airway resistance syndrome (UARS) are common in the general population, particularly among men [73], though OSA may not necessarily be more com-

mon in PD [74]. All patients with EDS should be evaluated for these conditions due to their prevalence and treatability. OSA is the prototypical syndrome and will be discussed briefly here. The reader is directed elsewhere (Chap. 20) for a more extensive discussion. The condition occurs when the neck structures collapse the airway passage during sleep. This leads to numerous microarousals and subsequent fractured sleep architecture. Patients often have resulting hypersomnolence the next day. Many have morning headaches. OSA has been linked to hypertension, strokes [75], and impaired cognition [76]. Patients with OSA have a higher risk of car accidents as well [77]. Further, OSA may be found in conjunction with other parasomnias, such as RLS and PLMD.

Risk factors include obesity, loud snoring, witnessed apneic events, hypertension, hypothyroidism, and large neck circumference. One can evaluate the risk further by a point system. One adds " centimeters" or "points" to the neck circumference with 4 cm added for hypertension, 3 cm for loud snoring, and 3 cm for witnessed choking/gasping on most nights. An adjusted value of 43–48 cm carries a 4–8-fold risk of OSA and a value of >48 cm indicates a 20-fold risk of OSA. As noted earlier, 10 % of OSA patients may have a normal body habitus and may not snore loudly.

Diagnosis is made by PSG. Treatment is most effective with a continuous positive airway pressure (CPAP) device worn at night over the face. Treatment should be attempted in the mildly demented patient as it may improve cognition [78]. Treatment has been shown to improve the quality of life, mood, and alertness of patients. It also decreases the risk of automobile accidents [79, 80]. CPAP improves hypertension and ejection fraction in patients with congestive heart failure [81]. Unfortunately, compliance with the mask is difficult for many individuals. In such persons, dental appliances and surgical options should be explored.

Nocturnal Stridor

Nocturnal stridor can mimic snoring and OSA [82] and is particularly likely to occur in multiple system atrophy (MSA). This phenomenon frequently is caused by bilateral vocal cord paralysis. In a small study of three patients with MSA, Vetrugno et al. [83] found that during wakefulness vocal cord adductors were normal, with no spontaneous EMG denervation in laryngeal muscles, but abnormal recruitment became evident in the cricothyroid and thyroarytenoid muscles during sleep, with consequent severe vocal cord adductor limitation. They concluded that there was impaired supranuclear control of the laryngeal adductor musculature and that nocturnal stridor was a form of sleep-related laryngeal adductor dystonia. They also noted that all patients with stridor had nocturnal tachypnea, paradoxical breathing, and motor overactivity of intercostalis and diaphragmatic muscles and suggested that this reflected a central overactive and dystonic motor output, possibly related to dysfunction in inhibitory brainstem autonomic pathways. They did not find a significant desaturation of oxygen in these patients but reported similar oxygen desaturation results in a previous study, leading them to believe that such patients may have an associated OSA condition causing the desaturations. This hypothesis forces the practitioner to consider multiple sleep disorders in the diagnosis and management of MSA patients with EDS. Physicians caring for patients with either known or suspected MSA should investigate for possible stridor because it can be life threatening [84]. Diagnosis can be made by PSG and treatment should consist of CPAP or tracheostomy if CPAP is not tolerated.

RLS

RLS is common in the general population [85, 86] and may be increased in the setting of PD [87–89]. RLS may cause EDS as a consequence of initiation insomnia or maintenance insomnia via microarousals and sleep fragmentation. Early morning awakenings are unusual. RLS has a significant impact on patients' well-being. It affects not only just sleep quality but also quality of life [90, 91].

Patients with RLS experience an unpleasant sensation of crawling or creeping in their legs. Criteria for RLS include (1) the urge to move

one's legs, often associated with uncomfortable sensations in the legs; (2) temporary relief with movement, such as walking or stretching; (3) worsening or onset of symptoms with rest or inactivity; and (4) worsening or onset of symptoms in the evening or at night.

RLS can be associated with PLMD and OSA. Patients often have difficulty falling asleep due to the irresistible urge to move their legs while supine. They may also experience periodic limb movements during sleep, causing microarousals and sleep fragmentation. RLS can occur unilaterally [92] and may involve the arms and torso in severe and chronic cases. In severe cases, patients may experience sensations even during the day and even when just sitting; this has been labeled augmentation. Many report such sensations during long car rides or when in movie theatres. There are both familial and sporadic cases; the former often have earlier onset and increased severity. The prevalence of RLS is higher in women. Multiple genes have been found but routine genetic testing is not usually done. Although some have theorized that the A11 dopaminergic system in the hypothalamus may be involved in RLS, Early et al. did not find evidence to support this in six autopsy cases with RLS [93].

RLS has been associated with iron deficiency [94]. Studies have shown abnormalities in iron, ferritin, and transferrin levels in the CSF of patients with RLS [95] even when serum concentrations are normal, suggesting dysfunction in brain transportation or utilization of iron. Early et al. [96] noted nighttime (as opposed to daytime) CSF ferritin levels to be lower in RLS patients compared with controls; levels in early onset RLS patients (younger than age 45) were even lower than in late onset RLS patients. This nocturnal CSF finding helps explain the nocturnal onset or worsening in RLS. Allen et al. [97] noted decreased concentrations of iron in the putamen and SN on MRI. Replacing iron often ameliorates the symptoms of RLS [98]. When the ferritin is below 18 mg/L or iron saturation is below 19 %, treatment is advised until the ferritin is above 50 mg/L or the iron saturation is above 20 %. [99]. The usual requirement is about 65 mg of elemental iron, which requires 325 mg of ferrous sulfate.

RLS has been linked in some studies to peripheral neuropathy. There also are secondary causes of RLS, such as stroke, pregnancy, and renal failure (whether nor not treated with dialysis). Other observed associations include gastric surgery and celiac disease. It has not been firmly established whether there truly is a higher prevalence of RLS in PD [87–89]. One possibility is that the levodopa given for the PD symptoms triggers augmentation (and thus an unmasking) of the RLS symptoms [100]. Ondo et al. [101] postulated that patients with PD assume RLS symptoms are part of their disease and thus underreport it. Others have reported RLS mimics [88].

Treatment for RLS has blossomed in the last decade. Options include dopamine agonists, gabapentin, benzodiazepines, and opioids. Currently, most use the dopamine agonists as first line agents. Studies have shown efficacy at low doses. These are best taken an hour before bedtime. In patients with either rebound or augmentation, starting earlier at night is useful. Though not FDA approved for RLS, we have used the extended release dopamine agonists with success in our RLS patients with severe augmentation that occurs throughout the day. Similarly, a double-blind trial of transdermal rotigotine showed efficacy, compared with placebo, at either 2 or 3 mg/24 h in moderate-to-severe cases of RLS, with sustained relief and a low rate of augmentation for the 6-month duration of the trial [102]. One should remain aware of either impulsive or compulsive behavior with these compounds, even in low doses or in extended forms [103]. However, in a head-to-head trial between pramipexole and ropinirole, neither dramatically altered sleep parameters, although both were useful in low doses for the RLS symptoms and leg movement parameters when compared with placebo [104]. In patients with adverse effects to dopamine agonists, we often use gabapentin or benzodiazepines, such as clonazepam. This is an important point, because PD patients often are already on high doses of dopaminergic agents. Allen et al. [105] reported that pregabalin reduced symptoms in patients with moderate-to-severe RLS with great efficacy in a 6-week double-blind study. A recent randomized, crossover trial of gabapentin

enacarbil demonstrated efficacy at a dose of 1,200 mg daily in both subjective and objective (polysomnography) measures for moderate-to-severe RLS with good tolerability [106]. Gabapentin enacarbil is a prodrug with a long half-life; it may be useful in those suffering with augmentation into the daytime. We try to reserve opioids for our most recalcitrant cases, given the possibility of tolerance and addiction, though the risk for this appears to be remote [107, 108].

PLMD is a related disorder in which the legs move involuntarily during sleep. The leg movements usually last about 0.5–5 s and recur at intervals of 4–90 s. These movements may be unilateral or bilateral and also have been described while awake (labeled "PLMW"). The movements may trigger microarousals that, in turn, cause sleep fragmentation. PLMD often coexists with RLS and has been documented in individuals with RBD. In a very recent study of 45 patients with PD who underwent polysomnography, Covassin et al. reported an increase of PLMD with more severe PD. Although PLMD did not alter objective measures of sleep, it was associated with an increase in sleep complaints and a reduced quality of life [109].

RBD

RBD is characterized by the loss of muscle paralysis during REM sleep associated with excessive motor activity while dreaming [110]. Current literature suggests that degradation of nuclei in the pontine tegmentum and medulla oblongata is responsible for the loss of atonia during REM sleep with associated dream enactment. RBD has been associated with PD and MSA, often occurring years before motor symptoms arise [111]. It has also been reported in patients with dementia [112]. In a large cohort of 457 individuals with PD, Sixel-Doring et al. found that RBD was associated with older age and longer disease duration [113]. However, unlike other investigators [112], they did not find a male predominance.

Patients themselves may be unaware of their dream enactment behavior, since they are often amnestic for the events; the behavior is often by first reported by caregivers who witness the events. Bruises to patients and caregivers are common and sometimes serious. Patients with RBD also may have PLMD and OSA [112]. Studies have shown a high prevalence of RBD in PD patients, based upon PSG monitoring; often patients are without subjective complaints. This highlights both the need for elevated suspicion for this condition and the importance of PSG in diagnosing causes of EDS [113, 114].

Clonazepam at night is usually effective and is the preferred agent, although clozapine also has been used successfully [112]. Other drugs reported to be effective include quetiapine, melatonin, and sodium oxybate [30, 115]. Iranzo et al. did not find any benefit from bilateral subthalamic nuclei stimulation on RBD [116]. Serotonergic antidepressants and mirtazapine may worsen RBD [117, 118]. The reader is referred to Boeve's excellent review of the subject for further details [115].

Nightmares and Vivid Dreaming

When frequent or very disturbing, these phenomena can disrupt sleep and cause EDS. Patients usually recall these events. They can be continuous with waking hallucinations and psychotic behavior. These episodes may be triggered or worsened by dopaminergic therapy. In such cases, we either allocate their last dose of levodopa or dopamine agonist to earlier in the evening or we lower the dose. These phenomena respond well to quetiapine, although occasionally the dose must be escalated over time, especially in demented patients. Clozapine is usually very effective but requires indefinite blood monitoring because of the risk of irreversible agranulocytosis. If patients are not entirely paralyzed during their dreams, nightmares and vivid dreams can be difficult to distinguish from RBD, although the latter is usually characterized by amnesia for the events. The two conditions can coexist.

Sleep Attacks

Sleep attacks are defined as the sudden onset of sleep while engaged in action, notably driving, and were initially reported by us in 1999 in eight patients taking pramipexole who experienced the sudden onset of sleep while driving [119]. Numerous reports have documented that these

attacks may occur with both ergot and nonergot dopamine agonists [50, 51, 119]. Korner et al. [120] noted that sudden onset of sleepiness occurred earlier in younger PD patients started on a nonergot dopamine agonist than in those on other dopaminergic agents. There has been a debate whether these are dose related, but we and others have had patients with events even when on low doses [121]. We also believe these attacks may occur without prior sleep deficiency, contrary to other suggestions that they occur in a background of sleepiness. Korner et al. [120] found that, although many do have sleepiness prior to their sudden onset of sleep, a percentage of patients truly have sudden sleep attacks.

It remains difficult to predict prior to treatment which patients will succumb to sleep attacks. Montastruc et al. reported a higher prevalence in males and in individuals with dysautonomia, but prevalence was not related to age or severity of disease [122]. In contrast, Korner et al. [120] did find a correlation with age and disease severity, in addition to male gender. These findings do not provide sufficient information to predict which patients are likely to have sleep attacks on a practical basis. Lang et al. reported that the ESS has only 50 % sensitivity for predicting falling asleep while driving [123]. This observation concerning the ESS was confirmed by Ferreira et al. in a matched study between PD patients and healthy volunteers [124]. In this study, control subjects also reported sleep attacks, though not with the same frequency as the PD patients nor as frequently in activities that required attention. In their study, Ferreria et al. used the PSQI to supplement the ESS. The ISCS was designed to screen for sleep attacks and is complimentary to the ESS. In their review of the topic, Homann et al. provide a classification of sleep attacks, but it appears to be based primarily on previous reports and after-the-fact reports by patients and, thus, is not helpful for primary prevention [125]. Of note, Rissling et al. [126] reported a strong association between the dopamine D2 receptor gene polymorphism Taq IA and sudden onset of sleep in PD patients, suggesting a predisposition for some to have sleep attacks. No other reports regarding a genetic link or specific gene to predict those at high risk have been published.

Although clinically we have not seen sleep attacks in patients on long-acting dopamine agonists, these medications still carry the same warning. We continue to use dopamine agonists due to their great benefits to patients, but do warn our patients about the possible risk of sudden sleep attacks when taking these medications. Contrary to reports [127], we have not seen sleep attacks in patients on levodopa, nor on either MAO-B inhibitors or on catechol-*O*-methyltransferase (COMT) inhibitors, although there has been at least one report on entacapone [128]. Therefore, in such cases, we often will switch to these other agents.

Driving Issues

Driving with EDS from any cause is a serious matter, legally and medically. In studies looking at EDS in other sleep disorders (e.g., OSA, narcolepsy and shift work), there is certainly a higher accident rate in individuals with sleep disorders than in normal controls. However, once the sleep disorder has resolved, patients are usually safe to drive [129]. This is not necessarily so with PD. Patients with PD, irrespective of EDS, have a higher risk of motor vehicle accidents (MVA) than controls. Wood et al. found that PD patients were less safe than controls in real-life driving situations [130]. Advanced disease, but not levodopa therapy or on/off time, was a predictor for higher risk, which was contrary to findings by Heikkila et al. [131]. Neither of these studies assessed EDS as a risk factor. Singh et al. confirmed that disease severity, but not length of medication or "on/off" time, predicted unsafe driving by PD patients [4]. They also noted that combining the presence of even one medical comorbidity to the assessment increased the risk of poor driving, especially if that other medical condition was dementia. They had no patients with complaints of EDS, even when directly asked. They postulated, based on their study involving real-life driving at a driving center that most patients

with PD *are actually safe to drive*; often adjustments to patients' cars, such as automatic transmissions, extra mirrors, right-hand gear stick, left foot accelerator and brake, steering wheel knob control, and hand brakes improved safety. Those patients who did have "off" times were often able to continue driving if they could predict those "off" times. Uc et al. [132] similarly found that dementia was a separate risk factor, as was poor visual perception, for higher rates of crashes in PD drivers. Nonetheless, studies do show that both patients and neurologists overestimate the ability of PD patients to drive safely [130]. This is true even when patients are aware of or report their sleepiness, or sleep disorder [133]. Although PD patients performed worse than controls overall, some drove normally and knowing the terrain mitigated unsafe driving in PD patients, according to Uc et al. [134]. They suggested that a standardized road test, in conjunction with a detailed evaluation battery addressing such issues as vision, motor function, and attention, would be helpful in deciding whether an individual with PD is safe to drive. Often it is the patients themselves who determine when to stop driving; Uc et al. noted that PD patients cease driving earlier than their elderly counterparts [5].

Knowing who is able to drive safely remains difficult. Practitioners need to assess their patients' driving abilities, state of sleepiness, stage of illness, and other comorbidities carefully and discuss their concerns with patients and family. Frank discussions early in the course of treatment are important, especially if EDS is already present. Patients should be informed of the possible hazards of driving with PD. When appropriate, the physician should refer the patient to occupational therapists and/or driving instructors for assessment of ability to drive and need for driving rehabilitation. This should include driver retraining and modifications to the vehicle for safety improvement. If EDS is present or there is a high concern for sleep attacks, driving restrictions are appropriate until the issues have been investigated and resolved if possible. Physicians should document their findings and discussions for legal purposes.

Deep Brain Stimulation and Other Surgeries

Deep brain stimulation (DBS) has been utilized primarily for its effects on the motor symptoms of PD. However, various reports have shown benefit in nonmotor symptoms as well, including sleep [135]. Current studies suggest that both unilateral and bilateral stimulation of the subthalamic nucleus (STN) benefit sleep [135]. Less information is available regarding the effect of globus pallidus interna (GPi) and pedunculopontine nucleus (PPN) stimulation on sleep quality.

Arnulf et al. utilized PSG to study ten patients who had undergone bilateral STN DBS; they documented reduced WASO, decreased nocturnal and early morning dystonia, and increased sleep efficiency with stimulation on, compared with stimulation off [136]. Iranzo et al. found that bilateral STN stimulation improved both the subjective quality of sleep and sleep mobility; continuous sleep time also increased, but neither RBD nor PLMD improved [116]. Cicolin et al. [137] reported reduced WASO, increased sleep efficiency, and decreased REM sleep latency in five patients with PD after 3 months of STN stimulation; no improvement in RBD or PLMD was evident. Lyons and Pahwa [138] evaluated patients up to 24 months following bilateral STN and documented increased total sleep time that correlated with decreased bradykinesia; early morning dystonia was also decreased, but there was no change in daytime sleepiness. Amara et al. [139] reported on 53 patients with unilateral STN stimulation contralateral to the most affected hemibody and described improvement in sleep quality based on the PSQI.

GPi DBS also has produced beneficial effects on sleep in a few studies. Using the Parkinson's Disease Quality of Life questionnaire, Rodriguez et al. [140] reported subjective improvement in daytime sleepiness in 6 out of 10 patients treated with GPi DBS. Of note, none of the ten patients had their antiparkinsonian medications reduced. Volkmann et al. [141] used the Sickness Impact Profile to document persistent improvement in sleep quality in 20 patients treated with bilateral

GPi DBS. Sleep-related benefits are not limited to DBS. Farve et al. reported subjective improvement in sleep quality at a median 7-month follow-up in 59 % (13/22) of patients treated with unilateral pallidotomy and 47 % (8/17) treated with bilateral pallidotomy [142].

There are very few studies on DBS of the PPN; most are quite small and provide little information regarding its effect on sleep. Lim et al. [143] evaluated three individuals receiving PPN DBS (one with PD and two with progressive supranuclear palsy) in the on and off stimulation states. They reported that PPN DBS significantly decreased the total duration of REM sleep and the percentage of total sleep time in REM. However, PPN DBS did not alter RBD in either the on/off stimulation state in the two patients who had RBD. Romigi et al. [144] studied one patient with bilateral STN and PPN DBS; they noted that, although both STN at low frequency alone and PPN stimulation alone improved sleep efficiency and time awake after sleep onset (WASO), only PPN DBS increased the percentage of REM sleep. They studied three additional patients, along with this patient, with the PSQI, ESS, and PDSS with three distinct DBS parameters, each for 2 weeks at either (1) STN-on, PPN-off, (2) STN-on, PPN-on, or (3) STN-on, PPN cyclic-on (on only at night). They noted improvement in daytime sleepiness with PPN-on and improvement in nocturnal restlessness, psychosis, and daytime sleepiness with PPN-cyclic-on. Alessandro et al. used PSG to study one patient with PPN DBS and reported an increase in REM sleep [145]. Arnulf et al. [146] also found a difference in sleepiness and alertness that varied with high and low frequency stimulation of the PPN. This may suggest that the sleep–wake cycle may have multiple receptors, but selective neuronal firing patterns.

One parameter that might be used to gauge sleep improvement in DBS is a reduction of dopaminergic therapy, although not every study has shown a marked decrease in dopaminergic medication dosages. Reduced dopamine agonist therapy may result in less daytime sedation. This also may help explain the lack of improvement in PLMD in DBS, since patients may be on less dopamine agonists. DBS also improves motor function in PD; this in turn may account for reduced dystonia and tremor and improved mobility at night. Other reports have documented improvement in nocturia. Perhaps other networks or nuclei are being stimulated or modified, such as the lateral–dorsal tegmental nuclei and the dorsal raphe nuclei, with subsequent direct effects on sleep and alertness centers. Most of the studies have used subjective measures, which pose difficulty in ascertaining the true cause(s) of sleep improvement. Further studies, especially with larger sample sizes and objective measures, are needed to elucidate these questions.

Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) has also been explored. Van Dijk et al. [147] studied 13 PD patients and found that TMS over the parietal region, but not the motor cortex, improved sleep fragmentation and sleep efficiency, and reduced nocturnal awakenings. However, Shill et al. [148] reported no significant difference on the ESS in a randomized double-blind trial of transcranial electrostimulation in 23 PD patients and Arias et al. [149] found no therapeutic effects on sleep in PD patients treated with repetitive TMS in another small double-blind trial. Larger sample sizes and objective measures are needed.

Other nonpharmacological treatments have been attempted. Shulman et al. [150] performed a nonblinded pilot study of acupuncture in 23 PD patients. They reported that acupuncture did not significantly change the UPDRS or Beck Anxiety and Depression inventory but did produce sleep benefit. Further studies have not been forthcoming, to our knowledge. Bright light has also been studied with modest success. Willis and Turner [38] noted improvement in sleep in PD patients exposed to bright light therapy at an intensity of 1,000–1,500 lux once daily at about 1 h prior to regular onset of sleep. Many were able to reduce medications without worsening of symptoms. Further reports have not been published, to our knowledge.

Conclusion

EDS remains a common and serious concern for patients with PD. Unfortunately, diagnosis remains a challenge due to the complexity of PD itself and its related disorders. A focused and detailed history allows for easier diagnosis and management. Hopefully, continued basic research and newer therapies, whether pharmacological or otherwise, will help unravel the networks involved, allowing for better treatments. In the meantime, physicians should remain vigilant for the recognition and treatment of EDS and be willing to intervene on their patient's behalf.

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Sleep Apnea

20

Robert A. Hauser and Cheryl M. Carlucci

Abstract

Two types of sleep apnea have been identified: obstructive sleep apnea (OSA) and central sleep apnea (CSA). OSA occurs when the upper airway collapses; in OSA, there is no airflow, often despite great respiratory effort. In CSA, the transitory cessations of breathing are because of a drop in respiratory capacity—there is no airflow and no respiratory effort. Excessive daytime sleepiness (EDS) is a consequence of both OSA and CSA. A comprehensive history, ideally obtained from both the patient and bed partner, is the essential first step in diagnosing sleep apnea, but the gold standard for assessing sleep apnea is the polysomnogram (PSG).

Keywords

Obstructive sleep apnea • Central sleep apnea • Polysomnography • Snoring • Excessive daytime sleepiness

Overview

The word "apnea" comes from the Greek terms "a" for no and "pnea" for breath. Hence, apnea means "no breath" and sleep apnea, by definition, is apnea that occurs during sleep. Individuals with sleep apnea literally stop breathing for brief periods of time when asleep and must at least partially waken in order to resume breathing. Sleep is therefore fragmented.

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Because there can be very brief episodes of decreased respiratory activity during normal sleep, criteria have been established for the diagnosis of sleep apnea. An apneic event is defined as cessation of airflow for 10 or more seconds [1]. Episodes of decreased, but not complete, cessation of flow are hypopneas. Hypopneas are defined as a decrease in airflow of at least 50% from the patient's baseline accompanied by either a drop in O_2 saturation of at least 3% or an arousal [2].

Obstructive sleep apnea (OSA) and central sleep apnea (CSA) are two forms of sleep apnea. There is no airflow in OSA, often regardless of significant respiratory attempt. OSA arises with upper airway failure, either during inspiration or

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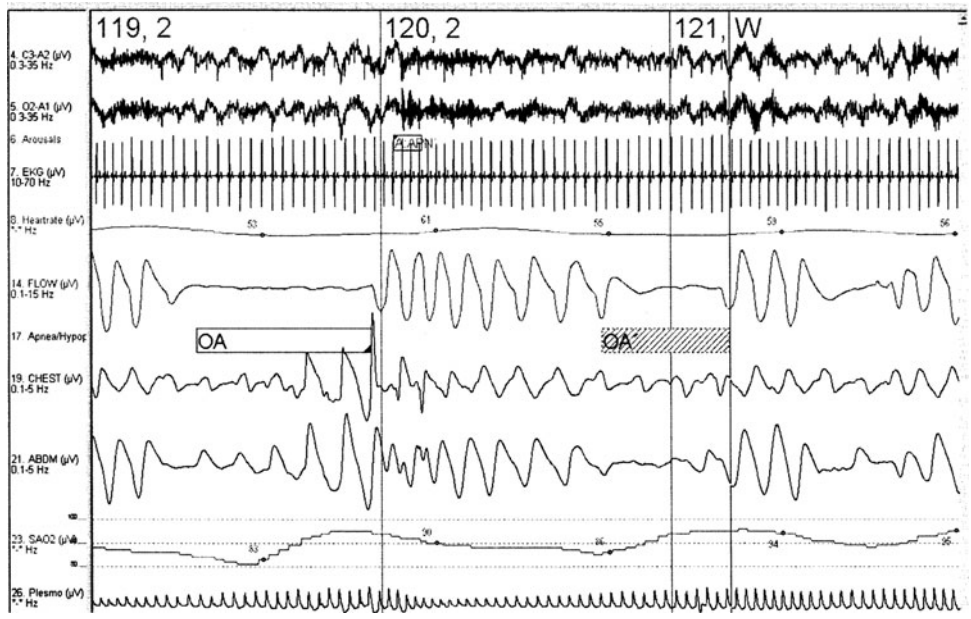

Fig. 20.1 Obstructive sleep apneas (OA and OA′). Figure courtesy of The Sleep Disorders Center at Tampa General Hospital

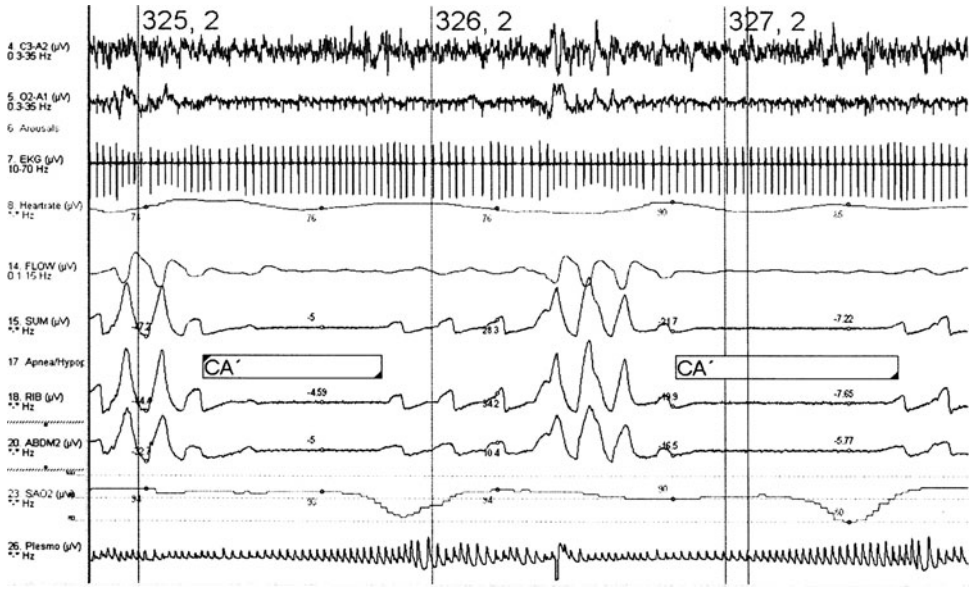

Fig. 20.2 Central sleep apnea (CA′). Figure courtesy of The Sleep Disorders Center at Tampa General Hospital

at the end of expiration, depending on the patient's upper airway anatomy. The patient is attempting to breathe against a closed airway (see Fig. 20.1). The transitory arrests of breathing in CSA are caused by reduced respiratory activity, where no airflow or respiratory effort exists (see Fig. 20.2).

Some apneic events are comprised of elements of both central apnea (i.e., the absence of effort) followed by obstructive apnea (increased effort in

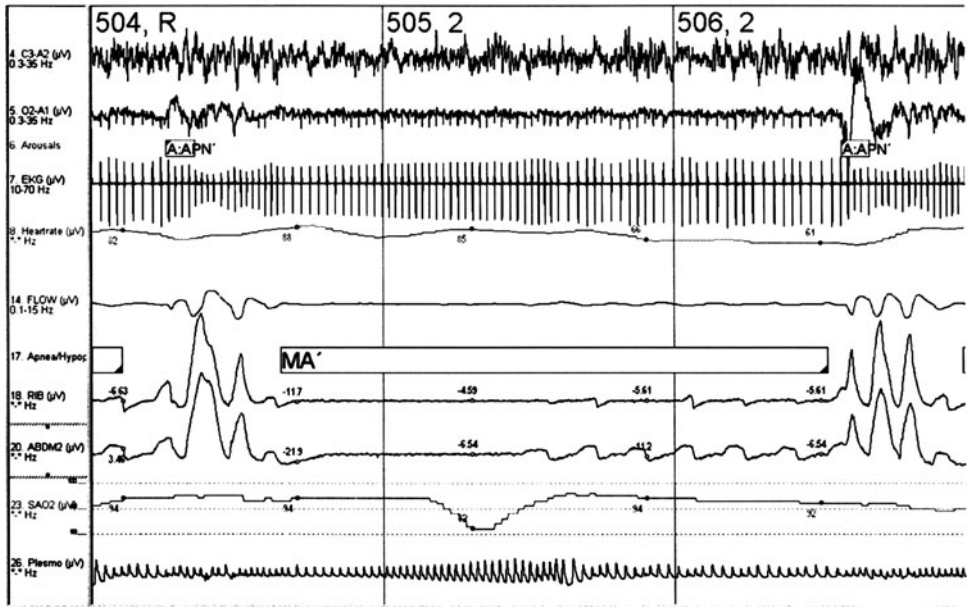

Fig. 20.3 Mixed apnea (MA′). Figure courtesy of The Sleep Disorders Center at Tampa General Hospital

the absence of airflow). These events are mixed apneas and may be the predominant type for some patients (see Fig. 20.3). Notably, almost every obstructive apneic event appears to be preceded by a very brief decrease in effort.

OSA occurs in approximately 4% of adult males and 2% of adult females [3]. OSA prevalence increases with age, and it is estimated that by age 60, 60% of men and 45% of women have symptoms (most commonly, snoring) suggestive of OSA [4]. Pure, or even primarily, CSA is considered rare and accounts for 4–10% of patients seen in sleep centers [5].

Obstructive Sleep Apnea

Although the nasal cavity accounts for half of the total resistance in the upper airway, its contribution is relatively constant [6]. In OSA in the general population, the main focus of concern is the pharynx, which can be divided into four segments: nasopharynx, velopharynx, oropharynx, and hypopharynx. Although most patients with OSA have several areas of pharyngeal collapse, the velopharynx (region immediately behind the uvula) and the oropharynx (region behind the oral cavity and tongue) are the primary sites involved.

Dilation of the upper airway is produced by over 20 skeletal muscles that surround the pharyngeal airway and stiffen the pharyngeal walls [7]. Control of these muscles is a complex process because any muscle action depends on the actions of other muscles and the state of the surrounding anatomical structures. For example, whether the mouth is open or shut affects the position of the tongue, and opening the mouth can destabilize the upper airway. The size of the tongue and position of the mandible can also have significant effects on the size of the pharyngeal airway. The functions of the various pharynx muscles are also affected by the status of the airway itself. If the pharyngeal constrictors are activated when there is a relatively high airway volume, the airway will be constricted. If they are activated at a low airway volume, the airway is dilated. Thus, the upper airway anatomy and functional state of the musculature determine the size of the pharyngeal airway.

Any factor that decreases muscle tone will also contribute to OSA. During rapid eye movement

(REM) sleep, skeletal muscles other than the diaphragm show a marked decline in tone. This stage of sleep is normally characterized by virtual paralysis with very brief episodes of intermittent phasic activity. Hence, OSA is generally at its worst when the patient is in REM sleep.

In addition to the tone of the intrinsic upper airway muscles, positional factors have been found to be influential. Many patients experience upper airway restriction only when they are supine. Neck flexion predisposes to airway closure, whereas extension of the neck promotes a more open airway [8]. Kyphoscoliosis can also contribute to OSA.

Finally, no OSA discussion is complete without including obesity as a cause for OSA. Obesity is one of the cardinal risk factors for OSA and is believed to affect the process primarily by narrowing the upper airway.

Central Sleep Apnea

Although many normal individuals exhibit irregular respiration at sleep onset with brief respiratory pauses, some individuals experience repeated episodes of CSA at sleep onset. In some cases, these events lead to arousals that awaken the patient, and it is not unusual for such patients to present with complaints of insomnia.

During sleep, metabolic mechanisms control ventilation and pCO_2 is the single most important factor [9]. A low pCO_2 reduces the drive for respiration. Hypocapnia can be the result of intrinsic disorders of chemosensitivity or hyperventilation. The latter is often associated with arousals and poor ventilatory control [10]. Severely diminished or absent sensitivity to pCO_2 results in sleep-disordered breathing, typically CSA [11].

Nasal congestion is certainly associated with OSA, but it can also have a significant role in CSA. Possible impact may be owing to occlusion of nasal receptors that are instrumental in respiratory control and to pharyngeal collapse that can occur secondary to nasal obstruction [12].

Various neurological disorders are related to CSA (see Table 20.1). The Shy–Drager syndrome (multiple system atrophy) has been associated with severe OSA with reports of death [13]. Brainstem infarction and medullary lesions from polio can lead to hypoventilation and abnormal ventilatory control, which predisposes to CSA. Even if the brainstem is intact, disruption of neuronal control of the respiratory muscles ultimately affects metabolic control of respiration. Neuromuscular disorders can cause decreased respiratory effort and waking hypoventilation, which can lead to loss of normal chemosensitvity and CSA [14].

Table 20.1 Disorders associated with central sleep apnea

Autonomic dysfunction
Multiple system atrophy
Familial dysautonomia
Diabetes mellitus
Brainstem infarction
Cervical cordotomy
Muscular dystrophy
Myasthenia gravis
Postpolio syndrome

Clinical Features of Sleep Apnea

Patients with OSA are typically unaware of their sleep problem. In contrast, the bed partner usually recognizes a sleeping problem because OSA is significantly associated with snoring. The snoring may be so loud that no one wants to share a bed or bedroom with an OSA patient. The bed partner may provide a highly suggestive description: the individual falls asleep, snores (typically very loudly), and then is silent. The silence lasts long enough for the observer to become aware of it, and the silence usually ends with a loud snorting sound. Bed partners frequently report having to hit or push the patient to get them to breathe again.

The most common complaint of patients with OSA is excessive daytime sleepiness (EDS). Indeed, the daytime sleep manifestations of severe OSA patients can be mistaken for narcolepsy to the extent that sleep is severely fragmented by frequent awakenings. Headache is another common complaint; morning headaches

Table 20.2 Common symptoms of obstructive sleep apnea

Excessive daytime sleepiness
Psychomotor dysfunction
Decreased motor skills
Memory impairment
Depression
Headache
Night sweats
Nocturia
Personality changes
Sexual dysfunction

are especially frequent. However, many patients also report nocturnal headaches. The headache of OSA typically is dull, nonfocal, and lasts a few hours ([15]; see Table 20.2).

As noted previously, OSA is more common during REM sleep. Depression, personality changes, and psychomotor dysfunction may occur secondary to disruption of REM sleep, but hypoxemia may also be a factor. Night sweats, nocturia, and sexual dysfunction result from hemodynamic and autonomic changes that develop due to apneic events.

The presentation of CSA can vary, depending on whether or not there is hypercapnia. Hypercapnic CSA is characterized by respiratory failure, cor pulmonale, polycythemia, and daytime sleepiness. When hypercapnia is not present, daytime sleepiness and insomnia owing to restless sleep may also be accompanied by mild and intermittent snoring, awakenings that may be associated with choking, and a normal body habitus [16].

Diagnosis of Sleep Apnea

Similar to other medical disorders, a comprehensive history is the crucial first step in diagnosing sleep apnea. If possible, the history should be obtained with the bed partner or housemate present. Denial of daytime sleepiness is common, and patients hardly ever report hearing themselves snore. If they are aware of nocturnal arousals or awakenings, they only rarely can identify the triggering factor.

The gold standard for assessing sleep apnea is the polysomnogram (PSG); this involves overnight monitoring of the patient, including electroencephalography, which is necessary for determining sleep onset and sleep staging. Extraocular eye movements are recorded (via electrooculography), as is mentalis muscle tone (via electromyography), to help determine when the patient is in REM sleep. In addition to these specific sleep parameters, the study includes transducers to record airflow, respiratory effort, and cardiac rhythm. Pulse oximetry is obtained to assess the severity of oxygen desaturations associated with apneic events. Motor activity of the legs also is recorded with electrodes on the anterior tibialis muscles. The patient usually is videotaped during the PSG. Although somewhat involved and time-consuming, a full PSG allows identification of sleep-related breathing disorders, sleep-related cardiac arrhythmias, and various movement disorders known to occur during sleep, such as periodic limb movements of sleep, and REM behavior disorder.

More recently, portable equipment to assess sleep and respiration has been developed [17]. Although these studies have not replaced laboratory-based PSG, they offer the potential to reduce cost, inconvenience, and delays in obtaining sleep studies.

Treatment of OSA

As with any other medical disorder, an understanding of the underlying pathophysiology provides the key to treatment. OSA can be successfully treated by alleviating the obstruction. There are two major ways to accomplish this goal; one is to remove the obstruction. Several surgical procedures have been developed that address the different areas of obstruction ([18]; see Table 20.3). Sufficiently aggressive surgery can effectively treat even the most severe OSA, but the patient must be willing to undergo the procedure indicated by the site of collapse.

The mainstay of OSA treatment is the use of nasally administered positive airway pressure. This is achieved by establishing a seal via a mask

Table 20.3 Surgical procedures for the treatment of obstructive sleep apnea

Site of obstruction	Procedure
Nose	Deviated septal repair
	Turbinate resection
	Adenoidectomy (rare)
Velopharynx	Uvulopalatopharyngoplasty
	Somnoplasty
	Tonsillectomy
Oropharynx	Mandibular osteotomy with genioglossus advancement
Hypopharynx	Hyoid myotomy with suspension
	Maxillomandibular advancement osteotomy
	Base of tongue resection
Bypass all upper airway obstruction	Tracheotomy

over the nose and administering room air under pressure sufficient to keep the airway patent during sleep. The earlier versions of these devices did so at a constant pressure and were therefore referred to as continuous positive airway pressure (CPAP) devices. Subsequently, bilevel positive airway pressure (BiPAP) devices, capable of varying the pressure to account for the decreased pressure needed to maintain the airway on expiration were developed. The latest advance is the use of autotitrating devices that adjust the pressure at the mask to account for changes in the resistance of the patient's upper airway.

Pressures required to maintain an open airway can range from as little as 3–5 mmHg up to 16–20 mmHg. As would be expected, compliance is generally better at lower pressures. At the highest pressures, serious consideration must be given to surgical interventions that may not cure the OSA but can result in significantly lower pressure requirements for positive airway pressure treatment. Reducing pressures improves compliance and decreases the incidence of CPAP complications, such as nasal irritation, conjunctivitis from air leaks under the mask, aerophagy, and very rarely, pneumothorax or pneumoencephaly. The use of positive airway pressure has been well documented as an effective means of eliminating apnea during sleep. The major problem is that the device has to be used on a regular basis and for extended periods during sleep. Unfortunately, compliance is a major problem with reports of actual use typically varying from 65 to 80% [19].

Other techniques and devices are aimed at addressing specific problems. Nasal dilators, both intrinsic and extrinsic, have been used effectively to reduce snoring but cannot be regarded as sufficient treatment for OSA. Devices to train the patient not to sleep in a supine position have some benefit for positionally related OSA. Weight loss, if it can be achieved, is also very efficient in reducing the degree of OSA in obese patients.

Treatment of CSA

Although it seems counter-intuitive, the use of positive airway pressure has been demonstrated to be a beneficial treatment for CSA. As noted previously, activation of nasal and pharyngeal receptors has a positive effect on respiration control. Typically, very low pressures are required, and BiPAP may be more effective for these patients, since it reduces the work of breathing on expiration compared with CPAP.

Prior to the advent of CPAP and BiPAP, several different medications were used in attempts to treat CSA. Acetazolamide, a carbonic anhydrase inhibitor, had been shown to reduce central apneas in a small number of patients, but long-term studies did not show continued efficacy, and exacerbation of mixed apneas was reported. In essence, none of the drug therapies that have been tried, including the progestational agent, medroxyprogesterone, or stimulants (e.g., theophylline) have proved effective [20].

Sleep Apnea in Parkinson's Disease

EDS in Parkinson's disease (PD) received very limited attention prior to the report by Frucht et al. that described eight patients taking pramipexole and one taking ropinirole who fell asleep while driving [21]. This report sparked a series of investigations into the prevalence of EDS in PD and its causes. One survey of 303 PD patients found that 50.2% had EDS as defined by an abnormally high (>10) Epworth Sleepiness Scale score [22]. Stepwise regression analysis revealed that sleepiness correlated with longer duration of PD ($p<0.0001$), more advanced disease ($p<0.0004$), male sex ($p<0.0001$), and the use of any dopamine agonist ($p<0.0004$).

Although many investigations have identified antiparkinson medications as a cause of EDS, other potential causes must not be overlooked. Several early sleep surveys in PD patients indicated that overnight sleep disturbances, especially frequent awakenings (sleep fragmentation), were common. Factor et al. noted that 88.5% of patients with PD reported difficulty maintaining sleep, and most awakened two to five times per night, whereas 74.4% of control subjects reported difficulty maintaining sleep and awakened one to three times nightly ($p<0.005$; [23]). Similarly, Tandberg et al. found a significantly higher prevalence of frequent awakenings in patients who had PD (38.9%) than in diabetes patients (21%) or healthy elderly controls (12%) ($p<0.001$; [24]). They speculated that frequent awakenings in PD might be due to motor disability, depression, or pain.

An early PSG study confirmed frequent and prolonged awakenings throughout the night in patients with PD [25]. In this study, hypoventilation and sleep apnea were not observed in 12 patients with PD or 12 normal controls.

However, another early PSG study found more apneic episodes and desaturations in patients with PD than in age- and sex-matched controls [26]. In this study, Efthimiou et al. studied 4 untreated PD patients, 6 treated PD patients, and 20 controls. The mean number of apneic episodes and mean number of desaturations during sleep were as follows: treated PD, 48.5/26; untreated PD, 24/3; and normal controls, 10.8/0.7. The percentage of apneic episodes that were obstructive or mixed were: treated PD, 83.5%; untreated PD, 93%; and normal controls, 9%. One patient with untreated PD fulfilled criteria for sleep apnea syndrome; interestingly, this patient was not obese.

Arnulf et al. subsequently evaluated 54 consecutive levodopa-treated PD patients with a complaint of EDS [27]. Of these, 20% had moderate or severe sleep apnea, as defined by an apnea–hypopnea index (AHI) of more than 15 per hour. This prevalence is substantially greater than that in an elderly American population (2.5–4.4%; [28]). Obstructive apneas and hypopneas were typical, whereas central and mixed apneas were extremely rare. Patients with moderate or severe sleep apnea had body mass indices (25.3 ± 5.2 kg/m^2) and mean daytime sleep latencies (MSLs) (5.3 ± 0.8 min) similar to patients with no or mild sleep apnea. These investigators also described a narcolepsy-like phenotype (≥2 sleep-onset REM periods) in 39% of subjects. These patients were sleepier than those without such a phenotype, as evidenced by shorter Multiple Sleep Latency Tests (MSLTs). Thus, preliminary information suggested that OSA might be more common in PD than in age- and sex-matched controls, although it is important to note that these patients had a complaint of EDS. There was also a suggestion that obesity was not as important a risk factor for OSA in PD as it is in the general population, perhaps reflecting a different physiologic basis for OSA, such as upper airway muscle dysfunction [29].

Maria et al. [30] evaluated 15 consecutively recruited PD patients and 15 healthy matched controls. The median AHI for PD patients was 11.0 compared to 5.7 for healthy controls ($p=0.048$). Nine PD patients fulfilled criteria for obstructive sleep apnea–hypopnea syndrome, predominantly mild, and one fulfilled criteria for central sleep apnea–hypopnea syndrome.

In a much larger study, Cochen de Cock et al. [31] studied 100 PD patients (50 consecutive PD patients matched with 50 PD patients referred for sleepiness) and 50 in-hospital controls. Sleep

apnea (AHI>5) was less frequent in the total PD group (27%) than in the control group (40%, $p<0.002$). Further, the PD group had significantly lower AHI scores and higher minimum oxygen saturations. PD patients referred for sleepiness had significantly higher AHI scores than unselected PD patients (17 vs. 6/h, $p<0.02$), although the frequency of sleep apnea was not significantly higher in sleepy PD patients vs. unselected PD patients (34% vs. 20.4%, $p=0.18$). Of the 27 PD patients with sleep apnea, 6 were mild (AHI 5–15), 11 were moderate (AHI 15–30), and 10 were severe (>30). The 27 PD patients with sleep apnea did not differ from the 73 PD patients without sleep apnea in terms of age, gender, body mass index (BMI), use of benzodiazepines, and symptoms usually associated with sleep apnea syndrome (snoring, nocturia, daytime sleepiness, depression, and cognitive impairment.) Epworth Sleepiness Scale scores were not significantly different in patients with and without sleep apnea.

Trotti and Bliwise [32] reported similar results from a study of a convenience sample of 55 PD patients. They found that AHI was not different from published, normative, population-based data. They also found that Epworth Sleepiness Scores, BMI, and snoring did not correlate with AHI in PD patients.

In a different type of study, Diedrich et al. [33] matched 49 PD patients who had undergone PSG with 49 controls in terms of age, gender, and AHI. Note that patients in this study were matched with controls of similar AHI. Results showed that PD patients had lower BMI ($p=0.04$) and maintained a more favorable respiratory profile, with higher mean ($p=0.006$) and minimal ($p=0.01$) oxygen saturation. The difference in minimal oxygen saturation was even maintained in PD patients with an AHI>15. Only in four PD patients with AHI>15 and BMI>27 did respiratory changes approximate those of seen in controls. The investigators concluded that in the early and middle stages of disease, nonobese PD patients commonly have AHI values suggesting sleep apnea syndrome but without the typical oxygen desaturation profile. They suggested this might be due to deficient respiratory muscle coordination, fluctuating muscle function, medication-related respiratory dysrhythmia, or dysautonomia.

Thus, current information suggests that sleep apnea is probably not more common in PD than in age- and gender-matched controls. Further, in many cases, it appears that an elevated AHI, even when present, may not be sufficient to explain EDS and may not necessarily require treatment. However, it seems likely that a moderate to markedly elevated AHI in an obese PD patient might behave like typical OSA in the general population.

EDS in PD can be caused by the disease itself, dopaminergic medications, and sleep disorders (e.g., sleep apnea). In patients with PD who experience EDS, reversible or treatable conditions that might be the cause should be sought. Typically, dopaminergic medications are first considered. Dopamine agonists may be lowered or discontinued, and if necessary and feasible, the levodopa dose may be reduced. However, if there is no improvement in sleepiness when dopaminergic medications are lowered or if such manipulations are not possible, consideration should be given to obtaining an overnight PSG to exclude potentially treatable sleep disorders like OSA.

Based on the information presented above, it is clear that obese PD patients with a high AHI should be treated for sleep apnea, usually with CPAP. Unfortunately, the situation is less clear in other cases. In clinical practice, a rational approach might be to determine whether CPAP improves sleepiness in those PD patients with an abnormal AHI. Clinical trials to define the response to CPAP in PD patients with elevated AHI are needed, and it would be especially helpful to identify clinical and PSG predictors of a CPAP response. Modafinil and other wake-promoting agents can be tried as symptomatic agents if CPAP is unsuccessful [34, 35].

Sleep Apnea in MSA

Numerous studies have demonstrated a high prevalence of sleep-related respiratory disturbances and nocturnal stridor in individuals with multiple system atrophy (MSA; [36–42]). There is a high prevalence of vocal cord abductor

dysfunction, and stridor may be caused by dystonia of the vocal cords rather than paralysis [43].

Chokroverty et al. evaluated ten men with olivopontocerebellar degeneration and found that five (50%) had sleep apnea [37]. Three had pure CSA, and two showed obstructive, central, and mixed apneas. The apneas occurred during non-REM sleep and lasted up to 45 s.

Munschauer et al. studied respiration during sleep in seven patients with MSA and autonomic failure (MSA-AF) and seven control subjects [39]. Although mean values for respiratory rate, tidal volume, and inspiratory flow rate were similar in both groups, the coefficients of variability were significantly greater in patients with MSA-AF. One patient had central apnea, five had loud snoring, and five had respiratory stridor during sleep. Four of the five patients with MSA who were examined had vocal cord paralysis, and four of five nontracheostomized patients had upper airway obstruction without significant oxygen desaturation. Three of these five patients subsequently died suddenly during sleep. The investigators concluded that MSA-AF is associated with upper airway dysfunction and disordered central respirations that can be life threatening. They suggested that even mild obstruction during sleep may warrant tracheostomy.

Silber et al. compared 17 patients who had MSA with nocturnal stridor, including 7 with daytime stridor to 25 patients who had MSA without stridor [36]. Analysis of 30 patients with follow-up information showed a significantly shorter survival from the sleep evaluation (but not from disease onset) for patients with stridor when compared to those without. Of patients with stridor, 9 of 11 died a median of 2 years from presentation, and the only two survivors had undergone tracheostomy. Patients with daytime stridor and immobile vocal cords had especially poor prognoses. Based on these findings, the authors recommended tracheostomy for MSA patients with stridor. However, 2 of 4 patients with tracheostomies also died, as did 6 of 19 without stridor. The investigators postulated that central hypoventilation may have been responsible for many of these other deaths and also recommended assessment for central hypoventilation and appropriate management if present.

Iranzo et al. studied sleep patterns and laryngeal function of 20 patients with MSA; they found sleep disturbances in all and vocal cord abduction dysfunction in 14 (70%; [44]). In three patients with nocturnal stridor and complete vocal cord abductor dysfunction, CPAP eliminated laryngeal stridor, obstructive apnea, and oxygen desaturation.

Thus, OSA is common in MSA and appears to be closely related to vocal cord abductor dysfunction. Although CPAP can eliminate OSA in MSA, compliance may still be an issue. It is not clear if CPAP can prolong survival, and some investigators have recommended tracheostomy if even mild obstruction is present. Patients with MSA may also experience central hypoventilation.

Summary

Recent studies suggest that OSA is probably not more common in PD than in age- and gender-matched controls. In addition, in PD, elevated AHI does not appear to correlate with sleepiness, snoring, or BMI. These findings suggest that sleep apnea may not be the underlying cause for EDS in many PD patients despite the finding of an elevated AHI. EDS in PD may be caused by the disease itself or by PD medications. Nonetheless, PD does not exempt individuals from OSA and a moderate to markedly elevated AHI in an obese PD patient probably behaves similarly to OSA in the general population and should be treated. It is not clear if nonobese PD patients with EDS should undergo PSG. Certainly, reduction of dopaminergic medications should be tried first, if feasible. If such an individual is found to have an elevated AHI, a trial of CPAP to evaluate improvement in EDS is reasonable, but a lack of benefit would not be too surprising. Wake-promoting agents such as modafinil could then be tried.

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Part IV

Sensory Dysfunction in Parkinson's Disease

Visual Dysfunction in Parkinson's Disease

21

Robert L. Rodnitzky

Abstract

A wide range of visual dysfunction is common in patients with Parkinson's disease (PD). Most of these abnormalities are relatively subtle from a clinical point of view, but all can have practical consequences under certain circumstances, including ordinary daily activities, and can significantly contribute to parkinsonian disability through their influence on cognitive and motor symptoms. Despite the potential functional implications of visual symptoms in PD, they are seldom of sufficient severity in themselves to replace motoric or cognitive dysfunction as a patient's primary clinical disability. Most of the visual abnormalities linked to PD are demonstrable in the very early clinical phase of the illness and are presumably present in the preclinical phase of PD as well. As PD is predominantly a disorder of the elderly, it is not surprising that patients in this age group are often aware of declining visual function. When symptoms such as visual blurring, difficulty reading, impaired near vision, or abnormal light sensitivity occur in a PD patient, it prompts both the patient and the clinician to wonder what, if any, relationship these symptoms have to the underlying neurological disorder as opposed to the natural visual concomitants of aging such as cataracts or macular degeneration. When complaints referable to the visual system are specifically solicited from PD patients, the most common are tired eyes or blurred vision when reading and diplopia. Can complaints such as this be logically related to the known pathophysiology of PD? In this chapter, the known aberrations of visual function that occur in PD will be discussed as well as their pathogenesis. In the course of the discussion, it will become apparent that several forms

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of visual dysfunction that occur in PD are very subtle and are more easily demonstrated through electrophysiologic or psychophysical testing than by clinical means. It will also become apparent that, although clinically subtle, visual dysfunction can have both direct and indirect influence on overall disability in PD.

Keywords

Visual dysfunction • Parkinson's disease • Dopamine • Visual evoked potential • Pattern electroretinogram • Visual Acuity • Farnsworth-Munsell 100-hue test • Visual contrast sensitivity • Visual hallucinations

A wide range of visual dysfunction is common in patients with Parkinson's disease (PD) [1, 2]. Most of these abnormalities are relatively subtle from a clinical point of view, but all can have practical consequences under certain circumstances, including ordinary daily activities, and can significantly contribute to parkinsonian disability through their influence on cognitive and motor symptoms [3]. Despite the potential functional implications of visual symptoms in PD, they are seldom of sufficient severity in themselves to replace motoric or cognitive dysfunction as a patient's primary clinical disability. Most of the visual abnormalities linked to PD are demonstrable in the very early clinical phase of the illness and are presumably present in the preclinical phase of PD as well. As PD is predominantly a disorder of the elderly, it is not surprising that patients in this age group are often aware of declining visual function. When symptoms such as visual blurring, difficulty reading, impaired near vision, or abnormal light sensitivity occur in a PD patient, it prompts both the patient and the clinician to wonder what, if any, relationship these symptoms have to the underlying neurological disorder as opposed to the natural visual concomitants of aging such as cataracts or macular degeneration. When complaints referable to the visual system are specifically solicited from PD patients, the most common are tired eyes or blurred vision when reading and diplopia [4]. Can complaints such as this be logically related to the known pathophysiology of PD? In this chapter, the known aberrations of visual function that occur in PD will be discussed as well as their pathogenesis. In the course of the discussion, it will become apparent that several forms of visual dysfunction that occur in PD are very subtle and are more easily demonstrated through electrophysiologic or psychophysical testing than by clinical means. It will also become apparent that, although clinically subtle, visual dysfunction can have both direct and indirect influence on overall disability in PD.

Prior to discussing clinical dysfunction of the visual system in PD, it is useful to first review the role of dopamine in the visual system and the abnormalities of this neurotransmitter that have been demonstrated within this context.

Dopamine and the Visual System

Dopamine is found in several anatomical structures that subserve vision. Perhaps most important is its localization within the amacrine and interplexiform cells of the retina [5]. In an autopsy study of PD patients, retinal dopamine concentration was decreased [6] but was normal in those who had received levodopa therapy shortly before death, suggesting that this therapy might be instrumental in reversing visual dysfunction related to retinal dopamine deficiency. Several observations support the concept that dopamine has a specific function in the retina of primates. The chemical protoxin MPTP (1-methyl,4-phenyl,1-2-5-6-tetrahydropyridine) produces a clinical parkinsonian syndrome when injected into primates and significantly lowers retinal dopamine. These changes are associated with

abnormalities in the latency and amplitude of both the pattern visual evoked potential (VEP) and the electroretinogram, both of which can be reversed by the administration of levodopa [7]. Similarly, intravitreal injection of the neurotoxin 6-hydroxydopamine into aphakic monkeys results in abnormalities in both the phase and amplitude of the pattern electroretinogram (PERG) and the pattern VEP, especially for stimuli with higher spatial frequencies [8]. This finding suggests a role for dopamine in retinal spatial tuning. In idiopathic PD as well, the visual evoked response [9] and PERG [10] are abnormal, and both can be improved by the administration of levodopa, especially the latter [11].

Other structures within the visual system have dopaminergic innervation, including the lateral geniculate [12] and the visual cortex [13]. Recordings from single units in the lateral geniculate body of cats during simultaneous iontophoretic application of dopamine have suggested that dopamine controls visual activity in this structure in several ways, including direct inhibition of relay cells through D_1 receptors and both direct facilitation of relay cell function and excitation of inhibitory neurons through D_2 receptors [14]. Asymmetric primary visual cortex glucose hypometabolism has been demonstrated in PD, with the most severe abnormality appearing ipsilateral to the most severe motoric dysfunction [15]. The laterality of this abnormality suggests that it is more likely related to dysfunction in the nigrostriatal system than the retina since the former structure is asymmetrically involved in PD while the latter, even if asymmetrically affected, has bilateral input to the visual cortices and would be expected to result in symmetrical hypometabolism.

Notwithstanding the potential widespread influence of dopamine within the visual system, its role in the retina seems to be most important. Dopamine content in the retina exhibits distinct circadian rhythms that can be driven by light/dark cycles or, in total chronic darkness, by the cyclic presence of melatonin [16, 17]. Dopaminergic neurons are thought to subserve a modulatory role in the retina and may mediate center-surround functions that are important to receptive field organization [18]. An investigation in which the PERG spatial contrast response was recorded after administration of dopamine D_1 or D_2 antagonists or a D_1 agonist suggested that D_1 receptors may be most important for the surround organization of retinal ganglion cells; D_2 receptors may play a role in center response amplification of other ganglion cells [19]. Within the D_2 dopamine receptor family, D_4 receptors predominate in the retina and appear to subserve the function of modulating the dopaminergic control of light sensitive cAMP [20]. Retinal dopamine receptors are not only found at synapses, but at extrasynaptic sites as well, suggesting that dopamine acts in the retina both via a paracrine mechanism and as a neurotransmitter [21]. In addition the neurochemical and functional abnormalities in the PD retina, structural abnormality in the form of inner retinal layer thinning has been demonstrated by optical coherence tomography [22]. There is a correlation between foveal retinal thinning and the severity of PD [23]. The neurobiology of retinal dopamine has recently been thoroughly reviewed [24].

Visual Acuity

Although common clinical experience suggests that there is not a severe and clinically impressive decline of visual acuity in PD, group comparisons between PD patients and controls do reveal a difference. Repka et al. [4] tested high contrast visual acuity in 39 PD patients and an equal number of age-matched controls. A small, but statistically significant, difference in visual acuity was found between the groups; the mean value in PD was 20/39 and that in controls 20/28. The visual acuity decline in PD patients correlated with increasing disease severity, further supporting the notion that this abnormality is linked to the evolving pathology of the underlying PD. Whether loss of visual acuity in PD is related to retinal or cortical dysfunction is not certain, but the authors speculated that the known reduction of retinal dopamine in PD might result in an increase in the receptive field size leading to a decrease in visual function. Although the severity of visual acuity loss in PD

appears to be related to advancing disease, it does not appear to be reversible with treatment since high contrast visual acuity (the type typically tested with a standard Snellen chart) is similarly impaired whether patients are on or off dopaminergic drugs [25]. One other link between retinal dopamine content and visual acuity is the clinical observation that administration of levodopa improves human amblyopia in both children and adults [26].

Although not directly related to visual acuity, one common efferent visual problem in PD that can significantly reduce visual efficiency, especially for reading, is convergence insufficiency [4]. This condition, which is extremely common in PD, is associated with an abnormally distant near point of convergence, greater than 10 cm, and slow convergence amplitude. A recent study suggested that many PD patients with convergence insufficiency have decreased convergence amplitude only, with a normal rear point of convergence [27]. It typically is associated with the subjective complaint of asthenopia or eyestrain and is especially bothersome for patients using bifocal eyeglasses for reading, since their proper use requires intact convergence. Near vision may be functionally impaired in such patients but amenable to correction with the use of prisms to compensate for impaired convergence or by instruction in the practice of monocular occlusion while reading. There is some evidence that convergence insufficiency in PD can be improved by therapy with levodopa [28], strengthening the link between this form of dysfunction and dopamine deficiency.

Color Vision

Abnormal color discrimination frequently has been reported in patients with PD [29, 30]. The impairment typically is most prominent in the tritan (blue–yellow) axis [31, 32]. Abnormalities of color perception have been demonstrated using both bedside clinical testing techniques, such as the Farnsworth-Munsell (FM) 100-hue test [32], or more elaborate psychophysical means, such as a computer-generated assessment of color contrast sensitivity. Haug et al. [31] offered an explanation as to why the tritan contrast threshold is most affected in PD. They noted that the blue cone system is preferentially affected in retinal disease because its response range is limited and it has the greatest vulnerability. The relatively selective involvement in PD can be explained by the fact that these short wavelength sensitive cones are relatively scarce in number in the retina and spaced widely apart, such that maintenance of their large receptive fields is dependent on interaction across considerable distances, a function mediated by the dopaminergic interplexiform and amacrine cells of the retina, the precise retinal elements that are most affected in PD.

The abnormality of color vision in PD can be demonstrated in very early patients prior to receiving pharmacologic therapy for their condition. It can be reversed by treatment with levodopa and other dopaminergic drugs [33, 34]. When color vision was tested in untreated PD patients, significant correlation was noted between the error score of the FM test and the severity of clinical parkinsonian signs as measured by the motor and activities of daily living subscales of the Unified Parkinson's Disease Rating Scale [35]. When PD patients are followed over time, color discrimination scores decline progressively as the underlying disease progresses [36]. Despite the apparent correlation with disease severity, one investigation demonstrated that color vision abnormalities in PD do not correlate with dopaminergic nigral degeneration as measured by I^{123} β-CIT single photon emission tomography of the dopamine transporter, suggesting that this visual abnormality is extranigral in origin [37]. A unifying explanation addressing why color discrimination does not correlate with nigral degeneration yet parallels the clinical severity of PD, is that retinal dopamine depletion, the probable cause of the abnormality in color vision, while independent of nigral dopamine depletion, occurs contemporaneously at a relatively constant pace over time. Regan et al. [38] questioned whether abnormalities of color discrimination tests in PD are real or just an epiphenomenon related to motor disabil-

ity. They pointed out that the FM test, used to demonstrate impaired color vision in many studies of PD, requires the patient to execute a motor response to correctly identify varying hues of color. They questioned whether it is the motor disability of PD patients, rather than a primary visual disorder, that causes PD patients to fail this test and at the same time explains why levodopa, which corrects the motoric abnormality, improves the color vision score. These investigators utilized a computer-controlled test of color vision that did not require a motoric response and found no difference between PD patients and a control group. Their hypothesis, however, fails to explain why other investigators [31] uncovered abnormalities of color vision in PD utilizing computerized testing techniques or why most studies have revealed a preferential loss in the tritan color axis with little or no abnormality in the protan (red–green) axis, both of which should have been similarly affected were the abnormal test scores simply a reflection of parkinsonian motor impairment. Additional evidence supporting the validity of color vision dysfunction in PD is the fact that abnormalities of the VER produced by color pattern stimuli are more responsive to levodopa therapy than are those evoked by black and white stimuli [39], and the underlying abnormality is more prominent when blue–yellow stimuli are used than when red–green stimuli are used [40]. Similarly, color contrast sensitivity in PD patients is most impaired along the tritan axis [31], and PERG amplitude is more reduced in response to tritan stimuli than to protan stimuli [41]. Lastly, other medical conditions characterized by impairment of dopaminergic transmission have been associated with abnormalities of color vision. In patients undergoing cocaine withdrawal, a hypodopaminergic state, a similar tritan axis deficit in color discrimination has been noted that is not seen during the hyperdopaminergic intoxication phase [42]. In schizophrenia, color discrimination abnormalities are general and not hue specific, leading to the hypothesis that axis-specific color discrimination abnormalities are a reflection of depletion of dopamine rather than its general deregulation [43].

Visual Contrast Sensitivity

Visual contrast sensitivity (VCS) is a function that traditionally is not considered or tested in the clinical realm, yet it is an important sensory function that pervades many activities of daily living. It is a visual function that consistently has been found to be abnormal in PD. VCS is measured by determining the minimal contrast required to distinguish objects from one another presented at a given spatial frequency. Visual targets spaced very closely together are said to have a high spatial frequency and those spaced farther apart represent a low spatial frequency. Another way to depict the concept of VCS is to ask how close in contrast adjacent images displayed at a given spatial frequency must be before they appear to be indistinguishable from a visually homogeneous field. Typically, sinusoidal gratings of various spatial frequencies are used to test this function in humans. In this context, the term "sinusoidal" refers to the gradual diminution of contrast between adjacent targets rather than a precipitous contrast change, such as would be seen between adjacent black and white squares on a checkerboard. In PD, VCS is most reduced at intermediate spatial frequencies [44–46] and the abnormality is most exaggerated when the gratings are temporally modulated at medium frequencies of 4–8 Hz [44]. VCS is sometimes less attenuated at lower spatial frequencies in PD than it is in normal individuals [47]. These abnormalities are different from the VCS abnormality associated with normal aging [48]. VCS loss has correlated with the overall severity of PD in some studies [49] but not in others [46]. However, on an hour-to-hour basis, over the course of an individual day, there appears to be a more consistent correlation with the severity of parkinsonian symptoms. VCS exhibits a circadian variability that conforms to the common pattern of improved morning and worsened afternoon motoric disability seen in PD [46]. Recent evidence demonstrating circadian cycles of retinal dopamine content are consistent with this observation [16, 17]. Similarly, VCS function can change in parallel to motor symptoms during transient "on" and

"off" phases in fluctuating PD patients [50] and can be improved by the administration of levodopa [51], but not by deep brain stimulation [52]. VCS loss that is spatial frequency selective and orientation dependent also is evident in patients with drug-induced parkinsonism, suggesting that dopamine deficiency of other causes can result in visual dysfunction that is similar to that present in idiopathic PD [53].

Whether the basic abnormality underlying abnormal VCS in PD resides in the retina or the visual cortex or in both is still unclear. The presence of interocular differences in VCS [46, 54] suggests a link to retinal pathology. Moreover, the PERG, which largely reflects retinal ganglion cell activity, is abnormal in PD [55, 56], with a characteristic amplitude loss at intermediate spatial frequencies similar to those associated with the greatest abnormality of VCS in PD [55]. As is the case with VCS, levodopa therapy improves the PERG abnormality in PD [55, 56]. In a recent study, the demonstration that contrast discrimination threshold in PD patients correlated with frequency-specific PERG abnormalities (a retinal phenomenon) but not VEP's (a cortical phenomenon) was viewed as further evidence that the VCS abnormality in these patients is predominantly a result of retinal dopamine deficiency [57]. However, there also is evidence supporting cortical localization of the abnormality causing VCS dysfunction in PD. VCS impairment in PD patients is orientation specific, in that the VCS deficit is more severe for horizontally oriented patterns than those arrayed vertically [44, 45]. Orientation specificity may be partially subserved by the lateral geniculate [58], although for the most part this perceptual function is considered to reside in the orientation-tuned receptive fields of the visual cortex [59]. This observation clearly raises the possibility of a central contribution to the VCS abnormality in PD. Asymmetric occipital glucose hypometabolism in patients with asymmetric motor signs of PD suggests that there is an element of occipital cortical dysfunction aside from that which might be related to abnormal retinal input to the occipital cortices [15]. On the other hand, preservation of the cortically mediated function of contrast adaptation in PD has been considered evidence that cortical pathology is not significant in this condition and is not likely to play a major role with respect to the reduced contrast sensitivity evident in these patients [60].

Like color vision abnormalities in PD, VCS impairment progressively increases over time as the underlying neurologic condition worsens [36]. This worsening appears at the intermediate spatial frequencies known to be most affected in PD, rather than at higher spatial frequencies, which would be expected to show the greatest decline if the progressive worsening were solely due to aging [61]. Consonant with this decline in VCS over time is a progressive reduction in amplitude and lengthening of latency of the electroretinogram in PD, once again linking abnormal VCS in this patient population to retinal dysfunction [62].

VCS is not commonly tested in PD patients and abnormalities that might be present go unnoticed in the vast majority of instances. Such abnormalities typically are present despite normal visual acuity, as measured by standard Snellen chart testing [63, 64], which is confined to extremely high contrast visual stimuli. The use of lower contrast letter charts in patients with PD and other medical conditions may detect visual loss not appreciated through the use of standard visual acuity charts [63]. Although PD patients and their physicians may not be aware of a contrast sensitivity abnormality unless specifically tested for, functional correlates of this deficit might exist. Intact spatiotemporal vision is functionally important on a day-to-day basis since much of the visual world is periodic in array [65]. For example, intact contrast sensitivity is important for the normal perception of depth and depth discrimination [66]. In PD patients, abnormal contrast sensitivity might predispose to gait freezing. Mestre et al. [67] described a PD patient exhibiting increased contrast sensitivity to low and intermediate spatiotemporal frequencies who experienced gait freezing in the presence of environmental stripes arrayed at this frequency but not at higher spatial frequencies or with his eyes closed. They postulated that a hypersensitivity to these low frequency visual stimuli resulted in an

adaptive "braking" reflex leading to gait freezing. Another group of investigators, utilizing a questionnaire regarding gait freezing, determined that decreased sensitivity at low spatial frequencies was associated with freezing [68]. Other investigators have demonstrated that the gait of PD patients improves in the presence of well-illuminated periodic stimuli (lines) in the visual environment [69], and that parameters of gait such as stride length are related to visual cues [70], and more specifically to contrast sensitivity [71]. It is not unreasonable to postulate that abnormal VCS in PD patients might lead to impaired function under low contrast circumstances, such as might exist at dusk or dawn. Uc et al. [72] found that PD patients driving an automobile under low contrast conditions had much poorer vehicle control and were at higher risk for crashes than control subjects.

Visual Hallucinations

Visual hallucinations occur commonly in PD. An incidence of over 25 % was reported in a recent evaluation of 214 consecutive patients with this condition [73]. In addition to known risk factors such as age, dementia, and therapy with anticholinergic or dopaminergic drugs, visual loss may also contribute to the development of complex visual hallucinations [74–76]. The occurrence of visual hallucinations in visually impaired, but psychologically normal individuals is considered a form of the Charles Bonnet syndrome [77–79]. Because patients afflicted with this syndrome are cognitively intact and have retained insight, this form of hallucinosis, which is usually devoid of personal meaning, tends to be somewhat less emotionally upsetting. Functional magnetic resonance imaging of patients with the Charles Bonnet syndrome has revealed increased activity in the ventral extrastriate region [80]; similar increased activation in visual association cortex and decreased striate activation has been noted in PD hallucinators without overt Charles Bonnet syndrome [81]. Whether this abnormal signal and the clinical syndrome with which it is associated reflect abnormal cortical excitation, a release phenomenon, or disrupted reentry signals is not yet known. In PD, the development of hallucinations has been associated with several relatively mild visual abnormalities, including abnormal color discrimination, reduced visual contrast sensitivity [76], and impaired color contour perception [74]. In these studies, patients exhibiting hallucinations had otherwise normal visual acuity, indicating that relatively minimal visual abnormalities need only be present to predispose a PD patient to hallucinosis. The appearance of Charles Bonnet syndrome in PD patients with somewhat subtle visual loss and the predominance in elderly individuals has led some to postulate that some degree of underlying cerebral degeneration is critical to development of the syndrome [82]. Treatment of the Charles Bonnet syndrome can be difficult. Therapy with atypical antipsychotic agents that improve other forms of PD-related hallucinosis has been unpredictable [83]. At least one favorable response to donepezil in a non-PD patient has been reported [84]. Improvement in the syndrome has been reported after institution of optical aids that result in improved functional vision [85].

Conclusion and Practical Clinical Significance

Abnormalities of electrophysiologic tests such as the VEP and PERG, as well as of psychophysical tests of VCS and color discrimination, leave little doubt that the visual system is involved in PD. Reversal of these deficits with levodopa and the correlation of abnormal electrophysiologic tests with reduced retinal dopamine in experimental parkinsonism establish a compelling link between deficiencies in this neurotransmitter and the visual abnormalities of PD. Although the role of retinal dysfunction seems certain, the contribution of cortical and lateral geniculate impairment to these visual symptoms is not yet clear.

The potential clinical relevance of these visual abnormalities in PD is not widely appreciated. Abnormalities such as impaired VCS and abnormal color discrimination are unlikely to be clearly apparent to the patient, but it is important for the

clinician to realize that a variety of more subtle or indirect forms of dysfunction as diverse as gait freezing, impaired depth perception driving an automobile, and visual hallucinations might be related to these categories of visual impairment. Another issue of clinical importance that emerges from these findings is the extent to which documenting abnormalities of vision might be of some diagnostic significance in identifying early or presymptomatic PD or in distinguishing PD from various other parkinsonian syndromes. The differentiation between idiopathic PD and multiple system atrophy has been investigated in this regard and distinct group differences between the two conditions have been identified in mean VEP latency and visual contrast thresholds [54, 60]. As these are group differences, they are not very useful in making a clinical distinction between the two conditions in individual patients. In progressive supranuclear palsy, mean VCS performance has been found to be more severely impaired than in PD but not so consistently abnormal in individual patients as to be useful in distinguishing this syndrome from other parkinsonian conditions [57]. In regard to the use of color testing as a diagnostic aid, Birch et al. [32] found that 23 % of PD patients had tritan color vision deficits, but none of 40 age-matched controls were abnormal. These results suggest that impaired blue–yellow vision supports a diagnosis of PD, but a normal result does not rule it out.

The prospect for using visual tests to identify PD in its earliest stage, or even prior to the onset of motoric symptoms, is slightly more promising. There are some indications that abnormalities of color vision and VCS may be present prior to the typical clinical presentation of PD. Color vision has been found to be abnormal in mild, untreated PD patients, very early in the course of the illness, suggesting that the abnormality may have antedated the clinical diagnosis of PD [30]. Perhaps the most useful application of VCS testing in the identification and diagnosis of PD is its use in association with other assessments as part of a battery. Camicioli et al. [86] found that a battery consisting of tapping rate combined with either olfactory assessment or measurement of visual contrast sensitivity discriminated between mild PD patients and control subjects with greater than 90 % accuracy.

Continued unraveling of the anatomic, neurochemical, and neurophysiologic substrate of the visual impairment typical of PD not only will advance our understanding of the mechanisms underlying this dysfunction but also very likely will enhance our ability to derive useful diagnostic, therapeutic, and prognostic information from its clinical investigation. Although it is clear that visual dysfunction in the various forms present in PD constitutes a less serious form of disability than the motoric impairment that is typical of this disorder, there can be little doubt that visual dysfunction contributes, in the aggregate, to overall functional impairment. As well, there is emerging evidence that visual dysfunction influences cognitive and locomotive function in PD. These facts alone should provide significant impetus for continued investigation into the mechanisms underlying visual dysfunction in PD and renewed interest in analyzing the mechanism and extent its clinical significance.

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Primary Visual and Visuocognitive Deficits

22

Ivan Bodis-Wollner and Andrea Antal

Abstract

Visual abnormalities in individuals with Parkinson's disease (PD) are unlikely to be uncovered during routine neurological examination. However, more sophisticated electrophysiological testing using techniques, such as the visual-evoked potential (VEP) and pattern electroretinogram (PERG), confirm the presence of visual system involvement in PD. Clinical observations, electrophysiological, and anatomical studies provide functional evidence that foveal vision is predominantly affected in PD. In vivo retinal imaging, using optical coherence tomography, reveals that the foveal retina is thinned in PD patients. In this chapter, we summarize the evidence of retinal impairment and its potential relevance to higher cognitive visual and visuomotor impairment.

Although the retina is the earliest, it is not the only site of visual pathology in PD. Foveal visual processing has a preferential role beyond the retina, beyond simple visual detection. Foveal signals are of crucial importance in visual categorization and, importantly, in visuospatial attention. More complex visuocognitive difficulties, e.g., impairment of consciously controlled visual information processing, have also been

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identified in PD. Some of these higher visual functions are affected in this disorder and one may ask if retinal foveal dysfunction contributes to visuospatial attention and other higher order visual impairment in PD. The exact relationship of foveal dopaminergic retinal deficits and visuocognitive impairment is not known in any detail; thus, the effect of foveal visual impairment on higher visual functions poses an exciting and challenging research question.

Visual event-related potentials (ERPs) in PD patients, obtained using foveal visual stimuli, demonstrate a delay in the P300 component, beyond a delay in the primary visual responses, and suggest slowness of visual information processing. Whereas some investigators have noted this abnormality only in demented patients with PD, others have indicated its presence in both demented and nondemented individuals. The visuospatial sketchpad, a component of the working memory system, shows a specific selective impairment in PD, and visual categorization deficits (suggesting involvement of the posterior part of the cortex) have also been found. Concurrent electrophysiological recordings of primary and visuocognitive responses reveal that the impairment of higher order visual processing in PD is not simply a consequence of retinal dopaminergic deficiency. Electrophysiological, neuropsychological, and functional neuroimaging data imply that both frontal and posterior cortico-subcortical circuits may be involved.

Foveal processing and visuospatial attention possibly may be linked through processes that involve saccadic eye movements. Saccadic eye movements are freely executed many thousand times a day by healthy observers. Part of their role is to "bring" eccentric targets to the direct sight line for closer scrutiny by foveal processing. This is called foveation: with functional imaging (fMRI), it was shown that the distributed centers of cortical control of saccades are disrupted in PD. It is even suggested that in the early stages of PD, patients have changes in visual input that impair their postural control.

Keywords

Vision • Parkinson's disease • Pattern electroretinogram • Optical coherence tomography • Visual-evoked potential • Visuocognitive • Event-related potential • Working memory

Introduction

Parkinson's disease (PD) generally is known as a movement disorder resulting from dopaminergic deficiency that affects the basal ganglia. Therapy with dopaminergic agents reliably improves motor symptoms. Although dopaminergic deficit is the pathognomonic feature of the disease, dopaminergic deficits and the clinical manifestations of the disease extend beyond the motor system. In the last four decades, it has become apparent that beyond or parallel with progressive motor impair-

ments, nonmotor symptoms are also present. One well-explored area of nonmotor dysfunction in PD is vision. Psychophysical, physiological, and anatomical evidence for visual abnormalities in PD is growing, but there is little evidence that such changes are large enough to have been noticed by sufferers themselves, probably because the time course of changes is very slow. Nevertheless, visual perceptual, visuospatial, visuomotor, and visuocognitive dysfunctions have been described in PD, using various techniques and tests. Because PD is predominantly a disease of the elderly, it is not surprising that many patients, like elderly healthy subjects, have visual complaints. They may represent various etiologies, and clinicians do not relate these nonspecific symptoms to a primarily motor disease. Indeed, visual abnormalities in PD probably stay uncovered during a routine neurological examination. Visual problems were often ascribed to decreased use of mental capabilities [1]. This chapter discusses the relationship of visual and visuocognitive abnormalities to motor symptoms and visual response to dopaminergic therapy. Visual electrodiagnostic, psychophysical, and whenever possible, imaging data on visual and visuocognitive processing in PD is described. Vision assessment relying on ordinary high-contrast visual acuity (VA) and visual field testing are unlikely to capture the visual deficit in PD. In this disorder, evidence exists for intrinsic retinal dopaminergic deficiency, affecting intraretinal processing of spatial and temporal contrast. To strengthen the case for considering certain visual deficits in PD germane to the disease, the evidence for retinal dopamine (DA) deficiency as a cause of visual impairment in PD is summarized. In the last decades, the evidence favored the retina as one site of visual dysfunction in this disorder [2, 3].

Bodis-Wollner and Tagliati [4] suggested that the primary visual dysfunction observed in PD may contribute to visuocognitive manifestations of the disease process and to the locomotor and postural disabilities [5]. However, aside from primary visual impairments, visuocognitive difficulties, such as impairment of consciously controlled visual information processing (including sustained and selective attention) and visual categorization, also are among the common cognitive symptoms observed in PD. Furthermore, DA is a neuromodulator at different levels of the visual system, including the thalamic and cortical relays and the cortex. Dopaminergic dysregulation of the prefrontostriatal circuits and related posterior cortical areas in PD patients also has to be considered in the higher levels of cognitive dysfunction. Therefore, caution must be paid to correlate visual symptoms with retinal activity only.

Background: Primary Visual Dysfunction and the Role of Dopaminergic Visual Processes

Retina

The retina is one of the tissues in the body richest in DA, yet the role of this system in various visual functions remains unclear. The cellular localization, modes of action, and possible visual roles of DA are quite consistent across vertebrates, implying that DA has a rather conserved role in visual processing. Retinal DA deficiency may alter retinal visual processing primarily by changing the receptive field properties of ganglion cells (GCs) [6]. Center-surround interaction of mammalian retinal GCs may be affected by dopaminergic deficiency, which leads to the observed visual and physiological deficits in PD.

Recent in vivo retinal imaging in PD patients, using Optical Coherence Tomography (OCT), reveals that the perifoveolar retina is thinned in PD patients. The effect of PD on the retina has been shown using the results of in vivo morphological quantification of retinal thinning. The availability of OCT makes it possible to bridge the results regarding visual dysfunction obtained in PD over three decades of research by various techniques. In PD patients, a thinning of the peripapillary retinal nerve fiber layer (NFL) was first shown by Inzelberg et al. [7] in ten patients. They reported significant peripapillary NFL losses. This was subsequently confirmed by several other groups [8–10]. The Fourier-domain of the

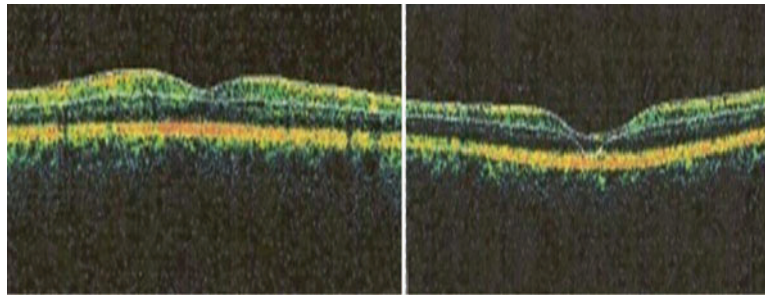

Fig. 22.1 The perimacular inner and outer layers of the retina in a healthy subject (*left side*) and in a PD patient (*right side*). Modified after Hajee et al. Arch Ophthalmol 2009.

OCT was used (RTvue™, Fourier-domain OCT from Optovue, Fremont, California) [10]; it has an imaging speed of ~25,000 axial scans/second, which is approximately 50 times faster than time-domain detection [11]. Because of the increased speed, the overall image quality of Fourier-domain OCT is superior, due to the elimination of many motion artifacts. This is particularly relevant in PD patients with tremor. The axial resolution of a time-domain OCT is 8–10 μM, while for a Fourier-domain it is ~5 μm, resulting in a more accurate representation of retinal topography. Since a "Parkinson's" OCT protocol does not exist, the standard "glaucoma" protocol was performed to quantify retinal thickness in 45 eyes of 24 PD patients and 31 eyes of 17 control subjects. All PD patients enrolled were relatively early in the course of the disease (average duration of PD 2.9 years). Twelve of the PD patients were on stable pharmacologic therapies; eleven had not yet been treated with dopaminergic agents (de novo patients). Of the treated patients, seven were treated with presynaptic (levodopa) medications, four were on combination of levodopa and a dopamine receptor agonist therapy, and one was on pramipexole alone. Their Hoehn and Yahr staging [12] ranged from II to III with a mean of 2.5. There was no difference between the superior or inferior outer retinal layer thickness in either PD eyes or control eyes. However, the mean superior and inferior inner retinal layer thicknesses of PD versus control eyes were significantly different. Additionally, we recently compared the results 39 eyes of the first group [10] of patients with a second, independent group of PD patients. The two groups were similar in size, staging for PD, age and sex distribution. The group results were comparable, showing that there is retinal thinning in over 60 % of relatively early (II/III) stage PD. The thinning affects the inner nuclear layer (the site of amacrine cells and the ganglion cells). However, the correlation between thinning in the left and the right eye of the same subject is not perfect: both very early and more advanced patients show deviations; nevertheless the inner retinal layer is significantly thinner in PD patients than in healthy subjects.

These data show that the inner retina, primarily the foveal region, not only the ganglion cell layer, is affected in PD (Fig. 22.1). The very center of the fovea, the foveola, is covered by the highest density of neurons in the retina and visual cortex. This provides the substrate for high visual resolution. The fovea provides the highest contrast sensitivity and color vision, and most of the pattern electroretinogram (PERG) and visual-evoked potential (VEP) responses reflect foveal processing [142]. Foveally transmitted visual information is richly represented in many visual cortical areas and is "privileged" [13].

DA-modulated electrical coupling among horizontal and amacrine cells, which are particularly relevant for the interpretation of the PERG changes, are observed in PD patients, since these neurons are responsible for the lateral interactions with regard to retinal information flow that likely contribute to the spatial-tuning function of GCs. Such a disrupted retinal functioning also has been proposed to account for contrast sensitivity (CS) changes. Bodis-Wollner and Yahr [14]

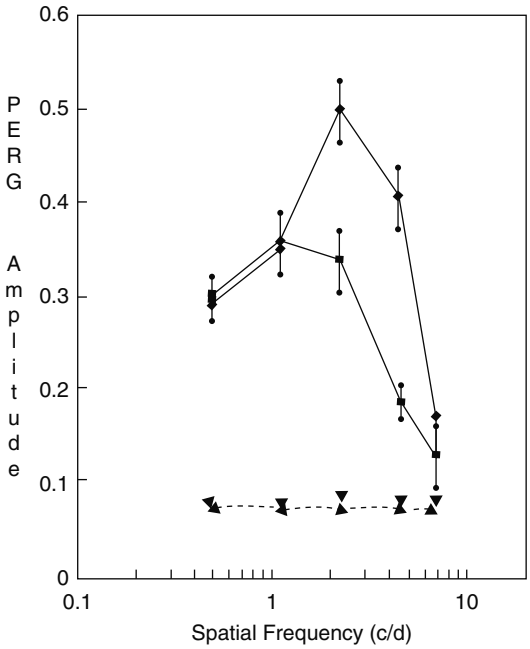

Fig. 22.2 The PERG tuning function in PD: PERG spatial transfer function obtained in patients (*squares*) and age-matched subjects (*diamonds*). The functions are parallel at lower SF and very close at the higher SF tested (6.9 cpd). Note lack of tuning of the PERG transfer function in PD (Tagliati et al., with permission of Clinical Neurophysiology 1996)

originally reported that over 50 % of treated PD patients had delayed VEPs. However, VEPs were not impaired in PD in other studies [15] or if they were impaired, the impairments were not significant [16]. Therefore, not only the prevalence but also the finding itself remained controversial until a number of electrophysiological and psychophysical studies addressed the importance of the specificity of the visual stimulus used for testing (for reviews, *see* refs. [6, 17, 18]) and found that VEP delays were dependent on the spatial and temporal frequencies of stimulation. The VEP and PERG abnormalities in PD are most evident for foveal stimuli of medium and high spatial frequencies (Fig. 22.2) (>2 cycles/degree [cpd]). This stimulus type is optimal for healthy observers, i.e., they require the least contrast to see them among any other stimulus patterns [19–21]. The psychophysically determined CS reveals the same stimulus specific abnormality: it is the most reduced above 2 cpd [6, 20, 22–28]. However, visual impairment remains clinically undocumented in the majority of patients, as many vision care specialists are unaware of testing for a potentially profound CS deficit in any patient with near normal VA. CS loss in PD becomes more profound when the stimulus grating is temporally modulated at 4–8 Hz [5, 24, 29], suggesting that a dopaminergic deficiency state also affects retinal, preganglionic temporal processing [30].

PERG responses also were investigated in posttraumatic parkinsonian patients who exhibited motor abnormalities as a consequence of focal lesions of basal ganglia, in the absence of systemic and retinal dopaminergic degeneration [31]. PERG responses were decreased in nontraumatic PD patients, particularly at medium frequency range (2.7–4.0 cpd). Levodopa therapy reversed the alterations in these patients, resulting in the recovery of a normal tuning function shape. In contrast, the tuning function was preserved in posttraumatic parkinsonian patients. The lack of PERG alterations in posttraumatic parkinsonism clearly excludes the idea that PERG alterations in PD patients are simply due to motor impairment.

VEP delay (P100 component) is observed both in untreated and treated PD patients using stimuli at middle (2–6 cpd) spatial frequencies [31–33]. A delay of P100 peak latency of the VEPs in patients with juvenile PD was found 24 h after cessation of levodopa [34]. However, one study [35] reported that VEPs in treated patients are more delayed VEPs than in untreated patients, suggesting that levodopa therapy has a deleterious effect on vision. Yet, this apparently paradoxical result may indicate that treated patients have more advanced disease, which results in worse retinal visual responses per se [21, 28]. Although both ERG and VEP improve with therapy, there is an apparent difference: levodopa therapy improves PERG abnormalities to a higher degree than it does VEP deficits [31, 35, 36]. One possible interpretation is that VEP changes in PD represent secondary nondopaminergic, and therefore more chronic, alterations in visual processing.

Essential proof of visual system involvement in PD was recently provided by a longitudinal study of visual dysfunction: CS impairment increases in parallel with the worsening of motor score [28]. Levodopa-treated PD patients without dementia and with normal visual acuity were tested twice on the monocular and binocular Pelli–Robson test and the binocular Vistech tables as tests of CS. The mean time interval between the examinations was 19.8 months. CS deteriorated progressively, especially at a spatial frequency of 6 cpd, but also at higher frequencies. The investigators concluded that impairments in CS in PD are progressive over time, and that visual deficits might influence overall motor function. These results also suggest that the visual system might share a progressive degeneration of dopaminergic neurons and/or progressive failure of the effect of levodopa therapy with the motor system.

Since DA affects photoreceptor-horizontal cell transmission, which contributes to chromatic processing in the retina, some abnormalities of color discrimination in PD should be expected. However, the available data are not consistent in this respect and both normal and impaired color discrimination has been reported in PD patients. This variability could be related to the degree of retinal DA loss. A prospective study [28] aimed to determine whether there was progressive, longitudinal deterioration of color discrimination in PD. Patients treated with levodopa were tested twice, on the Lanthony D15 test and the Farnsworth Munsell 100 Hue test, with a mean interval of 19.8 months. Significant progressive deterioration of color discrimination was evident. The deficit correlated with age and with impairment of motor function and activities of daily living. The authors concluded that impairment of color discrimination is progressive over time and may influence overall daily life and motor function and lead to increased motor impairment.

In summary, the spatial and temporal selectivity of visual losses detected with CS in PD is consistent with the results of electrophysiological tests (PERG and VEP). Morphological evidence of foveal thinning in PD is consistent with the functional deficits of visual processing. The interpretation of visual deficits in PD suggests that the disease process causes progressive pathology of neuronal processing in the human retina, leading to loss of spatiotemporal tuning and distorted retinal input to higher visual centers. According to this, in the following parts of this chapter, the position will be entertained that foveal retinal visual deficits, as shown by VEP, ERG, and OCT measures, may be to some extent, but not entirely, linked to higher level visuocognitive deficits in PD.

The foregoing discussion makes a case for the conclusion that visual dysfunction is an *integral* part of PD and that the neurodegenerative process also involves the retina. In PD, the visual deficit fluctuates with motor symptoms in "on–off" patients and worsens with the progression of motor symptoms. The role of DA deficiency is strongly implied by many studies, but DA deficiency may not be *exclusively* responsible for visual changes in PD. For example, although a deficiency in the retinal organization of the receptive fields might be responsible for the degradation of visual sensitivity in PD patients, this assumption is not sufficient to explain the dynamic specificity (e.g., motion sensitivity) of the disorders observed. Indeed, clinical support for a specific deficit of motion perception in PD was provided by Lee and Harris [37]. They found that PD patients reported difficulty in judging motion in everyday experience. PD respondents noticed significant changes in their perception of the world around them, reporting problems with judging distance and motion in the street and problems reaching for objects and moving through narrow space within the home. However, normal motion detection in PD participants was also observed, indicating no general dysfunction of motion processing and the dorsal visual processing stream in patients [38].

Cortex

PERG changes in PD are caused by retinal dopaminergic deficiency. However, the retina may not be the only site of visual pathology in PD; there are other dopaminergic loci. The lateral geniculate nucleus (LGN) [39, 40] and visual cortex have dopaminergic innervation [41–43] and asymmetri-

cally lateralized primary visual cortex glucose hypometabolism has been confirmed in PD [44]. The presence of occipital hypometabolism in PD is the more remarkable as cognitive decline in the aged is associated with hypometabolism in several cortical areas, but not in the occipital cortex [45]. Glucose hypometabolism in PD has been demonstrated to be contralateral to the most severely affected side [44]. A recent study [46] investigated longitudinal cerebral metabolic changes in patients with PD and incident dementia. Twenty-three PD patients without dementia underwent fluorodeoxyglucose (FDG) PET imaging at the entry of the study. PD patients underwent yearly clinical assessment to determine conversion to incident dementia. Follow-up FDG PET imaging was available in a subset of patients at 2 or more years. The authors observed that incident dementia in idiopathic PD initially presents as a predominantly neocortical disease of Brodmann area 18 and the posterior cingulum with limited involvement of the caudate nucleus. Nevertheless, progression of dementia is associated with mixed subcortical, especially thalamic, and cortical changes that also involve the mesiofrontal lobes. Similarly, a radionuclear study has demonstrated decreased blood flow in the posterior temporal and occipital regions in visual hallucinatory PD patients [47].

Consistent with the notion of intrinsic cortical pathology are the reported pattern orientation-dependent CS losses in PD [24, 26]. Orientation selectivity of visual neurons is first established in the primary visual cortex of primates and most mammals [48, 49]. The PD deficit is more severe for horizontal patterns than for vertical patterns [26]. This finding is not explained by retinal dopaminergic deficiency. One possible explanation may be visual cortical pathology in PD. The presence of intraocular differences in CS and VEP in PD is consistent with either retinal pathology [27] or with pathology affecting monocular columns in V1. Alternatively, orientation-dependent CS abnormality in PD suggests cortical pathology. However, contrast adaptation, which has a cortical origin, is spared in PD [50]. Studying the effect of dopaminergic therapy on orientation-selective losses in PD may be valuable.

Visuocognitive Processing

Besides the distal regulatory and modulatory role of DA in the visual process, a correlation possibly exists between cortical DA innervation and expression of cognitive capacities [51]. This is not surprising because of the known widespread cortical ascending systems and loops connecting the basal ganglia and various sensory cortical areas [52]. However, DA apparently is involved in much more than just "gating" bottom-up visual information flow. Several aspects of consciously controlled information processing, such as planning, problem solving, decision making, and response selection, are associated with the function of frontostriatal circuits [53–58]. Recent electrophysiological, neurophysiological, and functional imaging studies attempt to link cognitive symptoms and specific neuronal circuits of the basal ganglia and its connections. It has been hypothesized that the loss of nerve cells in the substantia nigra and consequent depletion of DA levels in the striatum affects a widespread neural network, including prefrontal structures via mesolimbic-frontal fibers that may contribute to the working memory deficit and to apparent higher level cognitive dysfunction in PD [54, 57, 59–61]. However, imaging techniques in various animal species and in humans reveal that normal aging alone may affect the dopaminergic system, too [62]. Imaging studies in humans show an age-related decline in DA cell counts [63] and both D1 and D2/D3 receptors [64–66] and dopamine transporter [67].

Electrophysiology: P300 Deflection of Event-Related Potentials and the Clinical Neuropharmacology of P300 Abnormalities

Identifiable positive and negative deflections of event-related potentials (ERPs) have been implicated to provide indices for the timing of stages in information processing, which include stimulus evaluation, response selection, and context updating [68]. ERPs are recorded in response to

an external stimulus or event to which the subject is consciously paying attention. They are often elicited when the subject distinguishes one stimulus (target) from other stimuli (nontargets). The most extensively studied ERP component is the P300, appearing 300–400 ms after the onset of the target stimulus [69]. P300 amplitude is maximal at the midline electroencephalographic electrodes (Cz and Pz) and is inversely related to the probability of the eliciting event.

Many visual ERP studies yielded a delayed P300 only in demented patients suffering from PD [70–74], but other studies reported a delayed P300 in nondemented patients [75–80]. This suggests the slowness of visual information processing may be independent of or precede global dementia. Although it is uncertain why visual P300 latency is reported to be affected in some but not in all studies of nondemented patients with PD, there may be some rational explanations. First, differences in visual stimuli and experimental paradigms should be taken into account. Wang et al. [81] have observed that different interstimulus intervals (ISI) could distinguish patients with PD from controls: cognitive processes reflected by P300 latency to rare target stimuli were influenced by longer ISI in patients who had PD but not in control subjects. Second, P300 latency during the oddball paradigm in PD was also influenced by age at test, age at onset, and duration of illness [75, 76, 81]. A significant inverse relationship between delayed P300 and score of the Mini Mental State examination was also observed [82].

Differences in the type of medication that patients receive should also be considered. Studies in MPTP-treated monkeys suggest that levodopa therapy alone does not affect the visual P300 [83]; however, D2 receptor blockade can be an influence [84]. D1 receptors are involved in visual working memory (WM) in the prefrontal area (for review, see ref. [85]), which was also identified as one of the generators of P300 [86]. Activation of both D1 and D2 receptor subtypes is needed to improve motor symptoms of PD [87]. Therefore, it is conceivable that the synergistic action of D1 and D2 receptors is needed to improve the visual P300. Levodopa treatment shortens the latency of P300 in patients [70, 88]. However, some investigators have described a prolonged P300 latency in medicated patients [89, 90]. One possibility is that medicated patients are more severely affected to start with, and P300 correlates with disease severity. Such correlation has not been studied in detail.

Another possibility is that cognitive slowing in PD is caused by abnormalities of nondopaminergic systems [91], but there is little direct evidence of correlation of the P300 in PD with cholinergic or other types of neurotransmitter alterations. Pretreatment-delayed P300 improved in PD patients following treatment with amantadine, a low-affinity noncompetitive *N*-methyl-D-aspartate receptor antagonist [92]. Amantadine is closely related to memantine, advocated for the treatment of cognitive impairment in Alzheimer's disease. The effect of amantadine was noticeable not only when administered as monotherapy but also in patients treated with levodopa. It is unknown how amantadine exercised this beneficial effect. A frequent assertion is that amantadine has DA-mimetic properties; therefore, it cannot be excluded that amantadine improves cognitive ERPs in PD as a DA-mimetic agent.

It has been suggested that visual hallucinations (VH) are associated with predominant visual cognitive impairments attributable to PD alone and not to its treatment. Visual and auditory ERP latencies among PD patients with and without VHs were compared [93]. To elicit visual and auditory ERPs, a facial discrimination paradigm and a conventional auditory oddball paradigm, respectively, were used. The mean visual P300 latencies in the hallucinating PD group were significantly longer than the nonhallucinating group; the mean auditory P300 latencies in the patient groups were comparable, which suggest that visual cognitive functions are selectively impaired in hallucinating patients with PD and that these impairments occur at the early stage of information processing.

Does P300 Abnormality Reflect Working Memory Impairment?

Working memory (WM) refers to the short-term, attention-demanding maintenance and manipula-

tion of information for purposeful actions [94]. WM is closely related to the notions of stimulus-representation matching and decision making. In the previously mentioned experiments, in which the classic oddball paradigm is used to elicit the P300 component, a target stimulus has to be stored in the active memory to compare with subsequently presented stimuli for same-different decision making. Cortical areas identified as generators of P300 (dorsolateral prefrontal and parietal cortices) also have roles in WM processes [86]. One part of the WM system, the visuospatial sketchpad, which relates to the maintenance of visual information [94], shows a specific, selective impairment in PD. The visual subsystem responsible for object-related visual analysis seems to be spared until the later stages of the disease, whereas the visual processing of spatial location, motion, and three-dimensional properties is impaired early [57, 95–97]. For example, in delayed-response tests, patients who had PD with mild symptoms were unable to briefly maintain the memory trace of spatial locations of irregular polygons, whereas they successfully kept online the shapes of the same stimuli [97]. Patients with PD also make significantly more errors in mental rotation of three-dimensional wireframe figures [98]. Wang et al. [81] has combined the oddball paradigm with a delayed-response test (S1–S2 paradigm). In this procedure, a simple geometric design is first presented (S1), followed by another (S2) stimulus that can be the same as S1. P300 is recorded only for S2 stimuli. When the time interval between S1 and S2 increases, nondemented patients with PD show particular deficits, suggesting impaired working memory for visual shapes.

The Relationship of Primary Visual-Evoked Potentials and the Concurrently Obtained P300

Latency

Comparing the P100 and P300 of the concurrently obtained visual ERP resulted in a somewhat surprising finding in two independent and ethnically different groups of patients with PD. A prolongation of the normalized P300 latency (P300–P100 latency difference, called central processing time) differentiated younger patients who had PD from controls [75]. These data suggest that younger patients with PD could be differentiated from other types of PD patients using a concurrent VEP and visual P300 recording but were confirmed in non-Caucasian patients with PD [76]. Amantadine also shortened the latency of the visual P300 with little or no effect on the primary VEP component [92].

Amplitude

Although numerous studies have analyzed P300 latency, only a few have examined P300 amplitude in PD. P300 amplitude increases when more attention is allocated, as when performing unexpected or complex tasks. With regard to the P300 amplitude, it has been observed that the anterior P300a is attenuated in amplitude in patients with PD without dementia [98]. Reduction of the classical P300b was also found and correlated with poor performance in the Wisconsin Card Sorting Test (WCST) [99]. These results suggest that the orienting responses of PD patients to novel stimuli are impaired. Recording P300 might provide a neurophysiological and quantitative measure of attentional and cognitive deficits linked to the frontal lobe in nondemented PD patients. However, it is conceivable that the interpretation of raw amplitude can be misleading, because a nonspecific, age-related low-voltage EEG recording could cause low P300 amplitude [75]. Measuring the P300/P100 amplitude ratio may provide a more reliable measure of amplitude alterations; this individually normalized P300 amplitude provided a significant distinction of younger nondemented patients with PD from older patients and age-matched control subjects [75, 76].

Inhibitory executive function in the frontal lobe also is impaired in PD. The amplitudes of the NoGo-P300 and NoGo-N200 (a negative component appearing around 200 ms after the stimulus onset) were significantly smaller in the PD group than in the control group [100]. The NoGo-P300 amplitude was significantly correlated with the WCST and the verbal fluency test scores, as well as with the number of commission errors.

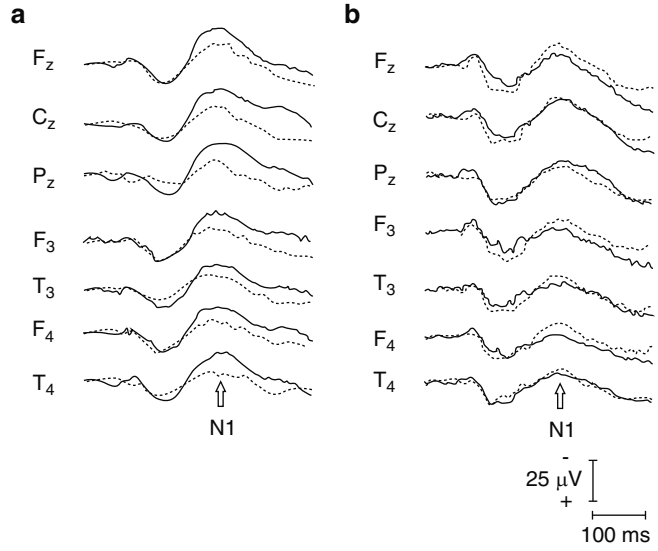

Fig. 22.3 Grand averaged ERPs for (**a**) nonanimal/distractor and for (**b**) animal/target stimuli in the control group (*continuous line*) and PD group (*dotted line*). Note that there is an amplitude difference of N1 component for distractors, but there is no N1 difference for targets (from Antal et al., with permission of Cognitive Brain Research 2002)

N200 of the Visual ERP

Apparently, P100 and P300 are independently affected in PD. Thus, it would be relevant to know the stage of visual processing at which their independence becomes established. Analysis of earlier cognitive ERP components, such as N200, showed that this component also changes independently of P300 [75]. The visual N200 that follows P100 and precedes P300 probably is a visual form of the auditory mismatch negativity [101]. This component is more negative for the infrequent deviant stimuli and distributed over the extrastriate visual areas and posterior-temporal cortex. N200 latency was delayed in nondemented patients with PD, even when P300 was not prolonged with a simple visual paradigm [75]. In a semantic discrimination task, the same result was found [78]. This further suggests that visual deficits and processes indexed by the P300 may reflect processing that is either parallel or well beyond the interface of bottom-up and top-down visual inputs [102, 103].

Electrophysiological Evidence of Visual Categorization Impairment

Although previous studies have suggested that the visual subsystem responsible for object-related visual analysis is spared until the later stages of PD [57, 95–97], recent electrophysiological studies have indicated otherwise. The vast majority of human mental activities are based on categorical processes that serve adaptive and purposeful behavior [104]. Basic visual feature encoding and initial stages of perceptual categorization occur in the first 200-ms poststimulus; conceptual and semantic properties are represented in later stages of information processing [105, 106]. Thorpe et al. found that nonanimal scenes elicited more negative responses than images with animals, at 150 ms following stimulus onset (N1; [107, 108]). Despite relatively preserved P100, this difference was not observable in patients with PD ([109, 110]; Fig. 22.3). However, the exact psychological and physiological mechanisms of this difference are not well established. It is hypothesized that the neostriatum mediates feature weighting and extraction processes, and that the differential N1 may refer to this function. This hypothesis is consistent with multiunit recording data from the basal ganglia of human volunteers. Electrophysiological responses revealed different neuronal responses when the subjects paid attention to select stimulus features (e.g., shape, orientation, and brightness; for review, *see* ref. [111]). This top-down attentional bias, probably mediated by frontostriatal circuits, can facilitate object categorization by feature weighting. In PD, a possible dysfunctional

weighting and selecting process is reflected by the diminished differential N1.

In addition to frontostriatal circuits, one should consider other possible circuits of relevance to visual categorization deficits. It has been suggested [112] that analysis of form and color of category exemplars takes places in the occipito-temporal extrastriate visual cortex. Support for the role of the occipito-temporal-posterior cortex in visual categorical perception is underlined by electrophysiological studies showing that response properties of monkey anterior inferior temporal (IT) neurons cannot account for all aspects of the categorical representation [113]. The prefrontal cortex contains category-specific units and receives input from the neostriatum, which receives inputs from large populations of IT neurons [114].

Similarly to the previously described N1 effects, the amplitude of the N400 component is reduced in PD patients [115, 116]. The ERP N400 component has been extensively investigated as an indicator of semantic relatedness: pictures and words appearing in an incongruent semantic context elicit more negative N400 [117–119]. Thus, an attenuated N400 may refer to impaired working memory functions responsible for the maintenance of context [57, 120].

Electrophysiological Deficits in Distributed Mechanisms of Visual Perception

There is growing evidence that visuocognitive processes require the interaction between distributed neuronal groups. The "binding hypothesis" essentially assumes that it is not feasible to provide specialized brain areas for each of the multitude of different tasks. Rather, different areas have to be coupled within very short time intervals to solve perceptual tasks, likely by synchronized or desynchronized activities of neuronal assemblies. The frequency range around 20–60 Hz is known as "gamma-band" activity. This rhythm exists spontaneously and/or can be evoked, induced, or emitted in different structures of the central nervous system in response to olfactory, auditory, somatosensory, and visual stimuli or in concomitance with attentional/perceptual-cognitive processes. In normal observers, gamma-band activity has been shown to accompany primary visual-evoked responses and be suppressed during the P300 period of the VEP [79, 121]. However, this suppression of gamma synchrony does not exist in PD [79]. Generally, cortical suppression of gamma is thought to reflect competitive hippocampal gamma activation associated with target (P300) processing [122]; therefore, hippocampal gamma activation may be caused by short-term memory updating. In patients who have PD, the lack of "cognitive" suppression may reflect on visuocognitive processing deficits during performance of the task [79]. Additionally, corticocortical frequency coherence can be modified by levodopa therapy in patients with PD [123]. Using a simple visual-tracking task, coherence increase was found after levodopa therapy; without levodopa, the coherence was much reduced. Ascending dopaminergic projections from the mesencephalon may modulate the pattern and extent of corticocortical coupling in visuomotor tasks. Time–frequency analysis of visual ERPs might help to differentiate patients with and without hippocampal dysfunction or, more generally, it might help to bring better understanding of the binding of different cortical areas in dysfunctional cognitive processing in PD.

Recently, it was suggested that early stage PD patients can learn new motor tasks similarly to healthy controls; however, when tested again over the following days, performance of controls significantly improved compared to training performance, while patients' performance did not [124]. This lack of consolidation, which is independent from therapy, may be due to abnormal homeostatic processes that occur during sleep.

Foveal Dysfunction, Visuospatial Attention, Saccadic Eye Movements, and Spatial Stability in PD

One of the recognized cognitive deficits in PD emerges on tests of visuospatial ability [125].

However, visuospatial deficits in PD are sensitive to other cognitive processes as well. Cognitive deficits in PD may be linked to a malfunction of frontal–basal ganglia neural circuits that are important in executive functions. Nevertheless, frontal–basal ganglionic dysfunction partially accounts for the visual–spatial deficits present in PD [126].

A survey of the literature (beyond the scope of this review) suggests it is not a single brain circuit or simple brain mechanism that underlies visual–spatial deficits in PD. In reference to the foveal pathway in PD, one may suggest that the frontal lobe is one site of the impaired circuit of visuospatial attention—more specifically, parts of the frontal lobe that are involved in voluntary saccadic eye movements and spatial attention. What is the relationship of foveal visual processing and directed attention and saccades? Foveal visual processing has a preferential role in object recognition, categorization, and also in visuospatial attention. Neurophysiological studies at the single cell level in the monkey show that the fovea is privileged, not only directing visuospatial attention but also in selecting among many potential eccentric targets [13]. Receptive fields of visually responsive inferotemporal neurons show on-line plasticity, depending on the proximity of visual targets to the fovea, and give different weightings to ensuing saccades. Cortical control of saccadic eye movements overlaps with cortical areas engaged in directing attention [127]. One part of this cortical circuit for voluntary saccades is profoundly affected in PD. The frontal eye field (FEF) is one of the critical cortical areas for attention and initiation of saccades [128]. A predominant impairment of intentional saccades, including visually guided (persistent visual target) and exploratory and memory-guided saccades, is associated with FEF lesions. Functional magnetic resonance imaging (fMRI) reveals that the distributed centers of cortical control of saccades are disrupted in PD, with a profound lack of FEF activity [129].

Patterned visual stimulation is accompanied by a phasic gamma burst. “Gamma” is a label attached to the 30–80 Hz oscillatory components of the surface EEG or obtained in intracerebral multicell recordings in animals. For example, in monkeys, synchronous perisaccadic activity was observed in V1 when the monkey was trained to perform a figure/ground discrimination task [130]. The strength of a shift from low to higher frequency predicted whether the monkey detected a stimulus. Dynamic connectivity of the frontal cortex to basal ganglia circuits has been postulated for preparatory saccade planning [130, 131]. Prestimulus synchronization in V1 may reflect “anticipatory feedback” [132] from higher visual areas. Gamma (30–60 Hz) synchronization of diverse neuronal groups was proposed as a mechanism for thalamocortical neuronal circuits for sensory-motor binding [133]. During a voluntary saccade, performed either in the dark or light, the perisaccadic gamma power of the EEG increases in the posterior channels [134]. In our recent study, we quantified the perisaccadic wavelet transformed EEG in 11 relatively early PD patients. Contrary to normal controls, there was no evidence of intrasaccadic gamma power increase in the posterior EEG channels, even though the saccades were performed well, although some of them showed hypometric and multistep saccades, which are typical in many PD patients. A recent imaging study [129] showed that when PD patients executed voluntary saccades, activity in the FEF was absent (below threshold) in all 12 patients studied. The absence of intrasaccadic gamma modulation in the posterior, rather than anterior, part of the brain channels (see above) seemingly contradicts the fMRI results. However, this is not necessarily so. The corollary discharge (CD) emanates from the frontal cortex when saccades are planned and executed [135]. Many consider CD as a signal of the planned eye movement. CD represents coding for the direction and size of a saccade from the initial eye position. The CD vector is based on the coordinates of the fovea (0 in retinotopic space but not necessarily 0 in body/head centered space). The foveal coordinates prior to the eye movement (fixation) and the intended new location for the fovea represents CD as a communication link between anterior and posterior brain regions. In PD, with hypometric saccades, the CD vector appears impaired. Possibly foveal retinal dysfunction contributes to this problem.

Is there a potential link between impaired foveal processing and postural stability in PD? Studies by Paulus et al. [136] have suggested that the central area of the visual field as compared with the peripheral retina dominates postural control. The foveal region exhibits a powerful contribution, in particular for lateral sway. However, the literature on the potential effect of vision on postural instability in PD has only indirectly addressed the effect of foveal vision: either occlusion of vision or usually flow patterns, flow stimuli (away from the fovea) have been used to assess visual effects on posturographically measured sway [137]. Some studies included optokinetic following measures, which require good foveal (fixational) ability. Some studies suggest that, even in the early stages of PD, patients have decreased stability and changes in the visual input impair their postural control. Recently, Suarez et al. [138] reported the importance of vision to postural control in early PD. In their study, 20 early (Hoehn and Yahr Stage 1) PD patients and a group of 24 normal control subjects were assessed before and after a sudden change in visual flow velocity. The stimulation paradigm was a horizontal optokinetic stimulation (60° per second and suddenly stopped) using a virtual reality system. After sudden changes in the visual flow velocity, PD patients showed impaired postural control.

Conclusion

In the last two decades, an increasing body of evidence has revealed specific and nonspecific visual abnormalities in patients with PD. Most prominently, the abnormal and levodopa-sensitive PERG tuning [21, 70, 139], levodopa-sensitive delayed VEPs [14], and reduced CS that fluctuates with the dopaminergic state [5, 6, 23, 30] provide evidence of a specific parkinsonian retinopathy. Improvements of these abnormalities by levodopa therapy in humans and in the PD monkey model have established a link between the visual symptoms observed in PD and retinal pathology. However, beyond the retina, electrophysiological, neuropsychological, and functional neuroimaging data suggest dopaminergic dysregulation of higher level visuocognitive functions in the cortico-subcortical system in PD as well.

Many studies of visual categorization deficits imply that the posterior part of the cortex is involved in this disease. A wealth of cognitive studies in PD are consistent with the hypothesis of Brown and Marsden [140], who proposed that PD patients are particularly impaired in self-initiated, effort-demanding tasks. At this point, it is clear that visuocognitive impairment is not a passive or predictable consequence of retinal dopaminergic deficiency. However, the anatomical site(s), particularly the exclusive role of the frontal cortex, has to be modified in view of recent studies implying a posterior stream of visual-working memory.

Several possible interpretations for the visuocognitive deficits are suggested [143]. One is that it arises from impairment of visual sensory function (a distortion in spatiotemporal CS function related to a deficit in the receptive field organization in the DA-deficient retina). Another possibility is an orientation-selective visual loss of central origin in PD patients, which might interfere with the perception of some of the complex patterns used in visuocognitive tasks. A loss of attention, arising from impaired oculomotor control, might also lead to inefficient scanning of the task. Impairment in attentional/perceptual switching in some tasks may be also a problem. Another theory of visuocognitive dysfunction in PD suggests that the cognitive deficits are in some way related to disruption of frontal–basal ganglia neural circuits important in executive function. Yet another theory favors dysfunction of the posterior parietal cortex in PD. Deficient perception and visual cognition in PD can generally be attributed to slow information processing.

Some human and electrophysiological evidence indicates that dopaminergic therapy improves visuocognitive impairment, at least in the initial phases of PD. As the disease progresses, dopaminergic therapy appears to be less effective, possibly because of the development of nondopaminergic disturbances in PD (noradrenergic, serotonergic, and cholinergic deficits and

cortical Lewy bodies). Recent imaging data suggest that cholinergic deficits are prominent and contribute to early cognitive changes in PD [46]. The most prominent acetylcholinesterase reductions in subjects with PD with early disease occur in medial occipital secondary visual cortex [141]. These results correlate well with prior postmortem data indicating that this region (the cuneus) experiences the greatest degree of cholinergic denervation.

In the future, novel pharmacological methods, targeting the neurodegenerative process itself (e.g., compounds acting on the glutamatergic *N*-methyl-D-aspartate and growth-factor receptors) and those aimed at improving cognitive functions in PD, may become warranted.

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Olfactory Dysfunction

23

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Abstract

Olfactory dysfunction is well documented as an early nonmotor manifestation of Parkinson's disease (PD). This chapter outlines the anatomy and physiology of the olfactory system and summarizes the pathological changes in the olfactory system in PD. We review the occurrence of olfactory dysfunction in parkinsonian syndromes and familial parkinsonism. Different methods to assess olfactory function are presented. Their usefulness in routine clinical situations is limited to special diagnostic situations. However, these methods have provided important insights into the pathophysiology of parkinsonism and can help to identify at-risk groups for future neuroprotective trials. Several lines of evidence now suggest that olfactory disturbance reflects Lewy pathology more closely than it reflects striatonigral dopamine deficiency.

Keywords

Parkinson's disease • Olfaction • Olfactory nerve • Hyposmia

Introduction

Olfactory dysfunction is one of the nonmotor manifestations of Parkinson's disease (PD) and may precede the onset of motor symptoms. Recent advances in neuroimaging and pathology have further elucidated the nature of the olfactory impairment and provided new insights into the mechanisms and patterns of neurodegeneration in PD. The aim of this chapter is to review the literature on olfaction in PD and other parkinsonian disorders. Emphasis has been placed on new results published since this book's first edition.

Olfaction in Humans: Anatomical and Clinical Considerations

The olfactory epithelium in the posterior nasal cavity is a specialized chemosensory epithelium stimulated by the plethora of odorants encountered by humans. It contains bipolar olfactory receptor cells with short processes that extend to the mucosal sur-

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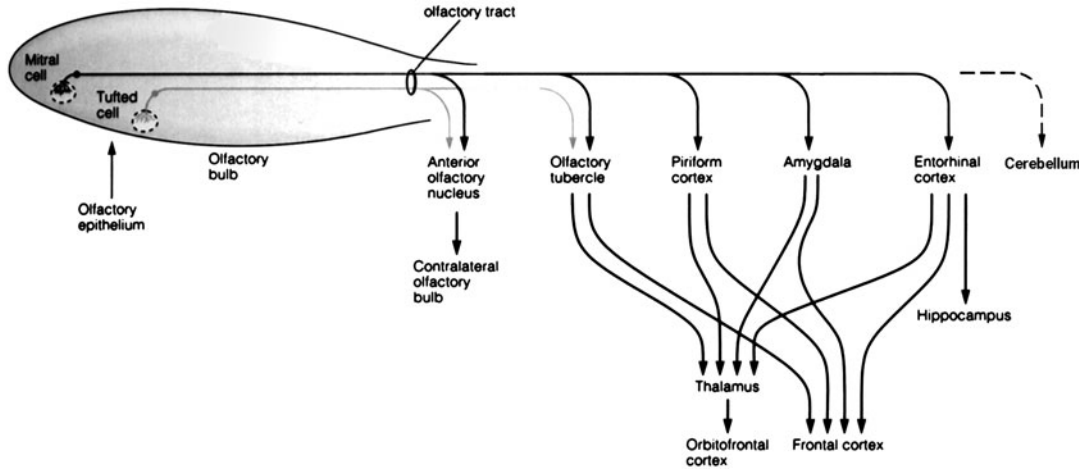

Fig. 23.1 Connections of the olfactory system. From Kandel ER, Schwartz JH, Jessell TM, editors. Principles of neural science. 4th ed. New York: McGraw-Hill; 2000. p. 633, with permission of The McGraw-Hill Companies. Modified by Andreas Puschmann

face, and long processes that form the olfactory nerve fibers (cranial nerve I) and synapse in the olfactory bulb beneath each hemisphere. Odorants are absorbed into the mucous layer overlying the receptor cells aided by olfactory-binding protein, which facilitates interaction of the odorant with receptor cell cilia. This interaction results in increased frequency of action potentials. The human genome contains 339 different genes encoding for olfactory receptors [1]. Genetic reorganization, such as alternative splicing, and combinatorial processing of the information from several receptor cells, enables mammals to distinguish a larger number of odors. Single neurons may respond to multiple odorants; on the other hand, one particular odorant may excite several neurons. Biologists are now beginning to understand how an olfactory neuron selects its characteristic receptor genes, and how these selections are coordinated to ascertain that different olfactory neurons express different receptor combinations [2]. The olfactory receptor genes have been highly conserved during evolution [1]. This emphasizes the vital role the detection of chemical substances in the environment plays for many organisms, perhaps somewhat in contrast to humans, who can rely on other senses and a complex social organization.

The unmyelinated axons of the roughly six million bipolar receptor cells form the olfactory nerve. A number of fiber bundles traverse the cribriform plate of the ethmoid bone and these axons terminate on the dendritic arbor of mitral cells and tufted cells in the olfactory bulb. Neurons in the olfactory bulb are among the very few known neuronal populations that continuously regenerate throughout life from neuroblasts in the supraventricular zone [3]. At least in rodents, this ongoing regenerative process is dopamine dependent [4]. With regard to parkinsonism, it is also noteworthy that dopamine from interneurons and centrifugal projections modulates signal transduction from olfactory receptor cells to mitral and tufted cells [5, 6]. The olfactory tract (axons of mitral and tufted cells) projects to the anterior olfactory nucleus, olfactory tubercle, piriform cortex, cortical nucleus of the amygdala, the periamygdaloid cortex, and the entorhinal area [6, 7]. All these recipient areas are commonly referred to as the primary olfactory cortex. Strictly speaking, this terminology does not accurately reflect embryologic development. The olfactory bulb forms as part of the paleocortex and thus should be called "primary olfactory cortex" [7]. However, this terminology is not widely used. Information is relayed to higher-order olfactory areas from these recipient structures. Projections to the orbitofrontal cortex are involved in the conscious perception of smell. Connections to the limbic system and the hippocampus are related to the

emotional perception of smell and odor memory [8, 9]. Positron emission tomography (PET) and functional magnetic resonance imaging (MRI) studies during olfactory stimulation show that activation of the amygdala is associated with odor intensity, whereas orbitofrontal cortex activation is associated with odor valence [10]. Activity also is present in the cerebellum: High concentrations of odorants activate posterolateral cerebellar areas, whereas the act of sniffing activates anterior areas, which suggests the presence of a feedback loop that decreases sniff vigor when high-intensity odors are encountered, and vice versa [11, 12]. Figure 23.1 shows the anatomical and functional connections of the olfactory system.

Testing Olfactory Function

The study of olfaction in humans comprises psychophysical tests that assess the threshold for an odor to be detected, the ability to identify odors and to discriminate between different odors, as well as odor memory. Experimental methods measuring sniff vigor have been developed, and olfactory event-related potentials (OERP) provide neurophysiological evidence of cortical activity associated with olfaction Table 23.1.

The University of Pennsylvania Smell Identification Test (UPSIT; Sensonics Inc., Haddon Heights, NJ) is a standardized psychophysical olfactory test that has been used widely. It contains 40 microencapsulated odors that are released by scratching an impregnated strip with a pencil; the subject then is asked to identify each released odor in a multiple-choice paradigm. The test is available in multiple languages, easy to use, and has a large amount of standardized normative data with reproducible results. It is, however, costly and each test packet can only be used once. Some of the odors it contains are culture specific and not familiar to non-US probands; for example, only 25 of the 40 items were found to be familiar to an Asian population [13]. The same manufacturer offers the Brief Smell Identification Test (BSIT, Cross-Cultural Smell Identification Test) consisting of only 12 odors. The OSIT-J test (Takasago International Corporation Ltd., Tokyo, Japan) includes 12 odorants from Japanese every-day life [14].

Another commercially available psychophysical test, "Sniffin' Sticks" (Burghart GmbH, Wedel, Germany), presents odors in reusable felt-tip-like pens [15]. Its complete version comprises

Table 23.1 Methods to assess olfaction

Test method	Content	Modalities assessed
Psychophysical smell tests		
UPSIT™ (University of Pennsylvania Smell Identification Test)	40 odors	Odor identification
BSIT™ (Brief Smell Identification Test, Cross-Cultural Smell Identification Test)	12 odors	Odor identification
OSIT-J™ (Odor Stick Identification Test for Japanese subjects)	12 odors	Odor identification
Sniffin' Sticks™ Screening12™ Test	12 odors	Odor identification
Sniffin' Sticks™ Extended Test	16 dilutions *n*-butanol or 2-phenyl ethanol	Odor threshold
	16 pairs of odorants each with 1 individual odor	Odor discrimination
	16 odors, blanks	Odor identification
Neurophysiological assessment of olfaction		
Olfactory event-related potentials (OERPs)	Short-lasting odorant stimulation	Averaged electrophysiological potentials recorded over various cortical areas
Functional magnetic resonance imaging	Odorant stimulation	Measurements of neuronal activation
	Sniffing	

different concentrations of the same odor to establish odor threshold, pairs of odors to assess odor discrimination, and a set of common odors for odor identification [16]. This test battery compares favorably to UPSIT and BSIT [16], and the assessment of a composite (abbreviated as "TDI") of odor threshold (T), discrimination (D), and identification (I) is better able to distinguish healthy controls from idiopathic PD patients than odor discrimination alone [17]. However, the three variables are not independent; a deficit in odor detection may influence odor discrimination and identification [18]. An abbreviated version is also available and marketed for office use but has not been tested extensively in scientific studies.

Less frequently used techniques involve recording OERPs in response to different odorants [19, 20]. Similar to evoked potentials, these provide a composite measurement of signals in cortex areas after olfactory stimulation. Functional MRI during olfactory stimulation has been used in research protocols [11, 21, 22]. Morphological evaluation of the olfactory epithelium has been performed during local or generalized anesthesia, and *postmortem* pathological analysis of olfactory structures has also been undertaken (see below). In a clinical context, imaging with computed tomography or MRI can identify structural causes of olfactory disturbance that can coexist in patients with parkinsonism. Structural lesions should especially be searched for if the olfactory disturbance is unilateral or occurs suddenly.

These tests have improved our understanding of human olfaction: We now know that generally (1) women have a better sense of smell than men; (2) odor identification is mediated partly by a heritable component; (3) a significant loss in sense of smell occurs after 65 years of age; (4) this loss occurs earlier in men than in women; and (5) olfaction is compromised by smoking and urban living conditions [9, 15].

Olfaction and PD

A considerable number of studies have substantiated that, on average, individuals with PD perform more poorly on olfactory testing than healthy controls. To our knowledge, Ansari and Johnson in 1975 [23] reported the first study of olfaction in PD, comparing 22 men treated for PD with subjects diagnosed with other neurologic disorders (e.g., seizures, multiple sclerosis, stroke, headache). Patients with PD had a higher detection threshold for amyl acetate [23]. In 1983, Ward et al. [24] analyzed odor detection threshold as well as the discrimination of common odorants in PD patients. Compared with controls, PD patients were significantly impaired in both tests; some were anosmic. Subsequent studies showed that olfaction was already disturbed early in the course of PD [18]. Olfactory dysfunction in patients with PD has been reported by several other groups [25–28] and widely confirmed in studies comparing olfaction in PD with other neurodegenerative diseases (see below).

Bohnen et al. suggested that PD patients have selective hyposmia for certain odors, instead of general hyposmia [29]. Analysis of the individual smell scores of 27 PD patients and an equal number of controls identified three odors with an accuracy of 75 % for the diagnosis of PD. These odors were banana, licorice, and dill pickle. Failure to identify these three odors also correlated with nigral dopamine transporter (DAT) PET activity. No such association was found for the whole UPSIT battery, leading the authors to suggest that PD patients have only selective hyposmia [29]. However, this study is based on the a priori assumption that olfactory dysfunction is directly proportional to nigral dopamine depletion. It may need to be reevaluated in light of subsequent findings that suggest that olfactory dysfunction does *not* correlate with nigrostriatal dopamine depletion but rather with cardiac sympathetic denervation and thus with Lewy pathology [30] (see below).

Different test methods will provide information about different aspects of olfaction. For instance, delayed or absent OERPs were found in PD patients [26, 31], indicating that signal transduction is inhibited en route from the olfactory epithelium to the cortical areas from where potentials are recorded. A smell testing protocol with a smaller number of tests covering different domains (e.g., odor identification plus detection threshold)

correlated better with increased PD risk than more detailed testing of only one domain [32]. Patients with PD also displayed a reduced sniff airflow rate and volume, which influenced their performance in olfactory function tests [33]. Increasing sniff vigor improved olfactory performance in patients with the poorest olfaction, but because the vigor of sniffing is not usually measured in tests of olfactory function, there may be an overestimation of the sensu stricto olfactory deficit in PD.

In a multicenter study, Haehner et al. emphasized the importance of age-matched control groups: 400 PD patients with a mean disease duration of 6.5 years performed olfactory testing, and the results were compared with historical controls [34]. In comparison with young normosmic subjects, 96.7 % of PD patients showed significant olfactory loss, but when adjusted to age-matched controls, this figure fell to 74.5 % [34]. In light of this finding, the results of a different study in which olfaction in a cohort of PD patients with a mean age of 60.8 years was compared with a healthy control group with a mean age of only 35.2 years [17] must be interpreted with care.

The olfactory deficit in PD may precede the onset of motor symptoms, in some cases by several years [25, 34–36]. This finding has spurred research into the possible use of olfactory testing to predict PD development. Clinically unaffected first-degree relatives of PD patients had a higher proportion of abnormal scores on a PD battery that included studies of olfaction than did controls with no family history of PD [35]. Some of these first-degree relatives later developed PD. However, olfactory function in PD does not deteriorate in a straight linear fashion over time but follows an unpredictable course. In fact, some PD patients had better olfaction at a follow-up assessment more than 4 years after the first test [37]. Duration of disease correlates poorly with the extent of olfactory dysfunction [18, 38, 39]. From the population-based Honolulu-Asia Aging Study, Ross et al. presented data on over 2,200 men with an average age of 80 years. These individuals did not have PD at the time of inclusion, when olfactory testing (BSIT) was performed. Those participants who had smell test results in the lower quartile (0–5 out of 12 odors identified) had an odds ratio of 5.2 to develop PD after a follow-up of 8 years, compared with those who had olfaction test results in the top half [40]. Although this was clearly statistically significant [40], 37 % of those who developed PD initially had test results in the top half, identifying 8 or more of the 12 odors correctly.

Olfactory testing has been combined with other possible PD biomarkers. Twenty-five hyposmic and 23 normosmic relatives of PD patients underwent DAT imaging with single-photon emission-computed tomography (SPECT) [41]. Four of 25 hyposmic relatives had reduced striatal DAT binding, compared with none of the 23 normosmic relatives. Two of the four hyposmic relatives with abnormal SPECT scans developed clinical parkinsonism within 6–12 months following the SPECT studies. A unilateral resting tremor developed in a third hyposmic relative, but no other features of PD were observed [41]. Another study evaluating asymptomatic first-degree relatives of PD patients combined olfactory testing and DAT scanning: 10 % of those individuals with hyposmia and strongly reduced DAT binding at baseline had developed clinical PD 2 years later, compared with none of the other relatives in the cohort [36]. In a second clinical follow-up of this cohort, poorer performance on each of three olfactory processing tasks was associated with an increased risk of developing PD within 5 years [42]. In a Smell and Taste Clinic setting, 30 patients presenting with idiopathic olfactory loss were assessed with olfactory testing, ultrasound of the substantia nigra and, if the latter showed pathological results, also DAT scans [34]. Neurological examination was performed initially and at follow-up 4 years later. The risk to develop PD was higher than expected in the general population [34]. Unfortunately, participant numbers were too small to determine if ultrasound and SPECT gave additional information to stratify PD risk. Taken together, these data indicate that a combination of olfactory testing and additional investigations is superior to olfactory testing alone in defining a group at high risk of developing PD.

The majority of research has concentrated on the loss of olfactory function in PD, but there are

also reports of another olfaction-related phenomenon. Olfactory hallucinations have been described previously in anosmic patients with advanced PD [23, 43, 44]. In contrast, two patients experienced a different type of olfactory hallucinations for several years prior to the onset of PD [45]. One of these had no olfactory dysfunction, and the second patient had slight olfactory deficit in tests but had not subjectively noticed any impairment. These phantosmias lasted only a few seconds to minutes and consisted of pleasant olfactory experiences such as fruits, fragrances, or perfumed candles. The phenomena disappeared spontaneously, but in a temporal relationship with the development of PD motor symptoms [45].

Olfaction in Other Parkinsonian Syndromes

Various studies have examined olfactory dysfunction in parkinsonian syndromes other than PD and found characteristic statistical differences on the group level. These findings have raised the hope that olfactory testing may provide a simple tool in the clinical armamentarium to distinguish idiopathic PD from other parkinsonian syndromes.

Patients with multiple system atrophy (MSA) had olfactory deficit, but this was much milder than in PD patients [21, 30, 38, 39, 46]. Patients with progressive supranuclear palsy (PSP) [38, 39], corticobasal degeneration (CBD) [38, 39], vascular parkinsonism [47], or parkinsonism induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [48] had normal or only minimally impaired olfaction. Patients with essential tremor (ET) had normal results on olfactory testing by UPSIT [31, 38, 39, 49] or OERP [31]. Test results were markedly different between ET and PD in the studied population, but the two groups' individual results overlapped [31].

In contrast, olfaction is impaired in Dementia with Lewy bodies (DLB) [50] and in various subtypes of the amyotrophic lateral sclerosis–parkinsonian complex found in the native Chamorro population of Guam [51]. Parkinsonism induced by dopamine-receptor 2 (D2)-blocking neuroleptic drugs was associated with olfactory dysfunction [52, 53], but generally to a lesser degree than in PD. Neuroleptic treatment may elicit extrapyramidal motor symptoms in a person with concomitant subclinical neurodegeneration. Olfactory testing identified those patients presenting with parkinsonism during neuroleptic treatment whose motor symptoms were not fully reversible 5 months after the discontinuation of the neuroleptic, possibly indicating that they were in fact developing PD [52]. Patients with pure autonomic failure (PAF) had olfactory test scores similar to PD patients and worse than MSA patients [30, 54]. Table 23.2 provides a summary of the olfactory function of patients with different forms of parkinsonism.

Table 23.2 Olfactory function in patient cohorts with different forms of parkinsonism (group level)

Disease	Olfactory function	References
Parkinson's disease (PD)	Impaired	Numerous, see text
Multiple system atrophy	Moderately impaired	[21, 30, 38, 39, 46]
Pure autonomic failure	Impaired	[30, 54]
Dementia with Lewy bodies	Impaired	[50]
Guamanian ALS–parkinsonism complex	Impaired	[51]
Lubag (X-linked dystonia-parkinsonism syndrome, XDP)	Impaired	[13]
Progressive supranuclear palsy	Normal or mildly impaired	[38, 39, 46]
Corticobasal degeneration	Normal or mildly impaired	[38, 39, 46]
MPTP-induced parkinsonism	Normal	[48]
Vascular parkinsonism	Normal or mildly impaired	[47]
Essential tremor	Normal	[31, 38, 39, 49]
Parkinsonism induced by neuroleptic drugs (fully reversible)	Normal or mildly impaired (see text)	[52, 53]

(continued)

Table 23.2 (continued)

Disease	Olfactory function	References
Parkinsonism induced by neuroleptic drugs (not fully reversible, possibly indicating subclinical PD development)	Impaired (see text)	[52]
Familial PD		
α-synuclein point mutation A53T (PD plus phenotype)	Impaired	[58, 66, 92]
α-synuclein duplication and triplication (PD plus phenotype)	Impaired	[55, 56]
LRRK2 G2019S mutation (PD phenotype)	Impaired	[59–61]
LRRK2 R1441C mutation (PD phenotype)	Impaired	[62, 66]
Parkin mutations (early onset PD phenotype)	Normal	[63, 64]
PINK1 mutations (early or late onset PD phenotype)	Mildly to markedly impaired (see text)	[65]
DJ1 mutations (early onset PD phenotype)	Normal	[64]
Family B (gene or locus not established, PD phenotype)	Impaired	[66]
Familial parkinsonism		
PPND family with *tau* N279K mutation (PD plus phenotype)	Impaired	[66, 67]
Alberta family (spinocerebellar ataxia type 2, *ataxin2* mutation, PD-like phenotype)	Impaired	[92, 93]
Family C (*PARK3* locus, PD-like phenotype)	Normal	[92]
Family G (*PARK3* locus, PD plus phenotype)	Impaired	[66, 92]
Family E (gene or locus not established, PD plus phenotype)	Normal	[92]
Arkansas family (gene or locus not established, PD, ET and RSL phenotypes)	Impaired in members with PD phenotype or with combined postural and rest tremor	[94]

ALS amyotrophic lateral sclerosis, ET essential tremor *MPTP* 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, *PPND* pallido-ponto-nigral degeneration, RLS restless legs syndrome

Olfaction in Familial PD/Parkinsonism

The identification of causative gene mutations for PD has enabled researchers to compare genetically defined subgroups of PD patients. The majority of the earlier clinical descriptions contain information about the affected carriers' olfactory function in pedigrees with known gene mutations, but the number of individuals therein often is limited.

Nishioka et al. reported "Sniffin' Sticks" smell test results from six patients with *SNCA* duplication, compared with 5 asymptomatic carriers and 22 controls [55]. Olfactory threshold, odor discrimination, and odor identification were significantly reduced in the duplication patients compared with controls. In the Swedish-American "Lister" family, an *SNCA* triplication carrier had impaired sense of smell [56]. Patients with the *SNCA* A53T mutation from Family H (Greek-American) had olfactory dysfunction [57], and the proband of an unrelated Swedish family with the same mutation [58] had complained of reduced ability to smell (Andreas Puschmann, unpublished results).

Silveira-Moriyama et al. compared 19 patients with parkinsonism caused by the relatively common *LRRK2* G2019S mutation with 145 sporadic PD patients whose mutation status remained unknown and with 135 matched healthy controls [59]. UPSIT smell testing revealed statistically significant differences between the healthy controls and the known mutation carriers, but not between the mutation carriers and the group of patients with sporadic PD [59]. In a French fam-

ily with three patients with the *LRRK2* G2019S mutation, Lohmann et al. reported moderate microsomia in one and anosmia in two patients [60]. However, the family's unaffected mutation carriers and all of the healthy nonmutation carriers had hyposmia or even anosmia in the UPSIT test [60]. The largest study of this kind evaluated UPSIT data from 43 PD patients with a *LRRK2* G2019S mutation and found only 22 patients (51 %) to have abnormal olfaction after 5.6 years mean disease duration [61]. Patients from Family D (Western Nebraska) with the *LRRK2* R1441C mutation also had impaired olfaction [62].

In contrast to the studies described above, there was no statistical difference in smell function as assessed with UPSIT between 13 PD patients with recessively inherited *Parkin* mutations and 11 normal controls [63]. Comparison of these mutation carriers to young-onset PD patients without *Parkin* mutations and to older PD patients with undetermined carrier status reached significance. Reporting normosmia in six patients with *Parkin* or *DJ1* mutations, Verbaan et al. corroborated this finding [64]. Detailed testing of 7 homozygous patients, 6 affected and 12 unaffected heterozygous carriers of the rare mutations in *PINK1* revealed impaired odor identification but only mildly reduced odor detection threshold [65]. Odor discrimination was markedly impaired in all *PINK1* mutation carriers, including those who were otherwise clinically unaffected [65].

In Lubag (X-linked dystonia-parkinsonism syndrome, XDP), olfaction is often impaired [13]. For the rural Philippine areas where this disorder occurs, olfactory testing has been suggested as a less expensive (albeit less specific) diagnostic means than genetic testing [13]. Olfactory impairment is also observed in patients with parkinsonism due to mutations in the tau (MAPT) gene [66, 67]. Table 23.2 includes data on olfactory function of other hereditary parkinsonian syndromes.

The overall picture is that olfactory function is disturbed in those monogenetic forms that closely resemble idiopathic PD, but largely preserved in the *Parkin* and *DJ1*-related forms, which are characterized by younger age at onset and low likelihood of cortical involvement. This may lend further evidence to the view that the disease process in patients with the recessive *Parkin*, *DJ1* and *PINK1* mutations remains confined to the upper brainstem [68]. The varying degree of dysfunction in the different olfactory function domains reported in one study in *PINK1* mutation carriers [65] is not easily reconciled with this concept.

Pathology of Olfactory Dysfunction in PD

Substantial progress has been made in understanding which of the anatomical structures involved in human olfaction are affected in PD. β-Amyloid staining of the olfactory epithelium from patients with PD revealed dystrophic neurites without Lewy bodies (LB) [69]. Immunohistochemistry using antibodies against α-synuclein and against markers identifying olfactory neurons, immature neurons, and stem cells did not detect any differences in olfactory epithelium from PD patients compared with healthy controls or individuals with impaired olfaction due to unrelated causes [70].

Pathologically, olfactory bulbs of PD patients appear flattened and shrunken, and the olfactory tracts are markedly thinned on gross examination [71]. LB are present in olfactory bulbs and the anterior olfactory nucleus of PD patients [26, 72]. They resemble cortical LB and are sufficiently distinctive to allow a presumptive diagnosis of PD [26, 72] (see Fig. 23.2a). Neuronal loss in the anterior olfactory neurons of the olfactory bulbs and tracts correlates strongly with disease duration but not with age of onset [71]. Braak et al. identified the olfactory bulb, tract, and/or anterior olfactory nucleus as one of the two structures with the earliest occurrence of Lewy pathology in PD, along with the dorsal motor nucleus of the glossopharyngeal and vagal nerves [73]. Twelve out of 94 PD brains studied by Braak et al. had no Lewy pathology in the olfactory bulbs, but all had Lewy pathology in the dorsal motor nucleus of the glossopharyngeal and vagal nerves [73]. Braak et al. hypothesized that unknown pathogens may use olfactory neurons as ports of entry

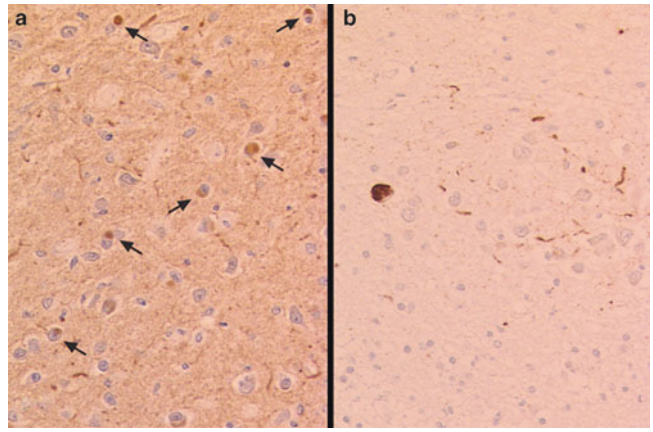

Fig. 23.2 Micrographs of the anterior olfactory nucleus from patients with a pathologic diagnosis of Lewy body (LB) disease. (**a**) LB of the cortical type (*arrows*) (immunochemistry stain with α-synuclein antibody; magnification ×200. Figure courtesy of Drs. Y. Tsuboi and D. Dickson, Mayo Clinic, Jacksonville, FL). (**b**) Mild tau pathology with neuropil threads and neurofibrillary tangles (immunohistochemistry with tau antibodies, magnification ×200. From Tsuboi Y, Wszolek ZK, Graff-Radford NR, et al. Tau pathology in the olfactory bulb correlates with Braak stage, Lewy body pathology and apolipoprotein epsilon4. Neuropathol Appl Neurobiol. 2003;29:506, with permission of Blackwell Publishing Ltd.

into the central nervous system [74]. Furthermore, tau pathology was detected in the olfactory bulb and adjacent anterior olfactory nucleus in nine out of ten brains with a pathological diagnosis of LB disease [72]. Tau pathology load was mild but significantly higher than in normal controls, and its severity correlated with cortical LB counts [72] (see Fig. 23.2b).

Because the olfactory bulb continuously receives new neurons from the subventricular zone, deficient adult neurogenesis may change its structure and functioning. Studies in rodents showed that a disturbance of neurogenesis weakened the odor discrimination of mice [3, 75]. Both natural aging [76] and dopamine depletion [4] impaired the proliferation of precursor neurons. However, dopamine from periglomerular neurons in the olfactory bulb exerts an inhibitory modulatory effect on signal transduction [77]. In PD patients, the number of dopaminergic neurons in the olfactory bulb is twice that of healthy controls [78]. This increase may be due to a compensatory mechanism responding to the nigrostriatal dopamine deficit. Consistent with this finding, olfactory dysfunction in PD does not respond to the dopamine agonist apomorphine [79], or to any other dopaminergic treatment.

MRI did not detect any gross volume change of the olfactory bulbs in PD patients [80], but MRI diffusion tensor imaging localized neurodegenerative changes in the olfactory tract of PD patients [81]. In a study protocol examining PD patients and controls without an a priori hypothesis about which CNS location may be preferentially involved, the olfactory tracts were the only structures displaying increased water molecule diffusion, indicating cellular damage [81].

Cell loss, volume reduction, and Lewy pathology also were found in the amygdala of brains from nondemented patients with PD at various disease stages [82]. Based on the anatomical connections, this may explain impaired olfaction in PD, but these patients had not been examined for olfactory dysfunction [82]. A functional MRI study revealed an asymmetric deficit of right amygdala activation in PD patients [22]. By contrast, healthy controls showed bilateral and symmetric activation in both amygdalae [22]. A study using DAT PET scanning identified lower activity in the hippocampus as more closely associated with low UPSIT scores than activation deficits in the amygdalae [83]. This may reflect another mechanism of smell loss in PD, since hyposmia in PD is associated with catecholamine deficiencies

in mesolimbic areas [84] and with dopamine deficiency in the parolfactory gyrus and the nucleus accumbens [85], which partly project to the hippocampus. Activation patterns of the cortical areas involved in olfaction have been largely normal in functional MRI studies [20, 22].

Olfaction of patients receiving deep brain stimulation (DBS) can be compared in the same individual when the stimulation is turned "on" and "off." PD patients with DBS in the subthalamic nucleus were able to discriminate best between odors when stimulation was ongoing, which was attributed to a general improvement of information processing [86]. Conversely, patients with ET and DBS in the ventrointermedius (VIM) thalamic nucleus achieved poorer olfactory test scores with the DBS "on," although they did not note any subjective difference. The anatomic proximity of cerebellothalamic structures to the VIM nucleus suggests that VIM DBS impairs an olfactomotor loop [87]. Furthermore, in healthy subjects, an unconscious reaction makes breathing rapid and shallow in response to unpleasant odors, and deep and slow in response to pleasant ones. This respiratory response to the odor's emotional validity is mediated via the limbic system. When compared with healthy controls, this response was weaker in a group of PD patients whose odor identification abilities were unimpaired [88]. Taken together with the activation of cerebellar structures in olfaction documented in the functional MRI studies named above, this demonstrates the importance of cerebellar sniff vigor regulation for olfactory function.

Practical Uses of Olfactory Testing

On a group level, olfactory dysfunction is associated with PD. Differential diagnosis, again on the group level, can be aided by olfactory tests. However, the currently available literature shows a considerable overlap of individual olfactory test results between the groups.

Poor olfaction in a healthy individual infers an increase in the relative risk for PD. The absolute risk, however, is much lower. In the Honolulu-Asia Aging Study (see above), more than 98 % of those participants with olfactory test results in the poorest quartile had *not* developed PD at follow-up 4 or 8 years later [40]. A high percentage of the populations studied have been exposed to active or passive smoking or other environmental air pollutants during their lives. In many countries, smoking has been reduced dramatically within the last generation. The incidence of smell loss in healthy control groups can be expected to decrease steadily in the coming generations, and it may be important to repeat olfaction studies some years from now.

Reliable olfaction testing is difficult and has many potential sources for error, such as nasal blockage or the common cold and issues regarding the complex interaction of memory, consciousness, and the ability to express the correct test answer. The test paradigms used in the published research studies often involve lengthy and elaborate protocols that are not feasible for everyday clinical use. Values for the specificity or sensitivity of olfactory tests that would be applicable to routine clinical situations are difficult to derive from the published research. After a systematic review of the available evidence in 2007, experts from the *M*ayo Clinic *E*vidence Based Clinical Practice, *R*esearch, *I*nformatics, and *T*raining (MERIT) Center concluded that "The diagnostic accuracy of olfactory testing for differentiating IPD from other disorders is insufficient to justify its routine clinical use", and that the "available evidence is derived from small samples and studies of questionable validity" [89]. To our knowledge, no data indicating otherwise have been published more recently. In certain clinical situations, olfactory testing might be useful to alter the pretest probability of a diagnosis of PD or one of its differential diagnoses.

Research studies on olfactory dysfunction have provided important insights into the pathogenesis of PD. The early occurrence of olfactory dysfunction and pathology in PD may suggest a pathogenesis related to virus or neurotoxin inhalation. Assessment of olfaction confirms the relative independence of the two main disease processes, nigrostriatal dopamine depletion on

the one hand and a more diffuse, widespread CNS dysfunction on the other hand. In a recently published study, olfactory testing, brain 6-[18F]fluorodopa PET scanning and brain MRI as well as myocardial 6-[18F]fluorodopamine PET scanning were performed in 23 PD, 8 PAF, and 20 MSA patients [30]. Results showed that the extent of olfactory dysfunction and of cardiac sympathetic denervation correlated in an individual patient. However, olfactory dysfunction did not correlate with the striatal dopamine deficiency [30]. This may mean that olfactory dysfunction is an indicator of Lewy pathology, rather than of dopamine deficiency in the striatum. The finding is in agreement with results from the studies of olfaction in familial PD in that olfactory dysfunction is found in carriers of *SNCA* and *LRRK2* mutations, usually associated with Lewy pathology, but not in carriers of most recessive mutations (*Parkin*, *DJ1*), who in general do not develop Lewy pathology. Furthermore, other synucleinopathies (LBD, PAF, and to a lesser degree MSA) are associated with olfactory dysfunction, but tauopathies such as PSP and CBD have normal or only slightly impaired olfaction [38, 39, 46].

Although a number of genes responsible for familial PD have been identified, about 80–90 % of cases of hereditary PD remain unexplained in most populations studied. In order to increase the number of affected individuals in a pedigree, and thus the power of genetic studies searching for new PD-related genes, olfactory testing has been used to determine if otherwise asymptomatic individuals can be regarded as presymptomatic for the purpose of such analyses [90]. However, this approach has so far been of limited value.

The major task lying ahead of the movement disorders research community is to find a neuroprotective treatment that clearly slows down or halts disease progression, or at the very least postpones the age of onset of clinical disease manifestations. When such agents become available, clinical studies on their neuroprotective effect would be much more powerful if performed in a cohort at higher risk of developing PD than the general population. Olfactory testing alone, or in combination with other possible biomarkers [91], may be useful to define such a group.

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Pain in Parkinson's Disease: Pathophysiology, Classification, and Clinical Approach

24

Christopher Hess and Blair Ford

Abstract

Pain is a frequent yet underrecognized symptom of Parkinson's disease (PD). Although routine clinical neurological examination generally does not reveal any abnormality of sensation in persons with PD, objective abnormalities of proprioceptive function and sensorimotor integration have been demonstrated with sophisticated testing. Painful symptoms pose a considerable diagnostic and therapeutic challenge to the clinician. For diagnostic purposes, it is helpful to classify painful or unpleasant sensory symptoms into one or more of the following five categories: musculoskeletal pain, radicular or neuropathic pain, dystonia-related pain, akathitic discomfort, or primary, central parkinsonian pain. The identification of parkinsonian pain is vitally important for the effective diagnosis and treatment of pain in PD.

Keywords

Sensorimotor integration • Pain • Musculoskeletal • Dystonia • Central pain • Akathisia

Introduction

Pain is an important symptom in Parkinson's disease (PD) that is often overlooked by clinicians due to the obvious motor impairments of the clinical picture. Yet, the presence of painful symptoms is well documented in all of the earliest descriptions of PD (Parkinson 1817; Charcot 1892; Gowers 1888 [1–3]). In recent years, there has been increasing recognition that painful symptoms in patients with PD are common and may have an important impact on quality of life.

Most surveys of painful symptoms in PD describe a prevalence exceeding 40 %. Based on the characteristics of painful symptoms, a clinical framework for diagnosing and categorizing pain in PD has been developed. Recent advances in neurophysiology and neuroanatomy have led to a

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deeper understanding of the neurobiological substrates underlying pain in PD.

Painful Parkinson's Disease

Historical Aspects

Nearly two centuries ago, James Parkinson wrote in his famous monograph that painful symptoms can be an early first sign of the disorder (Parkinson 1817), describing a man who was "very violently afflicted" with hand pain in the arm with tremor. Charcot noted the presence of "disagreeable sensations of a special order" that included not only "a nearly permanent sense of tension and traction in most of the muscles" and "an indefinable uneasiness, which shows itself in a perpetual desire for change of posture" but also "an habitual sensation of excessive heat," often associated with profuse perspiration [4]. Souques, in 1921, postulated the existence of a central pain syndrome in PD caused by "alterations in the connections of the corpus striatum … with the thalamus."

Prevalence of Pain in PD

Due to the motor impairments and complications of PD, it is not surprising that the prevalence of chronic pain in PD patients is higher than in the general population. Estimates of the prevalence of chronic pain in PD vary widely due to differences in study methodology. Recent studies of pain in PD estimate the prevalence of all types of pain to range from 40 to 83 % [6–14], with pain occurring daily in nearly 60 % of patients [12]. In a recent cross-sectional survey of patients referred to a specialist center in Norway, the overall pain prevalence was 83 %. Only 38 % of patients with pain reported nondopaminergic analgesic use for attempted relief, perhaps due to a lack of efficacy of such medications in this population. Approximately 24 % of patients with pain had undergone physiotherapy, compared with 1 % of patients who did not report pain.

Classification of Pain

The presence of pain in a patient with PD poses a considerable diagnostic and therapeutic dilemma to the clinician. The protean presentations and variable characteristics of pain in the PD setting easily can lead to diagnostic confusion and inappropriate treatment. Beginning in 1960, investigators began to classify painful symptoms experienced by patients with PD into diagnostic categories based on the patients' descriptions of their symptoms. Over the next 40 years, from these descriptions together with an appraisal of each patient's clinical features, a classification of pain symptoms was developed with these main categories: pain due to dystonia, pain caused by orthopedic complications of PD, neuritic/radicular/myelopathic pain, and primary or central parkinsonian pain. A fifth category of uncomfortable sensory experience, namely restlessness or akathisia, is often included in the classification. Nearly every survey demonstrates an overall consensus regarding pain prevalence, with differences in the apportionment within each pain category.

In the first of the modern surveys, Sigwald and Solignac [15] studied 203 randomly selected patients with PD and documented the presence of painful symptoms in 108. Symptoms were subdivided into paresthesias and pain symptoms. Painful sensations were classified by body region; the legs were the most frequently involved region, followed by arms, neck, lumbar region, epigastrium, and abdomen. No attempt was made to systematically classify painful symptoms by etiology.

Snider [16] surveyed 100 consecutive patients, 43 of whom experienced chronic pain. Twenty-nine of 43 individuals appeared to experience primary sensory symptoms as part of their PD. The pain typically was described as an intermittent, poorly localized, aching or cramp-like sensation, more likely to affect the proximal portion of a limb and involve the limb with the greatest motor deficit. Eleven patients described burning paresthesias, sometimes aggravated by levodopa. Koller considered all abnormal sensations to be primary sensory symptoms and, as noted previously, documented the presence of sensory symp-

toms in 38 % (19/50) of the patients with PD studied [17]. Patients were further classified as having numbness (12), tingling (8), pain and achiness (6), coldness (6), and burning (1).

The clinical approach to painful symptoms derives from the 1986 survey by Goetz et al. [18], which documented pain directly attributable to PD in 43 (45 %) of 95 subjects. The investigators divided patients' description of pain into five categories: 32 patients (74 %) had pain of muscular origin; 12 (28 %) experienced pain caused by dystonia; 6 (14 %) had joint pain; 6 (14 %) had radicular or neuritic pain; and diffuse "akathitic" pain occurred in 1 patient (2 %). Symptoms suggestive of central or thalamic pain were not described in this series.

More recently, in Sigwald's series of 50 patients with PD experiencing motor fluctuations, only 45 patients had sensory symptoms [19], divided into seven categories: akathisia, tightening sensations, tingling sensations, diffuse pain, restlessness, neuralgic pain, and burning sensation. Diffuse pain was experienced by 54 % of the 50 patients, neuralgic pain by 18 %, and burning sensations by 8 %. The vast majority of sensory symptoms, including those that might be considered painful, appeared during "off" states, but sometimes both diffuse pain and neuralgic pain were experienced during periods of dyskinesia. Musculoskeletal pain (70 %) was the most common type reported, followed by dystonic pain (40 %), radicular-neuropathic (20 %), and central neuropathic (10 %). When asked about the relationship of their pain to PD, patients with pain deemed to be dystonic or central-neuropathic were more likely to associate the pain with their PD, and more likely to experience pain relief with dopaminergic drugs.

All subsequent series have achieved similar estimates of pain prevalence, with confirmation of the diagnostic categories. Considering this background, there is general agreement that painful or unpleasant symptoms in PD can be usefully assigned into one or more of the following five classes (1) musculoskeletal pain, (2) radicular or neuropathic pain, (3) dystonia-related pain, (4) primary (central) parkinsonian pain, and (5) akathitic discomfort. Each of these pain categories will be discussed in detail following a review of the neurobiological substrate of pain in PD.

Abnormal Sensory Processing

Despite the well-documented presence of painful sensations in PD, it has long been observed that pain generally is not accompanied by objective evidence of sensory impairment. Gowers declared that "subjective sensations are frequent" but "cutaneous sensibility is never affected in paralysis agitans". In recent years, however, a considerable body of evidence has established the presence of subtle, but potentially significant, abnormalities of sensory function and sensorimotor integration in PD.

As pain is a complex perceptual experience comprised of sensory, affective, motivational, and cognitive components [20], its systematic study is fraught with confounds and difficulties of pain in both animals and man. However, some progress has been made in identifying the underlying mechanisms and processes that comprise the experience. Using sensitive techniques to study touch pressure and vibration perception on the plantar aspect of the foot, Pratorius et al. [21] demonstrated significantly higher sensory thresholds (at least two times) in patients with PD, compared with controls, and suggested that this abnormality might contribute to impaired balance control. Impaired joint position sense also has been demonstrated in PD, such that individuals with PD have more difficulty than controls in discriminating differences in the static angular position of their elbow joints [22]. Tactile discrimination, studied by testing the ability to differentiate specific shapes, is also diminished in persons with PD [23]. Patients with PD are impaired in their ability to discriminate differences in both location and temporal dispersion of sensory stimuli, as well as simultaneously applied bilateral tactile stimuli [24] and two-point discrimination in the index fingers and periorally [25–27].

Minor abnormalities of unclear significance have been demonstrated in the peripheral conduction pathways in patients with PD. One study

demonstrated a decrease in Meissner corpuscles and epidermal nerve fibers (with evidence of nerve fiber remodeling compared with age- and sex-matched controls [28]. A reduction of amplitude of sural sensory nerve action potential (SNAP) amplitude has been shown in patients with autosomal recessive juvenile parkinsonism (PARK2) [29].

Abnormalities in sensorimotor integration clearly have been delineated in PD. When making slow, active pointing movements, individuals with PD tend to make hypometric movements and undershoot the target when deprived of the ability to watch their moving hand [30]. This abnormality is present with both active and passive arm movement, suggesting the presence of a defect of kinesthesia. Further support for the presence of a deficit in kinesthetic processing in PD is provided by the demonstration that PD patients have impaired ability to accurately move the index finger from one target to another when vision is occluded (after the target location has been shown by passive movement of the finger [31]). Using a testing paradigm in which vibration is applied to the antagonist muscle, investigators have demonstrated that patients with PD display less pronounced vibration-induced undershooting of both wrist and ankle movements than do normal controls [32, 33]. In patients with asymmetric disease, this abnormality (reduced undershooting) was more evident on the more involved side, and tended to be less apparent when patients with motor fluctuations were in the "on" state [33]. These findings were attributed to a disturbance in proprioceptive guidance, likely owing to impaired central processing of proprioceptive input by the basal ganglia. Depressed frontal responsiveness to sensory stimuli, as tested by somatosensory-evoked potentials, also has been demonstrated in PD, further implicating a disturbance in sensorimotor integration [34].

Nociception and Pain Processing in PD

A number of recent studies have examined pain in PD patients using quantitative measurement of subjective pain thresholds [12, 35, 36] or electrophysiologic evaluation of pain pathways [37–40]. Djaldetti et al. [35] examined mechanical and heat pain thresholds in 36 PD patients with and without pain while "off" and 28 age-matched controls. Subjects with response fluctuations also were examined 30 min after levodopa administration. Heat pain thresholds were noted to be lower in PD patients, compared with controls, and in those patients with pain, compared to those without; however, they were not affected by levodopa treatment. Other studies using cold pain thresholds [36, 41] also showed lower thresholds in PD patients in the unmedicated state, compared with controls.

Positron emission tomography (PET) imaging of brain areas activated by cold pain stimuli reveals differences in regional cerebral blood flow (rCBF). During the "off" state, PD patients had a significant increase in pain-induced activation in the right posterior insula, right prefrontal and left anterior cingulate cortices compared with the control group; during the "on" state, this was limited to the right posterior insula. Levodopa significantly reduced activation in the right posterior insula and left anterior cingulate cortex in patients but had no effect on rCBF in controls.

In addition to quantitative measurement of subjective pain, electrodiagnostic techniques useful in pain research have been used to study pain in PD patients. The nociceptive flexion reflex (NFR) is a polysynaptic withdrawal reflex evident in response to painful stimulation of the A-δ and C type pain fibers. Its electrophysiologic representation, the RIII, is commonly measured in the biceps femoris muscle in response to transcutaneous electrical stimulation of the sural nerve [42]. Two studies [37, 38] have used this technique to investigate pain in PD patients. Gerdelat-Mas et al. [37] evaluated 13 patients without pain and 10 control patients in both the "off" state and after levodopa administration. In the "off" state, the stimulus intensity required to induce an RIII reflex was lower in PD patients compared with controls; after levodopa treatment, the RIII threshold was restored to normal.

Mylius et al. [38] utilized a diffuse noxious inhibitory control (DNIC) or heterotopic noxious conditioning stimulation (HNCS) paradigm, in

which a tonic, painful conditioning stimulus is administered distant from the area of interest and activates higher-level pain modulatory mechanisms that decrease the perception of pain from a discrete test-pain stimuli. While present, the DNIC-like effect was not different between groups.

Pain-related evoked potentials that are specific to pain processing pathways can be recorded over the anterior cingulate cortex (ACC) and parietal operculum (SII) after the painful laser stimulation of the skin. In this paradigm, the skin is subjected to laser stimuli that selectively excite A-δ and C fibers, which carry pain signals through the spinothalamic tract to lateral thalamic nuclei and eventually to a number of brain structures, including the ACC and SII, which are thought to produce the recorded potentials [40, 43–45].

Results with laser-evoked potentials (LEP) in PD have been interesting, though somewhat discrepant. Schetatsky et al. [39] examined patients deemed to have central pain both in the "on" and "off" state and healthy controls. They found higher LEP amplitudes in patients with central pain compared to controls and, similar to the prior studies mentioned, lower pain thresholds in PD patients. This effect was attenuated by levodopa treatment. Tinazzi et al. published a series of papers [40, 44, 46] examining LEP in PD patients and reported somewhat different findings. The first of these [46] demonstrated a decrease in LEP in PD patients without pain compared with control subjects; the decrease in LEP was not changed by levodopa treatment. The second study [44] included PD patients not yet being treated with dopaminergic agents, and found that, although treated patients continued to have lower LEP amplitudes, in untreated patients this effect was confined to the side predominantly affected by motor symptoms. In the most recent study, which included patients with musculoskeletal shoulder pain [40], 11 PD patients with shoulder pain ipsilateral to their hemiparkinsonism and 12 pain-free PD patients were examined in the "off" state, as well as 11 healthy controls. Both groups of PD patients had decreased LEP amplitudes, compared with control subjects, and rated the laser stimuli as more painful. In PD patients with pain, stimulation of the affected side resulted in reduced LEP amplitudes compared with both the nonpainful shoulder and with pain-free PD patients, but the stimulation of the nonpainful shoulder did not reduce LEP amplitudes, compared with pain-free patients or controls. Neither LEP amplitude nor stimuli pain rating was correlated with baseline chronic pain severity.

In consideration of the objective studies published to date, a number of observations and limitations become evident. Most studies found a decrease in temperature pain thresholds in PD patients, compared with controls, supporting the notion of increased pain perception in PD patients. The abolishment or attenuation of differences, initially noted in some studies in the "off" state, after levodopa treatment suggests dopaminergic modulation in the pathogenesis of pain in PD patients [37, 39, 41]. The NFR studies further support the presence of increased nociception in PD patients, with a smaller intensity required to induce an RIII reflex in PD patients, suggesting that the abnormal pain processing occurring in PD patients is occurring at or modulating nociception at the spinal cord level [38]. The changes in pain-induced activation of structures (such as ACC and SII) of the medial pain system demonstrated with PET scanning, however, suggest that modulation may be occurring at a higher level. Though intriguing, the abnormalities in LEP amplitude that have been reported are difficult to localize and interpret, since pain pathways become complex and partially converge with other pathways at the thalamocortical level [45]. The decrease in pain thresholds, combined with a decreased LEP amplitude (found in the majority of LEP studies), could be explained by alternate pathway recruitment (such as medial pain system pathways in the presence of disturbed lateral pain system transmission) producing a hyperalgesic response [45], or the LEP itself could represent inhibition of pain withdrawal responses [40] or could be secondary to a complex or inhibitory pain circuit [46]. Both increased and decreased LEP have been shown in chronic pain syndromes, with most diseases showing the decreased LEP amplitudes seen in the majority of PD pain studies [45].

Neuroanatomical Substrate for Pain in PD

Most types of pain experienced by patients with PD are attributed to the motor complications of the disorder. Some patients experience painful symptoms that seem to be part of the underlying disease itself, and may represent a fluctuating, dopamine-dependent symptom that is attended by affective and autonomic components. The pathophysiologic basis of the painful nonmotor fluctuations has not yet been elucidated, but a defect in central pain processing in the catecholamine systems of the brainstem and basal ganglia is postulated.

In experimental models, neurons within multiple nuclei in the basal ganglia have been shown to respond to mechanical stimulation with large, sometimes bilateral, receptive fields, with some neurons responding exclusively or differentially to noxious stimuli. Dense connections from SII and area 7b have been demonstrated, as well as projections from areas such as the AC, amygdala, and branches of the spino-hypothalamic tract [47, 48]. Failure of abnormal sensory circuits or gating of nociceptive information involving nuclei within the basal ganglia could possibly give rise to hyperalgesia in PD patients [48, 49]. The fact that 6-hydroxydopamine lesions in the striatum or ventral tegmental area decrease the latencies of nociceptive reflexes in rats suggests that the dopaminergic system has a role in modulating nociceptive information in the striatum and limbic system [50]. Given the role of dopamine in motor fluctuations, dysfunctional dopaminergic sensory processing in the basal ganglia could underlie the painful fluctuations experienced by some patients with PD.

Several anatomically defined pain substrates potentially relevant to PD lie outside the basal ganglia. Recent neuropathologic studies have identified aggregations of intraneuronal inclusions of alpha-synuclein associated with PD in lamina I of the dorsal spinal cord, an important relay of primary nociceptive afferents from the periphery [51]. It is possible that damage to spinal lamina I neurons early in the pain pathway gives rise to alterations in pain processing in PD patients, either through altered nociceptive transmission or impaired descending inhibition.

The pain pathways of the brainstem are divided into a *lateral neospinothalamic* system, involved with the discriminative aspects of nociception and projecting primarily to SI and SII, and a *medial paleospinothalamic system*, which underlies more of the motivational, affective, cognitive, and autonomic responses to pain, and projects from the intralaminar and medial thalamic nuclei to diverse areas of the brain, including the locus coeruleus and reticular formation, hypothalamus, ACC, SII, insula, and amygdala [20, 52].

In contrast to the structures identified in the lateral pathway, many of the nuclei thought to play a role in medial pain system processing, as well as descending modulation of nociception at the spinal cord level, show the pathologic changes of PD as well. Thus, abnormal processing of the medial pain system or higher levels of descending pain modulation may also underlie primary pain in PD [52].

Specific Pain Syndromes

In recent decades, descriptions of painful sensations experienced by patients with PD have led to a clinical framework for diagnosis and treatment. As a general clinical approach, painful symptoms should be considered in relation to symptoms of tremor, rigidity, akinesia, and dystonia that occur in PD. It is important to note the relationship between painful symptoms and the timing of antiparkinson medications. Painful symptoms in PD are more prominent during "off" motor fluctuations and often represent a consequence of increased rigidity and immobility. Pain caused by dystonia can be diagnosed when there is visible twisting, cramping, or posturing of the painful extremity or body part. Dystonia that develops during the "off" state may be painful, but medication-induced dystonia, occurring while the patient is "on" or during transitions between states, may be equally uncomfortable. Deep brain stimulation may also induce painful dystonic muscle spasms, attributed to the spread of discharge to the corticospinal tract. A careful appraisal of pos-

sible musculoskeletal or rheumatologic pain mechanisms is important in patients with PD. Akathisia, although not painful, can be intensely unpleasant and represents an uncommon but distinctive symptom in PD. Primary parkinsonian pain, unrelated to a disturbance in motor function, is presumed to be of central origin and may be inferred partly by the nature of its clinical features and partly through exclusion of other causes. In the sections that follow, categories of painful symptoms in PD are described in further detail.

Musculoskeletal Pain

Mechanisms of Musculoskeletal Pain

In individuals with PD, pain of musculoskeletal origin appears to be related to rigidity and bradykinesia. Deformities of posture, stiffness of limb movements and gait, and awkward mechanics for body motion and tasks also may place unusual stresses on the musculoskeletal system, and muscle cramps and joint-based pain may further fuel the discomfort. Aching, cramping, and joint pains in patients with PD presumably result from diminished mobility of affected limbs and joints. Muscle cramps and tightness typically involve the neck, arms, paraspinal, or calf muscles; joint pain most frequently originates in shoulders, hips, knees, and ankles [18]. Musculoskeletal discomfort in PD tends to be most evident during periods of increased parkinsonism [18].

Shoulder Stiffness

Gowers noted "aching pains in the limbs" to be an occasional early clinical feature of PD [53]. One of the most common musculoskeletal afflictions in PD is shoulder stiffness, and a stiff shoulder may be the first sign of PD [54]. The prevalence of the "frozen shoulder," also called periarthritis or adhesive capsulitis, is higher in patients with PD than in age-matched subjects without PD [55]. Among 150 consecutive patients with PD followed in a movement disorders clinic, 65 (43 %) related a history of some type of shoulder disturbance, including shoulder trauma preceding the development of parkinsonism [55].

Spinal Deformities

Spinal deformities are well described in PD and may be responsible for pain. The typical posture of the individual with PD is stooped forward with the neck held in flexion. Some patients develop a fixed postural deformity; others have an apparent truncal or neck dystonia that varies with posture and activity. Scoliosis occurs more often in PD than in the elderly general population [56, 57]. In one study, scoliosis was present in 62 of 103 (60 %) patients with PD; the side of the convexity was unrelated to that of maximal deficit [58].

In extreme cases, the spinal deformity in PD patients is severe enough to merit the label "camptocormia" or "bent spine" [59]. In some individuals with camptocormia, the thoracolumbar spinal curvature forces the upper body into a horizontal position, impairing ambulation; a severely flexed spine may preclude eye contact in some patients due to diminished upgaze. A hallmark of camptocormia is that the deformity is not fixed; it completely disappears when the individual assumes the recumbent position, in contrast to kyphosis of orthopedic origin, such as ankylosing spondylitis or osteoporosis. Due to its dynamic dependence on upright posture, camptocormia is considered by some form of truncal dystonia. Levodopa has been reported both to accentuate and ameliorate the condition [59]. In contrast, a recent report described camptocormic posture in a patient as a result of focal myositis of the paraspinal muscles [60].

There does not appear to be a specific or effective treatment for camptocormia. With advancing disease, the flexion deformity only worsens, despite treatment with antiparkinson agents. Insertion of spinal rods may straighten the curvature, but anecdotal evidence suggests that this often fails owing to hardware disruption or migration or the development of infection. Deep-brain stimulation does not seem to ameliorate severe truncal flexion of PD.

Rheumatologic and Orthopedic Abnormalities

A wide array of rheumatologic and orthopedic symptoms may be encountered in patients with PD, including temporomandibular joint disease,

bursitis, arthritis, Baker's cyst, plantar fasciitis, stress fractures, cervical spondylosis, spinal stenosis, sciatica, ankylosing spondylitis, contractures, and others. The incidence of these conditions in PD has not been studied, and it is not possible to conclude a statistical or causal association with PD because rheumatologic conditions are common in the PD age range. In women, the combination of osteoporosis and PD, especially when postural instability is present, is particularly dangerous.

Painful Contractures

Painful contractures, the consequence of immobility, are yet another important source of pain in PD. Contractures result from a pathological shortening of muscle fibers, tendons, or ligaments and may involve the ankles, knees, hips, fingers, hands, wrists, elbows, or neck. Contractures can result from the characteristic flexed attitude of the disease and represent a complication of immobility. They may form surprisingly rapidly, sometimes within a matter of weeks.

Hand and foot deformities have been described in persons with PD, both by the neurological masters of the nineteenth century [53, 61] and more recently [62–63]. The clenched fist in parkinsonism may begin as a dystonic posture, but it leads to fixed contractures, usually within several months of sustained hand and finger flexion. The clenched fist is often painful and leads to loss of hand function, poor hand hygiene, and palmar infections [63].

Diagnosis of Musculoskeletal Pain

When patients with PD develop what appears to be musculoskeletal pain, careful assessment of the muscles and tendons, bones, and joints is necessary. Painful symptoms must be considered in relation to parkinsonian signs, range of motion, posture, activity, and antiparkinson medication. It should be possible to arrive at an accurate diagnosis on the basis of the history and exam, but ancillary testing, including serological tests, X-rays, bone scans, ultrasound, or rheumatologic or orthopedic consultation, are occasionally needed. The presence of joint deformities or a concurrent rheumatologic condition should be obvious. Differentiating between parkinsonian rigidity, painful cramping, contracture, dystonia, and a fixed skeletal deformity can all be done on clinical examination.

Treatment of Musculoskeletal Pain

Treatment of musculoskeletal pain in PD depends on its cause. If parkinsonian rigidity is the primary cause, dopaminergic therapy, physical therapy, and an exercise program are indicated. The goal of treatment is to restore mobility. Once this is achieved, an exercise program can be invaluable in maintaining mobility and preventing further musculoskeletal problems. Nonsteroidal anti-inflammatory drugs (NSAIDs) and analgesics are helpful for rheumatologic and orthopedic conditions in tandem with physical therapy. Passive range of motion exercises are important to prevent contractures in patients with limited mobility, but once formed, a contracture generally requires surgical intervention.

Radicular and Neuritic Pain

Mechanisms of Radicular and Neuritic Pain

Pain and discomfort that is well localized to the territory of a nerve or nerve root is described as radicular or neuritic pain and accounted for 14 % of the pain syndromes experienced by patients with PD in one survey [18]. However, most case reports and surveys do not permit detailed evaluation of this type of pain because the descriptions do not provide adequate clinical information or neuroimaging data to confirm the pathological process. Thus, the true incidence of radicular and neuritic pain in PD is uncertain. One study [66] examining back pain in PD patients, compared with age-matched controls with stroke or brain tumor, found the incidence of back pain in the week prior to questioning to be 74 % in PD patients and 27 % in controls, with radicular symptoms in 38 % of PD patients, compared with 16 % of controls.

It is unclear whether PD itself actually fosters the development of neuritic or radicular pain. Postural deformities of PD might conceivably

predispose to the development of compressive radiculopathy, sciatica, or myelopathy. Immobility is certainly a risk factor for the evolution of compressive local neuropathy. A traumatic radial nerve palsy was described in one report [67]. Peak-effect dyskinesias may exacerbate radicular and neuritic pain [18, 68]. Both tremor and dyskinesia involving the wrist possibly may promote development of carpal tunnel syndrome. Trigeminal neuralgia has been described in PD [69].

Diagnosis and Treatment of Radicular and Neuritic Pain

Evaluation and treatment of pain in this category begins with careful clinical examination, supplemented (if needed) by electrodiagnostic studies and neuroimaging. Radicular pain often can be treated with a judicious mobility program, NSAIDs, and pain medication. In one interesting case report describing two individuals whose sciatica was exacerbated by dyskinesia, morphine treatment not only reduced the sciatica pain but also suppressed the dyskinesia [68]. In the presence of refractory pain, or a severe or worsening neurological deficit that coincides with an abnormality on radiological studies, decompressive surgery may be indicated. For a compressive peripheral neuropathy, avoidance of aggravating postures is important, sometimes with the aid of splints or braces. Decompressive surgery may also be required when conservative measures do not suffice.

Dystonic Pain

Characterization of Dystonia

Dystonia is characterized by sustained and forceful twisting movement that leads to abnormal postures and deformities. Dystonic spasms are among the most painful symptoms that a patient with PD may experience. Spasms may be spontaneous or triggered by movement or activity; they may be brief (lasting minutes), prolonged (lasting hours), or even continuous. Dystonia in PD can affect any limb, as well as the trunk, neck, face, tongue, jaw, pharynx, and vocal cords, usually developing in sites most severely affected by parkinsonism. Dystonia may precede the development of parkinsonism, develop as a late feature, appear after the onset of dopaminergic therapy, follow stereotactic neurosurgery, or be induced by deep-brain stimulation. The pattern of dystonia in PD may be classified as focal, cranial, segmental, or generalized. Dystonia developing during "off" periods most often involves the feet; drug-induced dystonia has a predilection for the neck, trunk, and cranial distribution [70].

Evaluation of painful dystonia requires especially careful consideration of its relationship to dopaminergic medication. Dystonia may occur as an early morning manifestation of dopaminergic deficiency or as a wearing-off phenomenon later in the day or in the middle of the night. In some patients, dystonia is a painful beginning-of-dose or end-of-dose phenomenon; in others, it develops at the peak of response to a dose of dopaminergic medication. The classic flowing, writhing, choreoathetotic dyskinesias induced by dopaminergic medication are not sustained or painful and generally are not considered to be dystonic. When the timing of the dystonia is uncertain, it may be helpful to observe the patient in the office for several hours to appreciate the relationship of dystonia to the medication dose cycle. Classifying dystonia in relation to the levodopa-dosing schedule provides a useful and rational framework for evaluating and treating painful dystonia in PD [71, 72].

Early Morning Foot Dystonia

The most thoroughly studied presentation of dystonia in PD is early morning foot dystonia, which develops in approximately 16 % of patients with PD and is defined by foot or toe cramping and posturing [73]. Every variety of foot posture is possible: plantar flexion, dorsiflexion, foot inversion, curling of the toes, or forced extension of the great toe ("striatal toe"). Foot dystonia is often accompanied by stiffness of the calf muscles. It has been argued that early morning dystonia is a complication of long-term levodopa therapy because it takes place usually in patients

with longer disease duration and in individuals in whom dyskinesia is present [73–77]. In a study of 42 patients with PD and foot dystonia, 41 (97.5 %) individuals experienced early morning foot dystonia before the first levodopa dose with subsequent milder attacks during the late evening or during the night, suggesting that dystonia is intrinsic to the parkinsonism in most cases, representing a wearing-off phenomenon [78]. Moreover, painful foot dystonia in PD was described long before the advent of levodopa [79] and may precede the other manifestations of the disorder [80].

Treatment of Dystonia

Early morning dystonia typically is relieved by activity, or it resolves shortly following the first dose of dopaminergic medication during the day. In some patients, early morning dystonia is so severe that subcutaneous injections of apomorphine, with its onset of action within minutes, can be justified [81]. When dystonia occurs as a wearing-off effect during the day, appropriate treatment is analogous to the treatment of wearing-off motor fluctuations and is aimed at reducing the duration of the "off" period. More frequent levodopa dosing, use of controlled-release levodopa preparations, levodopa supplementation with a catechol-O-methyltransferase inhibitor, use of dopamine agonists as adjunctive or monotherapy, or use of apomorphine as a "rescue" agent all can be effective. Although dopaminergic drugs usually are first-line therapy for off-period dystonia in PD, anticholinergic drugs [74, 78], baclofen [82], and lithium [83] have also been used successfully. In patients with levodopa-induced dystonia, treatment typically consists of reducing dopaminergic stimulation by decreasing levodopa dosage or by reducing its absorption; substituting a less potent agonist also may be effective.

Injections of botulinum toxin may be beneficial treatment for focal dystonia in PD. In an open-label study of 30 patients with painful foot dystonia, where dystonia was severely or completely disabling in 23 (77 %), injections of botulinum toxin A produced dramatic relief of pain and disability [84]. Injections were accomplished under electromyographic guidance and tailored to the specific appearance of the dystonic foot. The median dosage was 70 U (range of 4 and 100 U).

As noted earlier, the clenched fist seen in patients with PD may begin as a dystonic posture, but it can evolve into a sustained contracture relatively quickly. Treatment with intramuscular botulinum toxin injections, given to the flexor digitorum superficialis or lumbricals, can relieve the dystonic component of the process, sometimes for 4 months [63]. Active muscular contractions, as documented by electromyography, are associated with good result from botulinum toxin injections, whereas an absence of electromyographic activity, denoting contractures, predicts treatment failure [63]. The flexed neck posture that occurs in PD also responds poorly to botulinum toxin injections.

Neurosurgical techniques may decrease painful dystonia associated with PD. Painful off-period dystonia, present in 20 patients who underwent bilateral subthalamic nucleus stimulation, was completely alleviated in 12 individuals and considerably improved in 4 [85]. In a recent study that examined the effect of globus pallidus stimulation on parkinsonian pain [86], all types of off-period painful sensations were markedly reduced: dystonic pain, muscle cramping, dysesthesias, and "global pain," as measured using a rating scale. Benefit developed quickly after surgery and remained stable through the 1-year follow-up interval. Patients with unilateral globus pallidus stimulation experienced pain reduction primarily on the contralateral body side, whereas bilateral stimulation produced bilateral reduction in pain.

Deep-brain stimulation in the subthalamic nucleus or globus pallidus can also induce acute painful, dystonic spasms, possibly owing to the spread of current to the internal capsule. The necessary intervention in this situation is a change in stimulator parameters, usually a reduction in voltage or pulse width, which promptly reverses the muscle spasms. Intrathecal baclofen, effective for spasticity of spinal or cerebral origin, has shown little effect on the dystonia associated with parkinsonism [87].

Primary (Central) Pain

Characterization of Central Pain

Perhaps the most striking of the pain syndromes in patients with PD are those of central origin. Broadly defined, central pain is defined as pain produced directly by a lesion or abnormal function within the central nervous system. Primary (central) parkinsonian pain was outlined in the seminal description of Souques in 1921 [5], in which he described 17 patients with PD or parkinsonism, some of whom were afflicted with pain syndromes that he believed were intrinsic to PD. Souques was aware of the recently described thalamic pain syndrome of Dejerine [88] and noted similar characteristics in his patients with PD: bizarre unexplained sensations of stabbing, burning, scalding, and formication—all descriptions associated with "neuropathic" pain originating in the central or peripheral nervous systems. Souques noted that the presumed central pain syndromes in his patients typically afflicted the side of the body most affected by parkinsonism and could precede, even by years, the motor manifestations of the disorder. Using Dejerine's conceptual framework [88], Souques postulated a central origin of pain in PD caused by a disturbance in signaling between the corpus striatum and thalamus.

The argument for a separate central pain syndrome in PD finds support in several unusual case descriptions. In contrast to musculoskeletal conditions, which tend to affect the limbs, muscles, and joints most afflicted with parkinsonism, reports exist of unusual pain syndromes involving the face, head, epigastrium, abdomen, pelvis, rectum, and genitalia [15, 16, 72, 89], all areas in which painful dystonia or musculoskeletal conditions are unlikely or implausible. Sigwald and Solignac [15] described patients with pharyngeal, epigastric, and abdominal pain. In a modern series of eight patients with parkinsonism (seven with PD; one with atypical parkinsonism) and oral or genital pain [89], oral pain affected the gums, teeth, tongue, inner cheek, face, and jaw. These oral pain syndromes, resembling the idiopathic "burning mouth syndrome" [90], were described as burning, pulsating sensations, often strikingly lateralized within the oral cavity. The pain tended to correlate with "off" periods, but it was not necessarily abolished by dopaminergic therapy. Genital pain occurred in three of the eight individuals—all women—and consisted of burning, numbness, or vibrating sensations. In all patients, the pain had a relentless, obsessional, distressing quality that overshadowed other parkinsonian symptoms [89].

Consistent with its presumed origin within the central nervous system, peripheral nerve blockade does not abolish central pain in PD, as illustrated by a patient whose oral pain was unaffected by a complete dental nerve block [89]. In a similar vein, Sage et al. describe a patient with parkinsonism, dystonia, and severe leg pains, in whom epidural anesthesia with chloroprocaine sufficient to produce complete sympathetic, sensory, and motor blockade, relieved the dystonia but not all elements of the patient's pain, suggesting the presence of a central component to the pain, possibly from deafferentation [91].

Classic central pain is postulated to involve a lesion of the thalamus, but as described above, primary parkinsonian pain may be the consequence of an abnormality of nociceptive processing within the basal ganglia and its connections, in the spinal cord itself or its descending modulatory pathways, or in the medial pain pathway.

Treatment of Primary (Central) Pain

Treatment of presumed central pain in PD is challenging, especially if dopaminergic agents, the first-line therapy for this disabling problem, are not effective. Conventional analgesics, opiates, tricyclics, and atypical neuroleptics (e.g., clozapine) may be helpful [89]. In one report of a patient with intractable, recurrent, and severe painful fluttering sensations in her left-thoracic region, subcutaneous injections of apomorphine provided complete relief after all other classes of medication—dopaminergic, benzodiazepines, tricyclic antidepressants, opiates, baclofen, clozapine, and intercostal nerve blocks had failed [92].

Particularly due to the observation that many patients with PD pain have worse symptoms in the "off" state compared to the "on" state, intrac-

table primary PD pain has been used as an indication for subthalamic nucleus deep brain stimulation (STN-DBS) [93, 94]. One patient with severe pain during "off" periods thought to be central in origin and refractory to apomorphine, underwent STN-DBS and experienced a drastic reduction in pain during the day in addition to decreased motor fluctuations [93]. Near resolution of severe facial pain with allodynia after bilateral STN-DBS placement has also been described [94]. A 2008 study by Kim et al. [95] inquired about pain symptoms (both central and secondary to motor symptoms) both before and after STN-DBS placement for motor complications of PD. They found that 87 % of those reporting pain preoperatively noted an improvement in painful symptoms at 3-month postsurgery, with pain deemed to be dystonic (100 %) and primary (92 %) most likely to respond to surgery compared with other pain types (14–61 %).

With the increased application of deep-brain stimulation in advanced PD, it is possible that unusual painful or uncomfortable iatrogenic sensations of central origin may be reported, since stimulators can induce a variety of unpleasant sensations, such as the jolting dysesthesias that transiently occur during stimulator programming sessions, which are reported in up to 70 % of patients.

Akathisia

Characteristics of Restlessness or Akathisia

Restlessness is a frequent and potentially disabling complaint indicated by individuals with PD. Parkinsonian akathisia is characterized by subjective inner restlessness, producing an intolerance of remaining still and manifesting as a constant need to move or change position. In evaluating a complaint of restlessness, it is important to establish that the need to move is not caused by other factors, such as the primary symptoms of parkinsonism, other somatic complaints or urges, dyskinesia, anxiety, depression, or claustrophobia.

The definition of pure akathisia is meant to exclude additional neuropathic symptoms, but patients with akathisia often describe crawling sensations, burning, or tingling [96, 97]. Parkinsonian akathisia can be severe; patients may be unable to sit, drive a car, eat at a table, or attend social gatherings. Some patients remain in constant motion. In extreme cases, parkinsonian akathisia has driven individuals to suicide [1]. In about half of the reported cases of parkinsonian akathisia, symptoms have been noted to fluctuate with levodopa-dosing schedules and to improve with adjustment of dopaminergic medication [96].

Prevalence of Akathisia

Like many pain syndromes that occur in PD, restlessness is probably underrecognized and, if specifically inquired about, present more frequently than expected. Gowers provided an early description of this symptom in PD in his 1888 textbook [53]. In one survey of 100 patients with PD, 68 (68 %) complained of a periodic need to move [97]. In 26 of these individuals (26 %), restlessness represented genuine parkinsonian akathisia. Comella et al. studied 56 patients with PD; 25 (45 %) acknowledged the presence of akathitic movements [96]. The movements usually involved the legs and correlated with patients' own subjective descriptions of inner restlessness.

Akathisia and Dopamine

The appearance of parkinsonian akathisia as a wearing-off phenomenon and its levodopa responsiveness suggest that akathisia is related to impaired dopaminergic neurotransmission. The fact that two other major causes of the syndrome—postencephalitic parkinsonism and neuroleptic-induced akathisia—are also characterized by dopaminergic dysfunction strengthens the association. Akathisia is suggested to result from dopaminergic deficiency involving the mesocortical pathway, which originates in the ventral tegmental area and is known to be affected in PD [98]. Some indirect support for this is provided by the observation that clozapine, which has a

high affinity for D4 receptors and preferentially affects the mesocortical and mesolimbic dopaminergic systems, can be remarkably effective in treating akathisia [99–101].

Akathisia and Restless Legs Syndrome

Restlessness also is a core element of the restless legs syndrome (RLS), a disorder of unknown cause in which patients experience an intense and irresistible urge to move the legs, accompanied by sensory complaints and motor restlessness. Characteristically, the symptoms are worse at rest, relieved with motion, and increase in severity in the evening or at night. The possibility that RLS can be dramatically relieved by levodopa or dopamine agonists implies it is a disorder of altered dopaminergic transmission [102]. The relationship of RLS to, and its distinction from, akathisia in patients with PD is not always clear.

Headache

Headache is an important symptom that may occur in PD, but its relationship to the disease is uncertain. It does not fit into the pain categories already described, but instead represents a painful symptom that often requires its own specific evaluation and treatment. In a survey of 71 patients with PD, 25 individuals (35 %) acknowledged headache [103]. Headaches were generally located in the nuchal region, but they did not correlate with a clinical assessment of nuchal rigidity. Headaches ranged from dull aching discomfort to sharp squeezing or pulsatile pain. In a subsequent report, a specific early morning headache was described in three individuals, relieved within 2 h of the first levodopa dose [104]. In another report, patients who had PD with headache scored significantly higher on measures of depression and anxiety than those without headache [105]. Medication, especially the dopaminergic ergot alkaloids, pergolide and bromocriptine, may also be a source of headache in patients with PD. A severe or unusual headache accompanied by neurological signs can never be attributed to PD and requires thorough neurological evaluation, usually with neuroimaging.

Depression and Pain

Depression may alter the interpretation of painful symptoms in PD. The few studies that have directly addressed the issue showed that depression is a major influence upon the perception of pain in PD patients, but they have been inconsistent [13, 106, 107]. The most recent study [108] looking specifically at the relationship between pain and depression in PD found that patients with pain were more likely to have major depression after controlling for other variables. Although there is little systematic data to guide the clinician, it is important for any pain assessment in an individual with PD to consider the potential contributing role of depression, which itself may require specific treatment. In addition, there is some specific evidence for duloxetine in comorbid depression and primary PD pain [109].

Conclusion

Pain is not a cardinal feature of PD, but it is frequently an important complication of the disease that has a substantial impact on quality of life. The incidence of pain in PD is much higher than in the general population, and pain in PD constitutes a silent disability of epidemic proportion. Approximately 40–50 % of patients with PD experience pain that is often chronic; in a minority of these individuals, the problem is so distressing that it overshadows the motor symptoms of the disease. The main causes of pain in PD are related to the obvious mechanical and dystonic complications of the disease, but the neurobiology of PD also involves disturbances of sensory processing that further exacerbate the problem of pain. Most parkinsonism-related pain can be assigned to one or more of five clinical categories: musculoskeletal pain, neuritic or radicular pain, dystonia-associated pain, primary or central pain, and akathitic discomfort. The classification of pain provides a framework for the evaluation of pain and its treatment.

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Vestibular Dysfunction

25

Charles G. Maitland

Abstract

Vestibular dysfunction unquestionably occurs in a significant percentage of individuals with Parkinson's disease (PD). Potentially, vestibular-derived instability may develop as part of the disease process, per se, but more likely it is the consequence of decline in vestibular function due to aging, comorbid disorders, and/or the act of falling. Failure to identify dysfunction in this critical sensory system may contribute to further morbidity from falling, produce misleading findings on clinical examination, and potentially lead to mis-scoring on standardized tests of parkinsonian function, such as the Unified Parkinson's Disease Rating Scale (UPDRS).

Keywords

Unified Parkinson's disease rating scale (UPDRS) • Vestibular dysfunction • Vestibulospinal reflexes • Quantitative vestibular testing • Vestibulo-ocular reflex

Introduction

Vestibular dysfunction unquestionably occurs in a significant percentage of individuals with Parkinson's disease (PD). Potentially, vestibular-derived instability may develop as part of the disease process, per se, but more likely it is the consequence of decline in vestibular function due to aging, comorbid disorders, and/or the act of falling. Failure to identify dysfunction in this critical sensory system may contribute to further morbidity from falling, produce misleading findings on clinical examination, and potentially lead to mis-scoring on standardized tests of parkinsonian function, such as the Unified Parkinson's Disease Rating Scale (UPDRS).

Primarily, the vestibular system interacts with the basal ganglia indirectly via its input into the cerebellum and thalamus, then through polysynaptic pathways arriving at the sensory integration cerebral cortex, which then feeds forward into the basal ganglia. This complex system integrates sensory information, including vestibular, to provide a continuous flow of information about head

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movement and position of the head in space with consequent maintenance of balance and postural control during daily activity. Detection of head position and motion interacting with somatic (endocentric) and visual (retinotopic) information produces coordinates that result in an internal representation of three-dimensional space. In addition to responding to signals representing orientation of movements of the head as well as tilt relative to gravity, the vestibular system contributes by stabilizing foveal images during head movement. These functions are critical for coordination of motor responses. In normal health, inner ear signaling works efficiently and quickly over short latencies. However, compared with other sensory systems that provide external feedback clues, the vestibular system maintains a sense of balance that is accomplished largely subconsciously.

Anatomy

The vestibulospinal reflexes serve to stabilize the head and to control erect stance relative to gravity under both static and dynamic conditions by projection to the spinal cord neurons subserving antigravity muscles, specifically extensors of neck, trunk, and extremities. Under physiologic conditions, rapid vestibulospinal reflexes contribute little to postural stabilization, which is generally accounted for by proprioceptive-elicited reflex-like motor patterns [1]. On the other hand, continuous low displacement of the body strongly relies on vestibular input. In the vestibular nuclear complex, neurons in the lateral vestibular nucleus forming the lateral reticular spinal tract respond to changes in acceleration forces and project somatotopically to spinal cord at all levels to regulate extensor motor tone. Axons emanating from neurons of medial and inferior nuclei forming the medial vestibulospinal tract form predominantly an outflow pathway through which reflex head movements are controlled; others separately project to the flocculonodular lobe and uvula of the cerebellum, which in turn has abundant feedback to the vestibular nuclei. All nuclei produce secondary fibers that travel within the medial longitudinal fasciculus, synapsing with motor nuclei controlling oculomotor function and axial neck musculature [1, 2].

Vestibular projections to higher order neurons appear complex and not as clearly defined. Liedgren et al., using field potential recordings following peripheral electrical nerve stimulation, found vestibular representation both in thalamus and striatum [3]. Vestibular fields were found in the suprathalamic portion of the nucleus caudatus and dorsal medially in the putamen. Shiroyama et al. reported projections of vestibular nuclei to both thalamus and striatum in a leucoagglutinin study in rat [4]. Bottini et al. utilized positron emission tomography (PET) to measure changes in regional cerebral blood flow following caloric stimulation in an effort to identify human central vestibular projections. The temporoparietal cortex, insula, anterior cingulate cortex, and the putamen appear to be recipients of cerebral projections [5]. Their findings were consistent with the observations of Brandt et al. in humans with altered perception of verticality suggesting static otolithic vestibular dysfunction [6]. Bottini et al. further noted that the vestibular system seemed to project to a number of different brain areas coinciding with those believed to form a distributive network that serves as a representation and exploration of space [7]. This network theory matches vestibular input with visual and proprioceptive signals to provide a three-dimensional representation of orientation in movement and position of body in space. The role of striatal projections within the system likely represents intentional aspects of movement within that space [8].

The existence of a so-called vestibular cortex remains uncertain. Limitations using current imaging techniques make the study of this hierarchical issue difficult, since neither PET scans nor functional magnetic resonance imaging (fMRI) has sufficient temporal or spatial resolution to resolve the issue. Several distinct and separate areas in parietal and temporal cortices receive vestibular afferents, such as areas 2V, vestibular area 3A, parietal insular vestibular cortex (PIVC), and area [7] in primate studies [9]. Brandt and Dieterich [10] presented evidence to suggest that the parietal insular cortex is the human homolog

of the PIVC area in primates. Their conclusions were based on lesional studies demonstrating abnormal perceptions of tilt, rotation, and lateropulsion in that area [6]. Electrode recordings of these areas demonstrate that all neurons present are multisensory, responding to both somatosensory visual (OKN) as well as vestibular stimuli. This area can be activated by both otolithic and canalicular stimulation [11]. It would appear that the basal ganglia do not serve as a primary afferent reception area for substantial vestibular information, but rather derive their source from regional multimodal sensory cortical neurons in the parietal insular area, an afferent loop of which projects from vestibular nuclei through cerebellum and thalamus [12].

Attempts to identify vestibular dysfunction in PD are rendered particularly difficult since the generalized motor disorder as well as other nonmotoric elements of this disease may interfere with reactions of vestibular origin, thereby disallowing specific identification of vestibulospinal involvement. For example, Horak et al. [13], in an EMG-linked platform study, pointed out two main differences in the responses of PD patients with poor balance. Postural strategies were fixed independent of the support condition and PD patients then displayed inflexibility of learning how to predict motor strategies depending on the environmental circumstances and surface conditions. In contrast, individuals with vestibular disorders without PD display normal muscle activation patterns for balance and the capacity to reweight sensory information when the other senses of vision and proprioception are available. Pastor et al. reported that bi-sway responses induced by galvanic vestibular stimulation showed no significant differences between PD and control groups in latency to onset, latency to peak, peak amplitude of ground, or ground reaction force responses [14]. These results suggest that vestibular dysfunction does not explain the postural defects in mild-to-moderate parkinsonism, but rather that postural responses can be generated normally via the vestibulospinal pathways [14]. Consequently, results from studies attempting to measure balance recovery strategies, for example using dynamic platform posturography as a means of evaluating vestibular function in PD, are conflicting. Some studies do suggest there is a vestibular component to imbalance in some cases, however.

Nallegowda et al. [15] reported that PD patients performed worse than controls in condition 5 (eyes closed, platform sway referenced), a vestibular-derived condition, but the differences were not statistically significant. Rossi et al. [16] documented poor performance in patients under conditions 3, 5, and 6, all of which rely on vestibular input. An earlier study by Alzamil et al. also resulted in lower scores for PD patients, compared with controls, under visual and vestibular-derived conditions. The authors suggested the results could be interpreted as a means to identify patient-specific rehabilitation strategies [17]. Dynamic platform posturography (DPP) has been used as a means of demonstrating postural improvement following pallidotomy. Westerberg et al. found substandard scores in multiple conditions, including vestibular, on DPP that improved following pallidotomy [18] and Jagielski et al. reported statistically significant improvement, as measured by DPP, in the "off" condition, primarily in individuals postunilateral posterior ventral lateral pallidotomy [19].

Investigation of vestibular function by nonpostural responses has also shown variable and inconclusive results. Crucian et al. studied spatial ability utilizing a variant of the water jar test with head perturbations in an effort to compare relative contributions of vestibuloproprioceptive versus cognitive components. Perturbation of vestibular proprioceptive input was not found to alter spatial performance in their patients; rather, the authors concluded the difficulty was in faulty interpretation of cueing due to disruption of frontal striatal pathways [20]. The findings were in keeping with previous work by Bronstein et al. [21] but contrasted with the report of Procter et al. [22], who found significant changes in judgment of vertical with patient body tilting. Crucian et al. suggest that potentially two different patient populations were studied and that their cohort may have benefited from a sense of gravitational vertical from visceral proprioceptors of the body and neck.

Studies examining vestibulo-ocular function also have produced variable responses. Bassetto et al. [23], using electronystagmography (ENG), studied 30 patients with PD and reported altered vestibular test results in 83 % of patients, primarily peripheral vestibular disturbance, and either bilateral or unilateral hypoactive labyrinthine function. The study was limited by the absence of control patients and the inability to perform positional testing in the majority of patients [23]. Similarly, two-thirds of the patients of Reichert et al., studied with bithermal caloric testing, demonstrated significant abnormalities, one-third with reduced responses and one-third with absent responses. The authors reported a significant association between subjective postural instability and reduced or absent responses [24]. Rascol et al. [25], in their electro-oculographic study of eye movements in PD, found that despite less effective suppression of the vestibulo-ocular reflex (VOR) compared with controls, the gain of the VOR was normal, similar to previous reports [26, 27]. White and Saint Cyr [28], studying a small group of PD patients, reported that VOR gain was reduced, but their patients were advanced in age and most were on anticholinergic agents. Rascol et al. could not confirm dopaminergic control of the VOR due to lack of suppression of the reflex following a single-dose levodopa challenge [25].

Many patients with parkinsonism who complain of postural instability, loss of balance, and/or falls have significant nonmotoric comorbidities that contribute to balance dysfunction. Among these are well-documented problems with cognitive decline, memory disturbance, and attentional issues. Changes in the primary senses also undoubtedly contribute. For example, reduction in visual acuity secondary to well-defined common ophthalmologic problems, including cataracts, dry eye syndrome, macular degeneration, blepharitis, as well as more recently documented problems with low-contrast sensitivity [29], clearly may contribute to degraded motor performance. Proprioceptive defects due to coexistent disease conditions such as diabetes are reflected in balance difficulties, particularly in conditions with reduced visual input. PD patients may have comorbid vestibular dysfunction as well. However, whereas cognitive deficiency can be relatively easily identified through standardized neuropsychological testing (e.g., the Mini–Mental State Examination and the Montreal Cognitive Assessment), and primary sensory loss, both visual and proprioceptive, is usually identified by patients and confirmed by standard testing, dealing with the vestibular system is, for a number of reasons, less simple. First, patients have difficulty precisely articulating their symptoms. Second, there is no standardized nosology that patients can use to express the nature of their symptomatic experience. Third, a systematic approach to the problem of vestibular dysfunction has proved difficult to develop [30]. Fourth, screening and surrogate measures frequently fail to specifically identify vestibular involvement. Fifth, in a given individual, one expression (e.g., postural instability) may have multiple explanations. Lastly, standardized vestibular testing is rather limited in its capacity to define a specific vestibular problem. Furthermore, most clinicians are either not familiar with or do not utilize the standard available methods for vestibular assessment as part of their routine neurologic examination [31].

Clinical examinations of vestibular function in PD can help. The presence of spontaneous and/or gaze-evoked unidirectional nystagmus localizes lesions to the vestibular system. Since peripheral vestibular nystagmus is generally suppressed by visual fixation, funduscopic viewing in dark or with contralateral occlusion of the nonviewed eye may be utilized. Vertical malalignment of the eyes, so-called skew deviation, causes vertical diplopia and distortion of the visual vertical; accompanying head tilting suggests a unilateral disturbance in the otolithic ocular pathways. Resolution of diplopia in recumbency helps distinguish central skew from peripheral oculomotor imbalance.

All patients should be examined for nystagmus in both supine and lateral head positions as well as following a Dix–Hallpike maneuver [32]. Other commonly used maneuvers include tests for headshaking nystagmus and vibration-induced nystagmus as well as the head thrust sign. The latter is particularly helpful in identifying unilateral vestibular disturbance. It entails a high-

acceleration head turn while the patient maintains gaze on the examiner. During this maneuver, one looks for a "catch-up" saccade when the head is rapidly turned toward the lesion's side, a consequence of the failure of the gain of the vestibulo-ocular reflex. In cases of significant unilateral vestibular loss, the sensitivity and the specificity of this thrust test is virtually 100 %. Specificity is high, but sensitivity lower in patients who have varying degrees of, but incomplete, vestibular loss. Sensitivity of head thrusting is increased by placing the head down 30° in the pitch plane, maximizing the effect of the horizontal semicircular canal in the plane of movement of the head thrust [33]. Head shaking nystagmus is usually accomplished by to-and-fro oscillations of the head in the horizontal plane with eyes closed for approximately 30 s. This, in effect, charges velocity storage in the brain stem. Upon completion of the maneuver and opening of the eyes, generally nystagmus is seen, fast phase directed away from the side of the lesion. Head thrusting and storage nystagmus are not seen in normal individuals.

Oscillopsia is the subjective complaint of distortion or movement of the environment associated with head movement and generally reflects either an asymmetric nystagmus or, more commonly, bilateral vestibular loss. Dynamic visual acuity generally is significantly impaired in such individuals. Worsening of the visual acuity on a Snellen distance chart or Rosenbaum near card acuity test by three lines during horizontal head rotations at 1 Hz or more is considered abnormal. Walking in place while viewing a Snellen chart at the appropriate distance is an alternative method of testing for dynamic visual acuity [34, 35].

Examination of vestibulospinal function includes the Romberg test, performed with lower extremities apposed and eyes closed, the sharpened Romberg test in which one leg is placed in front of the other on a narrow base with arms folded on the chest and eyes closed [34], and Quix's maneuver, which has a number of variants but is simply tested by extending the extremities pointing toward the examiner's fingers. With eyes closed, the extremities are lifted directly upward, and after a period of 5 s, returned to the starting point. Deviation toward a weakened labyrinth is seen in the majority of individuals with one exception: in benign paroxysmal positional vertigo, approximately 80 % of individuals with eyes closed will deviate away from the semicircular canal affected by calcium carbonate debris [36].

Benign paroxysmal positional vertigo, the consequence of canalithic debris in one or more of the semicircular canals, is identified using the Dix–Hallpike maneuver most commonly and occasionally with head rolling maneuvers. Typical nystagmus associated with benign paroxysmal positional vertigo, or canaliasis, is evoked with a head hanging maneuver and begins after latency but within 30 s of assumption of the appropriate position. Generally it lasts no more than 30 s, commonly somewhat longer in patients who have cupulolithiasis rather than canaliasis. Persistent nystagmus in this position, particularly if there is no rebound or reversal in the sitting position, may in fact represent a central, rather than a peripheral, vestibular disturbance.

Quantitative Vestibular Testing

The Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology (AAN) points out that, although the clinical examination is gaining sophistication, there is still a need to better quantify vestibular function, particularly since some functional abnormalities are not identified clinically and require quantitative testing. Further, presently no comparison studies between clinical and standardized quantitative testing (e.g., caloric testing) are available. The most commonly employed method of recording eye movements is electro-oculography, or electronystagmography. This technique, using electrodes placed around the inner and outer canthi of the eyes, measures the change in corneoretinal potential. Recordings allow detection of direction, amplitude, and velocity of eye movements, both spontaneous and induced. Newer techniques, including infrared video nystagmography, are even more sophisticated in determining eye movements. The procedures utilize infrared cameras positioned to detect movement of the eyes in darkness. These

techniques are used to analyze both horizontal and vertical eye movements. The advantage of infrared technique over simple ENG is the capacity to identify torsional eye movements [34].

Vestibular stimulation can be accomplished by two conventional techniques: caloric irrigation (using air or water irrigation thru the external auditory canals) or head rotation. Caloric irrigation produces convection currents of endolymph from the canal that is oriented vertically because endolymph sinks when cooled and rises when warmed. Cool irrigation results in nystagmus away from and warm toward the stimulated ear. Caloric irrigation is inherently limited by the effectiveness of heat transfer through the middle ear, the strength of the caloric signal, canal anatomy, and technician skill. Consequently, caloric imbalance, as measured by slow phase velocities, in most laboratories is considered significant only when the calculated imbalance exceeds 25 %. The vestibulo-ocular reflex (VOR) can be measured using rotational chair testing performed at various frequencies and with either head-only or whole-body rotations. Eye movements that accompany head movement are measured to quantify the phase and the gain of the vestibulo-ocular reflex. Rotational chair testing is best at documenting bilateral peripheral vestibular hypofunction and is particularly helpful in determining whether reduced caloric responses are due to technically inadequate stimulation or true vestibular loss. It is less efficient in demonstrating peripheral imbalance. The utility of these tests in determining the presence of vestibular imbalance or generalized hypofunction is that it lends significant insight into decisions whether balance rehabilitation should be directed to training patients to reweigh reliance on visual and somatosensory cues in the case of generalized hypofunction or to provide exercises that stimulate residual vestibular function [34]. Alternative techniques not fully accepted by expert consensus include passive examiner-generated head rotation testing, active head rotation testing utilizing a velocity rate sensor attached to the head [37], galvanic vestibular stimulation [38], and click-evoked myogenic potentials [39]. Data on these techniques are still limited and they are not yet accepted as established techniques by the AAN subcommittee.

The frequency of vestibular system involvement in parkinsonism might be best approached from another perspective, i.e., an examination of causes of balance dysfunction in the elderly free of neurodegenerative disease, an age group in which PD most frequently develops. Complaints of dizziness, loss of postural control, and falling are extremely common in the elderly population [40]. Patients with various sensations of spatial disorientation or environmental movement use the term “dizziness” to attempt to describe their conscious or unconscious sense of bodily instability, thereby rendering the term ambiguous and, due to multifactorial causes for the sensation, virtually impossible to quantify. Nevertheless, some studies have attempted to identify and correlate etiologies with the term. Kroenke et al. [41], in a database search over a 30-year period, identified 12 articles containing original data on the etiology of dizziness, involving a total of 4,536 patients. Dizziness was attributed to a peripheral vestibular disturbance in almost one-half of patients; another 10 % were considered to have central vestibular dysfunction due to neurologic disease; and 30 % were imputed either to psychiatric disorders or to causes unknown. The variability and frequency of specific causes from study to study, different patient populations (e.g., specialty clinics versus emergency rooms) and the lack of standardized protocols limits generalization of the results of these studies. Data obtained from the Second Dutch National Survey of General Practice showed a prevalence of 8.3 % for complaints of dizziness made to family practitioners by patients 65 years and older [42]. Further, if acute vertiginous episodes are excluded, benign positional vertigo, vestibular imbalance, or hypofunction and psychiatric disorders predominate in patients with chronic dizziness [43, 44]. In the methodology applied to approaching the dizzy patient classically outlined by Drachman et al. [30], the authors observed that problems exist in dealing with elderly patients with disequilibrium due to multifactorial problems, the so-called multisystem stability disorder. Consistent with this fact, Colledge et al. [45]

investigated a cohort of recruited dizzy elderly in a controlled study with an extensive test battery. ENG testing was of no value because of the high percentage of abnormalities in both groups (80 % vs. 79 %). Posturography was significantly abnormal, but in all sensory conditions, which implied multisystem dysfunction. Although motor coordination was not scored, the authors implicated cervical spondylosis and central vascular disease as the most common causes. The latter diagnosis was based on findings of short-stepped gait, abnormal coordination, and increased tone or reflexes without MRI correlation. It is plausible that some of this cohort had PD and not "pseudoparkinsonism" of vascular origin. When vestibular dysfunction is accompanied by comorbidities, as seen in approximately 50 % of older persons, the consequence is frequently inadequate compensatory mechanisms for the primary cause and perpetuation of the symptom complex [40].

In an attempt to explore clinicians' perspectives and attitudes toward evaluating and managing patients complaining of dizziness, Polensek et al. [31] reported that clinicians infrequently screened for vestibular imbalance, hypofunction, and/or benign positional vertigo, a finding which may explain why the average patient with a vestibular neuropathy is symptomatic for more than a year before a rehabilitation program is initiated [46]. Based on study data in the elderly, it seemingly follows that any investigation into postural instability in individuals with PD of necessity should include vestibular screening. Components of a brief standardized examination should be performed on all patients:

- Check for spontaneous nystagmus in the light when the patient is fixating on a target and also with fixation blocked.
- Check the vestibulo-ocular reflex by doing a head thrust test.
- Do the Dix–Hallpike maneuver to check for benign paroxysmal positional vertigo and/or a central positional vertigo.
- Check smooth pursuit and saccadic eye movements.
- Check standing balance, Romberg and sharpened Romberg; check gait (widening of base of support while walking is infrequent in idiopathic PD).

Viewed from another prospective, the fall rate in elderly persons and the risk of falling increases exponentially with age [47]. In a 2-year longitudinal study of the incidence of falls in community-dwelling elderly adults, Vellas et al. [48] documented reports of one or more falls in 61 % of participants, about the average reported in other series. Low physical health, low mobility levels, and self-reported changes in cognitive status compounded risk compared with nonfallers. Murray et al. [49] conducted a pilot study of falls risks and vestibular dysfunction. Balance testing suggested a greater degree of underlying vestibular dysfunction in the group of fallers compared with nonfallers. Commensurate studies demonstrate that older individuals without a diagnosed vestibular disorder may have age-related changes involving their vestibular system that contribute to fall risk [50].

While advancing age itself confers increased risk of falling, the presence of PD may sum with other comorbidities to accelerate loss of balance and magnify risk of falling. Estimates of fall frequency among parkinsonian patients reported in the literature seem to exceed the frequency of falls in similarly aged community-dwelling elderly. Wood et al. [51], in a descriptive prospective study, reported a fall rate of 68.3 % in a PD group, with 50 % reporting at least two falls. Gait and balance were analyzed by a physiotherapist without standardized vestibular testing. Bloem et al. [52] prospectively evaluated a population of younger PD patients versus controls and found that the best predictors for falling were a history of previous falls and severity of disease, combined with a positive Romberg test. Conventional tests of balance, including the retropulsion (pull) test, were not found to have statistical significance [52]. Tests dedicated more specifically to vestibular function were not included in the test battery. Wielinski et al. [53], in a mailed survey covering a 2-year period, added older age, longer duration of disease, and dementia to the list of risks. The authors acknowledged that their study, as with other similar retrospective studies, was subject to recall bias. Faulty recollection due to cognitive

defects in PD, as well as comorbidity of traumatic brain injury resulting from even minor falls, also may reduce the validity of this type of study. Wenning et al. [54] determined the time course (duration) from appearance of first symptoms to onset (latency) of recurrent falls in PD and other parkinsonian disorders, including multiple system atrophy, dementia with Lewy bodies, corticobasal degeneration, and progressive supranuclear palsy, all of which were confirmed by postmortem examination. The authors found significant group differences for latency but not duration of recurrent falls and concluded that, although falls are frequent in all groups, early falls in other motoric disorders help to differentiate them from PD. The authors did not consider any sensory abnormalities as potentially contributory.

A multitude of factors in cross-sectional studies show a history of falling in parkinsonism significantly associated with any number of comorbidities, including increasing age, disease duration, advanced disease, greater postural sway, poor stability, gait freezing, muscle weakness, cognitive impairment, low-contrast sensitivity, and loss of arm swing [55]. Attempts to separate out vestibular dysfunction in PD patients have been limited. Some posturography studies have demonstrated, however, that PD patients have abnormally low balance scores under both visual and vestibular conditions [15, 56]. Rossi et al. attempted to identify dysfunctional processing of vestibular information in 30 idiopathic PD patients without a history of vestibular symptoms, compared with controls, utilizing the sensory organization component of a DPP system, weight shift testing, limits of stability tests, a timed up-and-go test, "tug test," and head thrust and head shake maneuvers. On average, PD patients performed significantly worse than controls under sensory organization conditions three through six, conditions in which the vestibular system acts as a primary referencing source. Quantitative motor coordination testing was not accomplished, nor were caloric or rotational tests performed. The authors concluded that the most salient findings indicated a deficient use of vestibular input [16]. To date, I am aware of no prospective study that has attempted to include a multimodal study of vestibular function in PD. As a consequence, the prevalence, type, and degree of vestibular dysfunction remain undocumented.

Just as in the elderly population free of neurologic disease, clinicians seldom diagnose vestibular impairment in PD patients. Polensek et al. have pointed out that office tests for positional nystagmus or vestibular hypofunction are infrequently performed. Perhaps one explanation for failure to test may be that clinicians have difficulty conceptualizing how vestibular rehabilitation may be of value for individuals with identified vestibular dysfunction [31]. However, a number of well-thought-out studies document success in vestibular rehabilitation. These studies emphasize the higher identification rates in conditions such as benign positional vertigo and emphasize the availability of both central nervous system and vestibular plasticity. Successful rehabilitation strategies include repositioning maneuvers, retraining in motor strategies, emphasis on utilization of other sensory input, reduction of sensory conflict, adjustment of the gain of the vestibular ocular reflex, adaptation to low contrast sensitivity, and parsing of cognitive allocation, among others [57–59].

Recent reports on rehabilitation protocols for PD patients are limited. The Quality Standards Subcommittee of the AAN does not mention treatment for vestibular dysfunction in its practice parameters. There are, however, reports of positive outcomes following various physical therapies emphasizing improved balance function in PD [60].

Ashburn et al. evaluated the effectiveness of a personalized home program of exercise as a falls prevention strategy. Participants were randomized to either exercise or no exercise. Exercise strategies consisted of muscle strengthening, range of motion, balance training, and walking. Evaluation at 2 and 6 months revealed a consistent trend toward lower fall rates in the exercise group, compared with controls. There also was a positive effect on quality of life measurements. Reduction of rates of falls was not statistically significant, although the rate of near falls and reputed near falls was significantly less in the exercise group than in the control group. Several

findings suggested subjects with less severe PD benefited to a greater extent from the exercise program [61]. High-intensity resistance training for a 12-week period demonstrated significant hypertrophy of quadriceps femoris muscle groups. Functional walking over 6 min and both stair ascent and descent were significantly improved over a 12-week period in a small cohort of PD patients vs. controls [62]. Nieuwboer et al. [63] utilized multimodal cueing training with visual light flashes, somatosensory pulsed vibrations, and auditory beeps and demonstrated a small benefit for gait performance and reduction in freezing episodes after 6 weeks. Outcome measures were tested without the cueing devices. The authors emphasized a decline in efficacy over time and suggested the need for permanent cueing devices.

Research specifically dedicated toward vestibular rehabilitation in patients with PD is even more limited. Hirsch et al. studied the effects of balance therapy, with or without high intensity resistance strength training [64], and reported both groups improved in sensory organization performance, measured on platform posturography; the effect was more robust in the combined group. In separate investigation, Toole et al. [65] used the same training strategy with a small number of participants to challenge stable posture and limits of stability. Equilibrium improved, as trained subjects seemed able to divorce themselves from absent or misleading visual information and utilized improved proprioceptive feedback and vestibular sensory sway feedback clues. In a small group of PD patients [10], computerized DPP was used as a feedback rehabilitation tool when there was presumed deficient vestibular input based on the "timed get up and go" test. The authors reported statistically significant improvement in sensory organization, limits of stability, and rhythmic weight shifting. Improvement remained significant at one year posttreatment [66]. Novel therapies are also being tested, including vestibular stimulation through chair rotation [67] and through the use of so-called "noisy vestibular stimulation" [68]. Transient improvements in gait, velocity, and reduction in hypokinesia have been reported. More studies are needed to determine any carry-over effect and/or the effect of prolonged or continuous stimulation.

Identification of vestibular dysfunction remains problematic in PD. Its presence in a significant percentage of affected individuals is certain by virtue of the prevalence of dysfunction in an otherwise elderly peer population free of neurologic disease but susceptible to the consequences of senescence, comorbidity due to myriad medical conditions, and likely the traumatic consequence of falling itself, all facts that have been confirmed by multiple investigational and epidemiologic studies. Vestibular dysfunction cannot be considered a nonmotoric sign of the disease process per se, although there is good reason to believe that both motoric and nonmotoric aspects of PD serve to mask its presence and perhaps even to degrade preexistent compensatory mechanisms developed after prior vestibular injury. Unrecognized, its dysfunction potentially may lead to misjudgment as to the cause of postural instability, summate with a compromised motor system and perpetuate the risk of falling. Specific tests of vestibular function, such as the head thrust test or Hallpike's maneuver, are valuable when positive. More frequently, clinical testing is less specific and burdened by convergence of possible alternative motor or sensory explanations for balance failure, a problem also faced by quantitative testing using balance platform studies. Evidence-based studies are lacking as to the utility of other testing systems. Although physical/balance rehabilitation therapy has been proven effective in settings of well-defined vestibular dysfunction, its value in PD patients with suspected vestibular involvement remains unproven, largely due to lack of evidence-based trials. Munneke et al. [69] have developed a network of physical therapists specially trained to treat the multifaceted motoric problems PD patients face, based on evidence-based interventions [70]. Considering the statistics regarding the frequency of vestibular dysfunction in the general elderly population as a cause for dizziness and falls, it would seem pragmatic to empirically incorporate a dedicated vestibular component into physical rehabilitation programs for PD.

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Part V

Other Nonmotor Dysfunction in Parkinson's Disease

Oculomotor Dysfunction in Parkinson's Disease

26

Christopher Kennard and Parashkev Nachev

Abstract

A disturbance of the oculomotor system is the principal neuro-ophthalmological manifestation of Parkinson's disease (PD). Although rarely symptomatic, this disturbance is a valuable subject for study because it illuminates two areas of wider interest: first, the nature of the motor and cognitive dysfunction in PD, and second, the role of the basal ganglia in oculomotor control. In this chapter, we shall give a brief overview of the anatomy and physiology of eye movements before proceeding to a detailed examination of the oculomotor abnormalities in patients with PD.

Keywords

Oculomotor system • Parkinson's disease • Oculomotor abnormalities • Saccades • Saccadic hypometria • Reflexive saccades

Introduction

Only a small region of the visual field that, subserved by the fovea, contains a detailed representation of objects that fall within it. The eyes must therefore move in order to acquire and maintain the object of interest in the foveal field of view: the oculomotor system has evolved so as to make this process as fast and efficient as possible. Saccades are rapid, conjugate eye movements that bring the image of a peripheral object onto the fovea of each eye; vergence movements are disjunctive movements that ensure the image in each eye corresponds to the same region in space; and smooth pursuit, vestibular and optokinetic movements lock the image on the fovea when either the object (smooth pursuit) or the entire head or body (vestibular and optokinetic) is in motion. In our survey of the neural mechanisms underlying eye movements, we shall confine ourselves to saccades and smooth pursuit because they are the best studied and are of the greatest relevance to PD.

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Saccades

It is customary to classify saccades according to the behavioral context in which they are performed.

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Thus, *spontaneous saccades* are executed at rest when the subject is not attending to any particular item in the visual field and is not performing any task; *reflexive saccades* are executed in response to the sudden appearance of a novel stimulus, usually a visual target; and *voluntary saccades* are executed deliberately by the subject in response to some kind of "internal" decision. Voluntary saccades are further divided into four categories, largely for the convenience of the paradigms used to study them, although some are valid from an ecological standpoint: a *memory-guided saccade* is made to the location of an eccentrically placed visual target a period of time after the target has been extinguished; a *predictive saccade* is executed in anticipation of the appearance of a target; an *antisaccade* is executed in response to a visual target but to a location equidistant from and in the opposite direction to the target; and an *endogenous saccade* is executed either in the absence of a peripheral target or in response to a stimulus other than the target.

Since few parameters are required to specify an eye movement, saccades are relatively easy to characterize. The metrics that are most commonly used are: latency, the length of time between the onset of the target and the onset of the saccade; gain, the ratio of the saccade amplitude and the target amplitude; peak velocity; and the final eye position (FEP) after the primary saccade and any secondary saccades required finally to foveate the target. These parameters are not independent; there is a strong positive correlation between the peak velocity and the amplitude of a saccade, which may be used to identify an abnormal eye movement as having been generated by the saccadic system.

The neuronal circuitry responsible for generating saccades is widely distributed within the brainstem: commands that specify the horizontal component of a saccade originate within the dorsomedial pons, in a region known as the paramedian pontine reticular formation (PPRF); those that specify the vertical originate within the rostral midbrain [1–3]. The saccadic generators in the brainstem receive inputs that are capable of triggering saccades mostly from the superior colliculus (SC), although saccades also may be evoked via direct projections from a number of cortical and subcortical areas including: the frontal eye field (FEF), supplementary eye field (SEF), and dorsolateral prefrontal cortex (DLPF) in the frontal lobe; area 7a and the lateral intraparietal area (LIP) in the parietal lobe; and substantia nigra pars reticulata (SNr) and caudate nucleus (CN) in the basal ganglia. There are extensive reciprocal connections between these areas, in particular, projections from the basal ganglia to cortical areas, either directly or via the thalamus.

Most of what is known about the role of the basal ganglia in oculomotor control has been derived from studies in monkeys that have focused on the relation between the CN, the SNr, and the SC [4]. A complex picture of their interconnections has emerged (see Fig. 26.1).

The neurons in the SC that are capable of generating saccades are found within its intermediate layer (SCi). These cells are under tonic inhibition from a population of GABAergic cells within the SNr whose firing is transiently suppressed when a saccade is executed, particularly when the saccade is memory guided. This transient suppression precedes the execution of a saccade—suggesting that it is required for a saccade to be executed—and is mediated through at least three pathways within the basal ganglia. First, a subset of inhibitory neurons within the CN project directly to the SNr. These cells receive rich inputs from the frontal cortex and have highly selective visuomotor responses, including increased activity during memory-guided saccades, compared with other types of saccades [4]. Other cells within this population do not project directly to the SNr but instead project to neurons within the globus pallidus externa (GPe), which in turn send inhibitory efferents to the SNr forming a second, indirect pathway. The third pathway involves the subthalamic nucleus (STN), which sends excitatory, glutaminergic projections to the SNr and receives afferents directly from the cortical eye fields in the frontal lobe and from the striatum via the GPe.

A striking feature of caudate neurons involved in these pathways is marked modulation by the behavioral context of the saccade, especially reward [5]. In modified memory-guided saccade tasks, some of these neurons show anticipatory

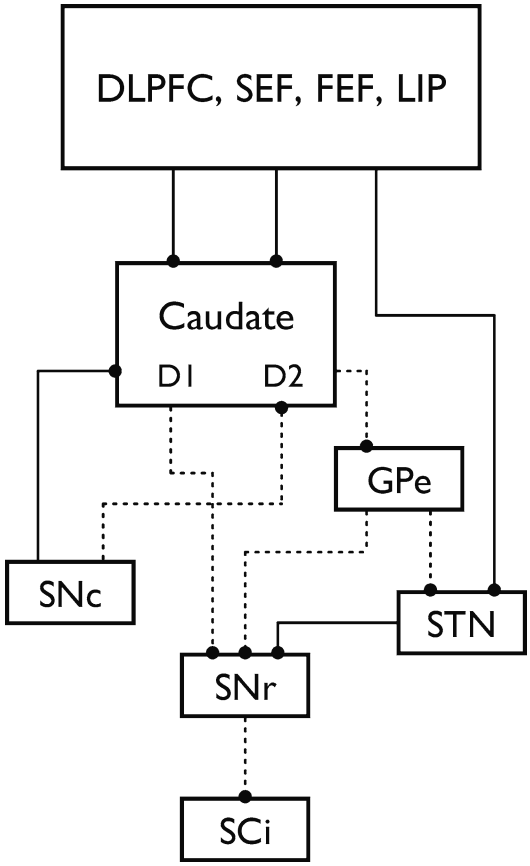

Fig. 26.1 Oculomotor connections of the basal ganglia. *Thick lines* denote excitatory connections, *thin lines* inhibitory (Not all known connections are shown. Refer to text for abbreviations)

activity that depends on the association between the location of the spatial cue and the expectation of reward from executing a saccade to that location [6]; this activity may be selective for specific features of the cue [7] and may be differentially modulated, depending on the probability of reward [8]. Furthermore, saccadic latency and peak velocity (but not other parameters) are significantly influenced by the expectation of reward [9], and latency correlates with the degree of neuronal activity [8]. Such activity has been reported in other brain areas with close connectivity to the caudate, including SNr [10] and SC [11].

The mechanism by which the reward signal is transmitted to the striatum remains obscure, but it is speculated that dopaminergic projections from the substantia nigra pars compacta (SNc) are critical. Caudate neurons that project directly to the SNr express D1 receptors preferentially; those that project via the GPe express D2 receptors. There is some evidence that D1-mediated activation may be facilitatory, whereas D2-mediated activation is inhibitory; if this is the case, dopamine deficiency may produce saccadic abnormalities via dysfunction of either the direct or the indirect pathway, and one would expect "internally guided" saccades to be preferentially affected. Indeed, the reward-dependent bias of saccadic latency is attenuated by D1 blockade and enhanced by D2 blockade in the caudate [12].

In further support of this supposition, dopamine depletion following systemic exposure to MPTP in humans [13] and experimental animals [14, 15] results in infrequent, slow, and hypometric saccades, although the systemic manifestations make the study of the oculomotor disturbance in these circumstances very difficult. Since dopaminergic neurons in the SNc project diffusely to the basal ganglia [16], it is difficult to be certain about the critical locus of dopaminergic action in oculomotor control. However, when MPTP is unilaterally infused directly into the regions of the monkey CN where neurons with oculomotor functions reside, thereby reducing any global effects, specific deficits emerge: saccadic hypometria, especially during memory-guided saccades, a marked reduction in the frequency of spontaneous saccades, and a paucity of saccades executed in the contralesional hemifield [17, 18]. The animals in these experiments also showed evidence of spatial neglect, with both a motor and an attentional component.

Smooth Pursuit

The oculomotor system responsible for smooth pursuit is less well understood and appears to be segregated from that responsible for saccades, although the degree of segregation is a matter of dispute [19]. Broadly, the areas involved are the middle temporal and middle superior temporal cortices, FEF, LIP, the dorsolateral nuclei in the pons, the floccular region of the cerebellum, and the vestibular nuclei, though a role for the basal

ganglia is increasingly appreciated [20–22]. Smooth pursuit movements are harder to study; the usual parameters of interest are the fidelity with which the eyes can follow a moving target, either a simple ramp stimulus or a sinusoidally modulated target. This can be expressed by measuring the discrepancy between the eye pursuit velocity and the velocity of the target.

Oculomotor Abnormalities in PD

Although pathologically proven PD can occasionally simulate conditions associated with marked oculomotor disturbance such as progressive supranuclear palsy [23], gross eye movement abnormalities that are obvious at the bedside are rarely seen; their presence should always raise the possibility of another parkinsonian disorder. There is no doubt that there are subtle abnormalities, but no clear consensus has emerged as to their precise nature and extent. The major difficulty with the existing literature is that there is considerable heterogeneity in the selection of patients and the experimental protocols used to study them, in particular the severity and treatment history of the disease and the details of the paradigms used to elicit eye movements.

Saccades

Major Abnormalities

The most consistent oculomotor abnormality in PD is saccadic hypometria, i.e., undershoot of the primary saccade. This was initially demonstrated in saccades executed to verbal command [24], in the dark [25, 26], or to fixed targets [27]. Predictive saccades also show hypometria in addition to difficulty in anticipating the stimulus [28, 29], and in unilaterally affected patients the abnormalities were found to be lateralized [30]. In agreement with the findings in dopamine-depleted animals, memory-guided saccades are most strikingly affected; this is so regardless of whether the remembered stimulus is visual [31–34], vestibular, or cervical [35]. The first question that this raises is whether the impaired performance is a consequence of a deficit in spatial working memory or some other resource that is engaged by the memory-guided saccade task. If the former is true, then patients should have difficulty in identifying the target location; in fact, although the primary saccade is hypometric, patients make secondary saccades that produces an accurate final eye position (FEP) when the memory delay is short [32, 34, 36, 37], but perhaps not when it is longer than 5 s [38]. Thus, although abnormalities of FEP are seen in monkeys with dopaminergic blockade of the DLPFC [39], if there is a spatial working memory deficit in PD, it is only revealed by tasks with a high working memory load. Indeed, an abnormal FEP is found when patients are asked to perform sequences of memory-guided saccades [33, 40], and we have shown that this is present only when novel sequences are compared with rehearsed ones [41]. Any deficit in spatial working memory may be compounded by global abnormalities in executive function that interfere with the planning of gaze strategies [42]. Nonetheless, these findings do not account for saccadic hypometria of gaze, which occurs equally in the execution of both novel and rehearsed saccadic sequences [42].

In contrast to memory-guided saccades, although some studies have shown mild impairment in reflexive saccades to peripheral stimuli [27, 28] most have not [30–34, 37, 43, 44], and two studies even have found a reduction in saccadic reaction time compared with controls when a "gap" was introduced between the disappearance of the central fixation point and the appearance of the peripheral target [45, 46]. A recent meta-analysis of 47 studies suggests that the discrepant findings might be explicable at least in part by an alteration in the normal variation of reaction time with target eccentricity, with peripheral saccadic responses being slowed but very central ones possibly [47]. Where posterior cortical involvement may be expected, such as in PD with dementia, reflexive saccades are more clearly impaired [48]; unreported contamination of patient cohorts with subclinical comorbidities of this nature is bound to account for some of the heterogeneity.

That reflexive saccades should be normal or enhanced when memory-guided saccades are

definitely abnormal suggests a dissociation between behavior that is reflexive or exogenously driven and that which is volitional or endogenously driven; there is good evidence from imaging [49] and from saccadic adaptation [50] that this dissociation reflects the operation of separate neural networks in the oculomotor system.

If endogenously and exogenously driven saccades are differentially affected in PD, a task that pits one against the other should demonstrate an impairment. The simplest such task is the antisaccade task, in which the subject has to suppress a reflexive saccade to a peripheral target and execute an endogenously driven saccade to the opposite location. Perhaps surprisingly, three studies have found no significant impairment in the performance of PD patients compared with age-matched controls [32, 34, 44], and another three have shown impaired performance [32, 45, 51]. It is difficult to draw firm conclusions from these studies because of methodological difficulties; however, the one study that employed a "gap" paradigm and tested patients in their "OFF" state, demonstrated more errors, increased latency, and reduced gain in patients with mild-to-moderate PD [52], compared with controls.

The antisaccade task involves not only suppressing a reflexive saccade but also doing something unnatural: looking away from a salient event. A deficit in its performance may therefore arise because one has to *switch* from a well-learned pattern of responding—prosaccades—to a less well-learned one. When this aspect is accentuated by mixing pro- and antisaccades, deficits emerge [53]. As the oculomotor paradigm is made more complex, the locus of any deficit is inevitably shifted towards the cognitive domain: the connection with the oculomotor system inevitably becomes less specific.

Response to Treatment

Although it seems reasonable to suppose that the saccadic abnormalities in PD are related to dopaminergic depletion, evidence that they can be reversed with dopaminergic treatment is sparse. A few studies have shown beneficial effects on the parameters of voluntary saccades [24, 54, 55] and on the ability to perform sequences of memory-guided saccades [38], but none has demonstrated improvement in the most characteristic abnormality in PD, the hypometria of memory-guided saccades. One study has found an *increase* in prosaccadic latency, which is seemingly at odds with the clinical effects of dopaminergic treatment [56]. One explanation might be suggested by the *improvement* of antisaccade performance reported by another study: the increased latency is indicative of the element of procrastination without which flexible behavior is not optimal [57].

By contrast with dopaminergic treatment, high-frequency stimulation of the subthalamic nucleus (STN) in PD patients with implanted deep brain stimulators seems to improve the saccadic parameters of reflexive saccades [58, 59] and of memory-guided saccades [60]. Similar improvement in memory-guided saccades as well as antisaccades has been reported in a patient with a GPi electrode when the stimulator is turned on [61]. A relatively large study involving a battery of oculomotor tasks found improvements across the board, though not in the frequency of prosaccadic errors in the antisaccade task [62].

Smooth Pursuit

Abnormalities in smooth pursuit in PD are recognized [26, 27, 54, 55, 63–66], particularly in smooth pursuit gain [55, 66] but have been less well explored. The mechanisms remain uncertain and, as with saccades, it is not clear whether the dysfunction is [54] or is not [55, 67] sensitive to dopaminergic replacement. In a recent study, infusion of apomorphine in patients previously untreated with levodopa or dopamine agonists produced an increase in smooth pursuit velocity and gain, but the improvement was not as great as the improvement in limb motor function [68].

Other Abnormalities

Apraxia of eyelid opening usually occurs as an isolated focal dystonia but is occasionally seen in PD [69]. It may be treated with botulinum toxin

injections and may be ameliorated by mechanical stimulation of surrounding skin, such as is produced by wearing goggles [70]. Deranged convergence is rarely reported in PD. In one case, it was found to be responsive to levodopa [71].

Differential Diagnosis

The oculomotor abnormalities in PD generally are too subtle to detect at the bedside; for this reason their presence or absence is rarely a helpful diagnostic criterion in routine clinical practice. On the other hand, the presence of marked oculomotor abnormalities is often a helpful pointer to another parkinsonian disorder. Clinically obvious impairment in vertical eye movements is characteristic of progressive supranuclear palsy (PSP), although it may be seen in other conditions such as diffuse Lewy body disease [72–75], corticobasal degeneration (CBD) [76], Guam Parkinson–Dementia Complex [77], Whipple's disease [78], amyotrophic lateral sclerosis [79], postencephalitic parkinsonism [80], and Creutzfeldt–Jakob disease [81, 82]. In PSP, slowing of vertical saccades precedes ophthalmoplegia and is probably the earliest sign of oculomotor involvement along with an increase in the number of square wave jerks, which are of normal frequency in PD. A supranuclear gaze palsy may occur in corticobasal degeneration, but usually only when the disease is advanced [83]. Eye signs rarely are an early feature of multisystem atrophy (MSA), but in some cases may mimic PD [84].

It is not clear to what extent eye movement recordings are helpful in discriminating between different types of parkinsonism. One small study examined simple saccadic metrics in the vertical, horizontal, and diagonal planes in patients with PD, MSA, pure akinesia, PSP, and CBD [85]. Compared with age-matched controls, only patients with PSP had slow saccades (in any direction), and only patients with CBD had increased saccadic latency. Other parameters such as hypometria, vestibulo-ocular responses, and smooth pursuit did not discriminate between groups, although deviation of oblique saccades towards the horizontal plane was more marked in patients with pure akinesia and PSP. In another study [44], patients with CBD had greater saccadic latency, and those with PSP more marked hypometria and worse antisaccade performance, compared with patients with PD, but there were no saccadic criteria by which patients with MSA could be differentiated from those with PD.

Thus, detailed eye movement analysis may be helpful in identifying patients with PSP and possibly CBD, but until there is more data on its sensitivity and specificity it is difficult to recommend it for routine use in the diagnosis of parkinsonian disorders.

Biomarking

The proliferation of genotypic markers for genetic susceptibility to PD has generated interest in phenotypic markers that could predict disease onset in advance of clinical symptoms. In a small cohort of subjects with the *Parkin* mutation in the presence and absence of clinical PD, reflexive saccades were not found to discriminate carriers from controls, although, blink amplitude did [86]. Others have reported a sensitivity of 87 % and specificity of 96 % for characteristic abnormalities in clinical PD, principally of memory-guided saccades, with some weak evidence of increased incidence of similar patterns of abnormality in siblings genotypically at higher risk [87]. Only longitudinal studies can provide a definitive answer here; these are yet to materialize.

Complications of Treatment

Although the oculomotor manifestations of PD do not consistently respond to treatment, neither is treatment associated with any deleterious effects on the oculomotor system. The eyes are generally spared in treatment-induced dyskinesia, although there are isolated reports of patients whose peak-dose dyskinesia has an oculomotor component in the form of large amplitude oscillations [88] or brief tonic deviations of gaze [89]. Pallidotomy produced no improvement in saccadic hypometria in one study of 31 patients with

PD, and resulted in only slightly reduced peak velocities in the context of improved peripheral motor function [90]. In one small series, an increase in the frequency of square wave jerks was found in the absence of any change in other saccadic parameters [91]. Transient conjugate eye deviation following the implantation of a GPi stimulator has been described in one patient [92], but the deviation was evident only at supratherapeutic voltages and may well have resulted from stimulation of neighboring regions.

Conclusion

The most characteristic oculomotor disturbance in PD is hypometria of voluntary—especially memory-guided—saccades in the context of essentially normal reflexive visual orienting behavior. Although deficits in spatial working memory and executive function may be contributory, the physiological changes underlying this disturbance remain obscure.

Microelectrode recordings in monkeys suggest that caudate neurons may modulate the metrics of saccades in response to the expectation of reward; it is tempting to speculate that similar modulation mediates "internally guided" behavior in humans, and the saccadic abnormalities in PD are consequent upon the dysfunction of these cells within a dopamine-depleted striatum. Until we have further evidence, however, this will have to remain in the realm of speculation.

Even if the role of striatal neurons can be proved, a satisfactory account would need to explain why the abnormalities are confined largely to saccadic gain, and why they are not rapidly responsive to treatment with levodopa. Here, we present a hypothetical explanation that addresses these questions.

Saccades in infants are markedly hypometric, with a gain of around 0.6. During childhood, saccadic gain increases, but there is always a tendency to undershoot the target even when development is complete; this increase in gain is accompanied by a reduction in saccadic error. Simulations have shown that the relationship between gain and error during development is such that saccadic flight time is minimized [93]; thus, the larger the saccadic error, the more advantageous it is to undershoot the target because a corrective saccade in the same direction can be executed faster.

Experiments in which the saccade target is displaced intrasaccadically so as to generate error in the saccadic end position have consistently shown in both monkeys and humans that over a large number of trials a corrective adjustment in gain occurs: this phenomenon is known as saccadic adaptation. There is strong lesion [94] and imaging [95, 96] evidence that adaptation relies on the integrity of midline cerebellar structures, at least in adaptation tasks that employ reflexive saccades. In monkey experiments, when the target is shifted so as to produce a small constant error in the end position of each saccade, saccadic gain is reduced even when the error is positive, i.e., the saccade is made to undershoot its target [97, 98]. Thus, although the question has not been addressed directly, it appears that in line with Harris's prediction [93], the adaptive mechanism responsible for maintaining saccadic accuracy will tend to reduce saccadic gain when saccadic error is increased.

A few studies have shown increased variance in the gain of memory-guided saccades in PD [29, 30] but have not attributed any great significance to it. An increase in variance in these circumstances is also seen in limb movements [99] and is predictable from some models of motor dysfunction in PD, where the principal problem is envisaged as a failure adequately to facilitate goal-directed motor plans combined with a failure to inhibit competing ones [100, 101]. The hypometria may therefore be the consequence of a normal adaptive response to increased variance in saccadic gain that is produced by a failure to inhibit competing "internally guided" motor plans; if so, its failure to respond immediately and consistently to treatment with levodopa or to fluctuate in synchrony with "On/Off" periods would not be surprising. The only study to examine saccadic adaptation in PD has found it intact to visually guided saccades [102, 103]; if variance in gain is indeed increased, greater hypometria is exactly what we should

see. An empirical evaluation of this hypothesis is currently underway (MacAskill, personal communication).

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Fatigue: A Common Comorbidity in Parkinson's Disease

27

Joseph H. Friedman

Abstract

Parkinson's disease (PD) is a neurobehavioral disorder defined clinically by its motor features. Pathologically, it is defined by the loss of pigmented neurons in the brain stem, coupled with the presence of Lewy bodies in those degenerating centers. However, advances in histology have led to the recognition of pathological changes in regions far more widespread than recognized even a decade ago, and there is every reason to believe that more surprises are in store in the near future. The correlations between pathology and clinical phenomena have yet to be made for most brain regions, leaving our understanding of the mechanisms of the clinical features of the disease incomplete. The behavioral and nonmotor aspects of PD are particularly difficult to understand because of the major overlap among problems due to neuronal degeneration, psychological responses to progressive disability, iatrogenic complications, and the secondary effects of primary disorders, such as excessive daytime somnolence due to sleep disorder.

Keywords

Parkinson's disease • Human fatigue • Fatigue • Peripheral fatigue • Central fatigue • Mental fatigue

Introduction

Parkinson's disease (PD) is a neurobehavioral disorder defined clinically by its motor features [1, 2]. Pathologically, it is defined by the loss of pigmented neurons in the brain stem, coupled with the presence of Lewy bodies in those degenerating centers [1, 3]. However, advances in histology have led to the recognition of pathological changes in regions far more widespread than recognized even a decade ago, and there is every reason to believe that more surprises are in store in the near future [4, 5]. The correlations between pathology and clinical phenomena have yet to be made for most brain regions, leaving our under-

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standing of the mechanisms of the clinical features of the disease incomplete. The behavioral and nonmotor aspects of PD are particularly difficult to understand because of the major overlap among problems due to neuronal degeneration, psychological responses to progressive disability, iatrogenic complications, and the secondary effects of primary disorders, such as excessive daytime somnolence due to sleep disorder [6–8].

One of the most common nonmotor symptoms associated with PD is fatigue [6, 7]. "Fatigue is a complex and enigmatic entity" [9]; it is a symptom complex, rather than an isolated symptom or sign, and may be considered in a sense analogous to depression or even to the historical name of the disease itself, paralysis agitans. Patients with PD are never paralyzed, or even particularly weak, but they often feel weak and complain about it. Unlike weakness, which can be objectively measured, fatigue is, by its nature, an elusive concept.

In addition to being a problem in many if not most medical disorders [10, 11], fatigue also poses a problem in epistemology. What is fatigue? While we may know, as individuals, what it means to be fatigued, it is difficult to explain and more difficult to measure. Subjectively, it often is described as an "overwhelming sense of tiredness, lack of energy, or feeling of exhaustion" [12]. Exemplifying the difficulty in defining what we mean by fatigue, many words have been used in its definition: "lassitude, overtiredness, lacking in energy, weariness from bodily or mental exertion" [13]. Synonyms of fatigue similarly are varied and imprecise and include "tired, debilitated, weary, enervated, languor, listlessness, heaviness, drowsiness, tedium, overtiredness" [14]. In the medical literature, there are also many definitions of fatigue, as shown in Table 20.1.

There is a physiological definition of fatigue, which refers to decreased function due to repeated use [24], but this definition applies to isolated cells, organs, or physiological systems and not to the overall sensation of fatigue described by humans. For example, we may speak of fatigue as the refractoriness to depolarization of a myofibril or neuron after repeated firing or due to the accumulation of metabolic byproducts.

Sleepiness, a distinct construct, complicates our interpretation of fatigue for several reasons. First of all, we use the word "tired" interchangeably with both sleepiness and fatigue, although one might be sleepy without feeling physically fatigued, or fatigued, such as from exercise, without feeling sleepy. In some circumstances, we feel both sleepy and fatigued, e.g., after engaging in prolonged physical work. We may respond to fatigue by resting, which also has ambiguous meanings, encompassing sleeping, and sitting or lying quietly without sleeping.

Human fatigue is often categorized into physical and mental components, with the mental component subcategorized into emotional and intellectual aspects [15, 25]. Another classification distinguishes central and peripheral fatigue [26]. Peripheral fatigue refers to local muscular fatigue where an individual can no longer produce adequate force during repeated muscular contractions [22, 27]. Even with peripheral fatigue, where there is an objective, measurable meaning, there is no agreement on the appropriate terminology. For example, Lou et al. [25] use the term "physical fatigue," and Schwid et al. [23] use the term "motor fatigue." Muscular fatigue has been identified in patients with PD [25, 28–30], but this is only one aspect of the persistent, disabling symptom complex that is experienced by so many PD patients [6].

Further obscuring our understanding of fatigue is the possibility that the nature and etiology of fatigue may be different in different medical disorders. For example, the fatigue that is associated with multiple sclerosis is not necessarily the same as fatigue in PD. Thus, knowledge of fatigue in one disorder may not apply to another.

In this chapter, I provide an overview of epidemiology and clinical features of fatigue in PD and discuss its measurement, potential causes, and treatments.

Table 20.1 Fatigue definitions

1.	An overwhelming sense of tiredness, lack of energy and feeling of exhaustion. It is distinguished from symptoms of depression. Fatigue is also distinguished from limb weakness [15].
2.	A sense of physical tiredness and lack of energy, greater than expected for a usual task [16].
3.	A sense of tiredness, lack of energy or total body give out [17].
4.	A condition resulting from previous stress, which leads to reversible impairment of performance and function. Affects the organic interplay of the functions and finally may lead to disturbance of the functional structure of the personality; it is generally accompanied by a reduction in readiness to work and heightened sensation of strain [18].
5.	A chronic form of tiredness, which is perceived by the patient as being unusual or abnormal, and absolutely disproportionate with respect to the amount of exercise or activity the subject has carried out and is not removed by resting or sleeping [19].
6.	Inability to maintain force. Sensation experienced when the effort to perform work, whether physical, mental, or both, seems disproportionate to the task involved [20].
7.	A sense of physical tiredness and lack of energy, interfering with physical functioning and social life, distinct from mental exhaustion, sadness, sleepiness, and impaired motor function secondary to PD symptoms [21].
8.	A subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities (Masoudi et al. Personal communication). • Physical fatigue [is the inability] to maintain the desired force during sustained or repeated exercise [22]. • A state with reduced capacity for work following a period of mental or physical activity [23].

Epidemiology of Fatigue

Fatigue is a common problem that is pathological or normal, depending on circumstances. It is a common problem in primary care [31–35]. In a community study in Norway, Loge et al. [36] found that "substantial fatigue" lasting 6 months or more affected 11.4 % of the population, aged 19–80. Other studies have found fatigue is the presenting complaint in 4–9 % of primary care office visits [32–34]. In one study [37], a sense of chronic fatigue was reported as a "major problem" by 25 % of consecutive patients seen in a primary care clinic, with 75 % of these patients suffering with it for at least 1 year. Fatigue is costly in terms of direct health care expenditures and indirect costs, such as lost employment [31]. For instance, fatigue was estimated to account for 9.3 % of formal health care expenditures in the UK [31].

Fatigue is associated with worse physical and mental health [32, 38, 39] and often adds morbidity to common medical disorders such as diabetes [40], chronic renal failure [41], and cancer [42]. It is a diagnostic symptom of mood disorders, such as depression and generalized anxiety disorders [43], and occurs in many psychiatric illnesses [44]. Fatigue is consistently associated with several neurological disorders [6, 45–49] and affects 80–100 % of patients with systemic lupus erythematosus [19, 50, 51]. In one study, fatigue was deemed the most bothersome symptom in more than one-fourth of multiple sclerosis patients [52]. Although fatigue is considered a hallmark symptom in multiple sclerosis patients, it was not recognized until 1984, when an influential paper by Freal et al. [16] reported that 78 % of patients described fatigue as a symptom, making it both the single most common symptom as well as the one most likely to interfere with activities of daily life.

Fatigue is a prevalent and frequently disabling symptom in patients with PD [6, 7, 12, 15, 21, 53–58]. Affecting up to two-thirds of all patients with PD [7], 15–33 % of all PD patients report fatigue to be their most disabling symptom, and more than 50 % rank fatigue among their three worst symptoms [6, 7, 54]. In an American study of newly diagnosed PD patients who enrolled in a drug study, hence an inherently motivated group, over one-third were classified as fatigued at entry into the study [55]. In southwest Norway [56], every patient diagnosed with PD who might require medication was identified and, after excluding depressed and demented patients, 50 % were found to suffer from fatigue. These numbers extend worldwide; fatigue affected 58 % of 1,072

consecutively seen Italian patients [57] and was common in China [58]. Of note here is the observation by Hoehn and Yahr in their classic 1967 paper [59] that fatigue was the presenting symptom in 2 % of PD patients.

Types of Fatigue in PD

Central fatigue and peripheral fatigue have been identified in PD patients [15, 26]. Although some believe these are distinct types of fatigue, there is evidence that central mechanisms may underlie the accelerated muscle fatigue thought to be corroboration of peripheral fatigue [25, 26]. Central fatigue is characterized by difficulty in initiating and sustaining mental and physical tasks in the absence of cognitive or motor impairment [26]. Mental fatigue has two subdivisions: mental lassitude induced either by hypo- or hypervigilance. The former occurs with repetitive and boring tasks. In PD patients, reduced stimulation due to physical dependence and social isolation consequent to the disease may result in a hypovigilant state. Sustained hypervigilance can also cause mental fatigue, for example, when keeping close track of breaking news stories and making complex decisions. Sustained emotional stressors, such as a critical illness in a close relative, may result in emotional fatigue.

Impact and Nature of Fatigue in PD

Fatigue in PD was first mentioned in 1967 by Hoehn and Yahr [59], which is notable because fatigue, rather than motor dysfunction, was the presenting complaint in a handful of patients. The study of fatigue was begun in earnest in 1993, with studies by Van Hilten et al. [21] and Friedman and Friedman [6].

Van Hilten et al. [21] published the first report focused on fatigue in PD. They compared nondemented patients with PD with age-matched controls to test the hypothesis that fatigue in PD worsened over the course of the day. Activity monitors were used to assess movement of the nondominant hand, and fatigue was assessed by frequency rather than severity and found to be "often," "very often," or "continuously present" in 31 of 65 patients. Of the fatigued patients, there was no discernible diurnal distribution of activity, nor any correlation between fatigue, motor activity, and bedtime.

Following shortly after the paper by Van Hilten et al., a survey of fatigue in PD patients conducted by Friedman and Friedman [6] was published. PD patients were compared with a same sex friend or relative without PD who was within 5 years of the subject's age. PD patients reported significantly greater levels of depression and fatigue than the control subjects, and one-third of patients reported fatigue as the single worst symptom of PD. More than half (58 %) of the PD patients "agreed" or "strongly agreed" with the question: "Fatigue is one of the three most disabling symptoms of PD." Most described fatigue as having a different quality than the fatigue experienced prior to the onset of PD. Although fatigue correlated with depression, not all patients with fatigue were depressed. Fatigue was not associated with motor dysfunction, as hypothesized by other authors [21, 58].

Other studies have followed these seminal papers, but fatigue in PD remains an uncommon topic in the scientific literature. Most studies have described the nature and correlates of fatigue; few have evaluated treatments of fatigue in PD. What is clear from the literature is that there is strong, consistent evidence of a higher prevalence of fatigue in PD patients, compared with healthy subjects. Several studies, using a variety of instruments and performed in different countries, have documented a higher frequency of fatigue in PD patients, compared with healthy age- and gender-matched control subjects [6, 12, 21, 25, 54–58]. These studies have shown consistently that about one-half of PD patients suffer from fatigue, but it is notable that fatigue is not a symptom common to all patients with PD. There is also some evidence [56] that the prevalence of fatigue in PD patients is higher than in other patients suffering with some other chronic disease, although these findings need confirmation by others. A study by Herlofson and Larson [56] found that a higher proportion of patients with PD reported fatigue, compared with patients with diabetes and prehip surgery patients.

Friedman and Friedman [60], following patients over 9 years, found fatigue not only to be a consistent finding over time, but also, in addition, noted that fatigue did not substantially change in severity in most patients, even with treatment and changes in disease severity. PD patients score higher on all dimensions of fatigue, compared with healthy controls [25]. Lou et al. [25] reported this, including physical fatigue, general fatigue, reduced motivation, reduced activity, and mental fatigue, although mental fatigue was not significantly different between PD patients and control subjects. These results suggest that physical fatigue and mental fatigue are independent symptoms that should be evaluated separately.

PD patients often complain of weakness, which probably is a reflection of fatigue of the skeletal muscles in performing repeated exercises [25, 28–30]. Ziv et al. [29] observed that PD patients fatigued twice as quickly as healthy control subjects, and that fatigue improved following a dose of carbidopa–levodopa, although the magnitude of this improvement was associated with disease severity. These results were confirmed in a recent report by Lou et al. [61].

Hwang and Lin [28] used stimulated single fiber electromyography to evaluate the neuromuscular junction in PD patients, hypothesizing that fatigue was due to a cholinergic defect at the level of the muscle. However, none of the patients had an abnormal individual mean consecutive difference in single fiber potentials, suggesting that the peripheral cholinergic system is intact in PD patients with fatigue. These results all suggest that peripheral muscle fatigue is central in origin and perhaps is just one more manifestation of central fatigue. Myasthenia gravis, a paradigmatic example of peripheral fatigue, also is plagued by central fatigue. Supporting this possibility are several examples in other patient populations. Paul et al. [47, 62], studying patients with myasthenia gravis, found high levels of "cognitive fatigue," demonstrated by diminished cognitive performance correlated with self-perception of fatigue. This is somewhat surprising, because the weakness and neuropathology of myasthenia gravis are limited to skeletal muscles, despite the known inflammatory process. Similarly, a study of fatigue in patients who had recovered from Guillain–Barre syndrome concluded that fatigue was not only a common sequela but also inversely correlated with the degree of recovery [63].

What is not in doubt is that fatigue in all of its manifestations occurs in PD, and it has a strong negative influence on quality of life and physical function in PD patients [64–67]. Fatigue has been reported to cause emotional distress and problems "in the areas of physical functioning, role limitation (physical), and social functioning and vitality" in nondepressed PD patients in multiple studies [64, 65]. An inverse association between fatigue, habitual physical activity levels, physical function, and functional capacity in PD patients has been reported by Garber and Friedman [66]. Fatigued patients tend to be less active and have poorer functional capacity, compared with those with lower levels of fatigue [66]. Van Hilten et al. [21] hypothesized that motor activity would have a diurnal pattern in PD patients, but their results documented only a lower activity level in the morning. After this "slow start," the activity of PD patients' increased and did not decline as expected as the day progressed. The pattern of activity also did not correlate with fatigue levels.

Causes of Fatigue in Parkinson's Disease

There are multiple factors that probably contribute to the sense of fatigue in PD. One of the most obvious factors is disease severity. Although studies show an association between more severe disease and fatigue [21, 54, 56], none has found an independent association between disease severity and fatigue [6, 12, 21, 54, 55, 66], suggesting that disease severity in itself cannot explain fatigue. Friedman and Friedman [60] found that, even with progression of disease, fatigue declined but did not change substantially in PD patients followed clinically.

Other explanations for fatigue in PD include sleep dysfunction causing excessive daytime sleepiness, depression and other mood disorders,

medication effects, and the motor dysfunction itself. Fatigue has, in fact, been associated with other comorbid conditions, including mood and sleep disorders in some, but not all [68], studies.

Drugs have been implicated both in exacerbating and reducing fatigue. For example, pramiprexole has been associated with increased fatigue in several studies [69]. However, most of the reports of increased fatigue related to drug therapy have come from randomized clinical trials of the efficacy of drugs in the treatment of motor symptoms of PD, and the data on fatigue have been collected as an adverse effect. Interpretation of the cause and effect relationship between a drug and adverse effects is notoriously difficult [70], so these results should be interpreted with caution, particularly because fatigue is a frequent complaint and a commonly reported adverse effect of many drugs.

Studies evaluating the effect of pharmacologic agents on fatigue in PD are rare. Carbidopa–levodopa has been reported to reduce central and peripheral fatigue [29, 61, 71] but is a predictor of fatigue in cross-sectional studies (e.g., [66]). Abe et al. [72] compared fatigue in patients taking pergolide or bromocriptine and found that patients receiving pergolide had reduced levels of fatigue; there was no change in patients taking bromocriptine. These results suggest that the D-1 receptor is involved in the sensation of fatigue in PD patients, but more work confirming these findings is needed. Modafinil has been tested and found to be of equivocal benefit for sleepiness and no benefit for fatigue [73, 74]. The only positive study reported was of methylphenidate at 15 mg three times daily [75].

There have been more studies evaluating drug therapy for fatigue in multiple sclerosis; however, none has been shown to have clear benefit [76–78]. Amantadine has been evaluated in several studies for the treatment of fatigue of multiple sclerosis (but not in PD); however, a Cochrane review [77] of its efficacy reports, "… [amantadine's] efficacy in reducing fatigue in people with (multiple sclerosis) is poorly documented and there is insufficient evidence to make recommendations to guide prescribing." More recently, trials of Prokarin (a mixture of histamine and caffeine) [78], pemoline [79], and 4-aminopyridine [76] have reported preliminary, although slightly promising, results in reducing fatigue in multiple sclerosis. Whether these results will be verified by other studies, or the drugs might be used to treat fatigue in PD, remains to be seen.

Depression is often associated with the general feelings of tiredness and malaise that are often associated with fatigue [80, 81], but the link between depression and fatigue is complex. Lou et al. [25], reporting on a sample of PD patients and healthy controls, found that PD patients on average had higher scores on the Profile of Mood States (POMS) and depression. Depression correlated with all dimensions of fatigue except physical fatigue. Karlsen et al. [54] also found an association between fatigue and depression, as well as between fatigue and the use of sleeping pills. However, they also found fatigue to be equally prevalent in patients with and without depression and depression was not predictive of fatigue. Herlofson and Larsen [56], using a multivariable analysis, also found that sleep disorders and pain were not independent predictors of fatigue. These results suggest that fatigue is an independent symptom of PD, overlapping with but not causally related to depression.

The same may be said about sleep disorders and fatigue. Sleep disorders are undeniably common in PD [7, 21, 82–87]. Although associated with fatigue, sleep disorders do not predict fatigue in PD patients [56]. Van Hilten et al. [21] reported that the prevalence of daytime sleepiness was similar in PD patients and controls; both had a diurnal pattern of sleepiness peaking in the early afternoon. In these subjects, fatigue was fairly constant throughout the day and more common in PD compared with controls.

Hogl et al. [86] evaluated daytime sleepiness in control subjects and in patients with PD. They found that, while daytime sleepiness was more common in PD patients compared with control subjects, in both groups, sleepiness was associated with heavy snoring, suggesting that daytime sleepiness reflects the presence of a sleep disorders. Other studies [80] have supported these findings, but not all. Fabbrini et al. [17] found no differences in daytime sleepiness in PD patients

as compared with healthy control subjects, but they did find that sleepiness was associated with PD drug treatments, suggesting that sleepiness is a side effect of treatment rather than caused by the disease itself.

PD patients have higher resting energy utilization than age-matched controls [18, 88, 89]. The resting metabolic rate decreases with treatment in those patients who were stiff and, in general, there is a loose correlation between the improvement in rigidity and the decline in energy requirements [88]. Levodopa-induced dyskinesia produces yet higher energy requirements [88]. Even early, untreated patients have an increased energy requirement [20]. Several authors have proposed that the increased energy expenditure may be a contributing factor to the weight loss that so frequently affects PD patients [17, 88]. Energy use for respiration also is increased in PD, which partly explains the increased resting energy requirements (Masoudi et al. Personal communication).

Given the increased energy requirements of PD patients at rest, it is a natural question to then ask, "Do PD patients who exercise less efficiently; that is, require more calories to perform a given exercise, suffer more from fatigue than those who are more efficient?" Unpublished data from our laboratory (Masoudi et al. Personal communication) suggest that PD patients use a higher proportion of their ventilation capacity, compared with health control subjects at a similar exercise workload. Thus, exercise may be more fatiguing in PD subjects due to greater ventilatory effort.

None of these factors discussed explain the phenomenon of fatigue in PD; they only assist researchers in identifying "clues" that may help to determine the underlying etiology of fatigue, which is not known. Several hypotheses have been proposed to explain fatigue in PD and other chronic diseases, but these remain largely untested [11, 26]. Testosterone does not correlate with fatigue in men with PD [90]. Hypothesized mechanisms of fatigue range from altered activation of the hypothalamic–pituitary–adrenal axis due to prolonged stress, inflammatory processes [91], to alterations in neurotransmitters and neurotransmission within the CNS, including disruption of the nonmotor functions in the basal ganglia and dysfunction of the striato-thalamo-cortical loop [11, 26].

It remains a problem that fatigue, depression, sleep disorders, drug adverse effects, and other comorbid conditions are common in PD patients and, importantly, these symptoms and conditions often are not recognized by clinicians in their PD patients [8]. To illustrate this problem, Shulman et al. [8], studying patients with PD, found that 44 % reported depression, 39 % were anxious, 42 % were fatigued, and 43 % had sleep problems; these problems often were not diagnosed by the patient's neurologist. Of these same patients, 35 % had been diagnosed with depression, 42 % with anxiety disorder, 25 % with fatigue, and 60 % with sleep disturbance. The latter is interesting, showing how patients often do not recognize sleep problems in themselves.

Fatigue Rating Scales

A review of fatigue scales in PD concludes that no new scales need to be developed. The Fatigue Severity Scale was recommended for both screening and severity rating; the Fatigue Assessment Inventory was suggested for both screening and assessing severity of fatigue; the Functional Assessment of Chronic Illness Therapy-Fatigue was recommended for screening and suggested for severity, and the Multidimensional Fatigue Inventory was suggested for screening and recommended for severity. The Parkinson Fatigue Scale was recommended for screening and suggested for severity. The Parkinson Fatigue Scale, the only scale specific to PD, has not yet been fully validated but was not thought to be more useful than the other scales [92]. The terms "suggested" and "recommended" were technically defined terms based on validity data.

Conclusion

In summary, fatigue is one of most common disabling symptoms in patients with PD. The impact of fatigue on the quality of life of patients is sub-

stantial, although health care providers often underestimate it. Fatigue has two components that may be related but are likely independent: peripheral (local muscle) fatigue and mental fatigue. Fatigue is associated with sleepiness and depression, but patients with fatigue may not be depressed or have sleep disorders. Drugs may exacerbate or improve fatigue. Research into the causes of and treatments for fatigue is sorely needed [17].

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Maxillofacial Signs and Symptoms of Parkinson's Disease and Their Dental Management

28

Arthur H. Friedlander

Abstract

Neurologists caring for patients with Parkinson's disease (PD) need to be familiar with how the disease and the medications used to treat it adversely affect the orofacial complex. They also need to be aware of how dentists can assist patients in managing these morbid effects of the illness. Lastly, given the fragile nature of individuals with advanced stages of PD, neurologists need to be able to comfortably consult with the patient's dentist in order to operationalize certain dental treatment modifications that will ensure that care is provided in the safest possible manner.

Keywords

Parkinson's disease • Orofacial complex • Parkinsonian tremors • Pharyngeal motor deficits

Neurologists caring for patients with Parkinson's disease (PD) need to be familiar with how the disease and the medications used to treat it adversely affect the orofacial complex. They also need to be aware of how dentists can assist patients in managing these morbid effects of the illness. Lastly, given the fragile nature of individuals with advanced stages of PD, neurologists need to be able to comfortably consult with the patient's dentist in order to operationalize certain dental treatment modifications that will ensure that care is provided in the safest possible manner.

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The orofacial complex exhibits numerous signs of PD. Parkinsonian tremors are often seen in the lip, tongue, and muscles of mastication. These tremors may give rise to involuntary mandibular movements, which may induce orofacial pain, temporomandibular joint (TMJ) discomfort, cracked teeth, dental attrition, and create difficulties in controlling and retaining dentures [1].

Individuals with PD tend to have problems eating because of involuntary muscle movements, significantly reduced tongue strength and endurance, and a slowness in both the initiation and execution of oral movements [2, 3]. This manifests as slowness in chewing reduced tongue movement with consequent loss of bolus formation and propulsion of the food to the back of the oral cavity, an inability to fully close the mouth

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and infrequency and difficulty in swallowing because of pharyngeal motor deficits [4]. In a small (3 patients) uncontrolled study, use of dental implant supported prostheses was associated with marked subjective improvement in chewing ability and an average gain in weight of 5 pounds [5]. The authors of this study concluded that implant supported over dentures overcome some of the eating difficulties encountered by edentulous patients who wear conventional complete dentures and have PD-associated deficits in their oropharyngeal musculature and changes in quality and quantity of saliva [6]. Although expensive, implant supported prostheses also may assist in overcoming difficulties in controlling and retaining conventional dentures because of tremors and rigidity in the orofacial musculature, and they may help to preserve self-esteem and assure continued social contacts.

Drooling of saliva from the corners of the mouth is apparent in approximately 75 % of individuals with PD and was historically interpreted as resulting from hypersecretion of saliva because of autonomic dysfunction [7, 8]. Contemporary research findings, however, present a more complex picture. The production of saliva by non-medicated patients with PD actually is decreased [9, 10]. This alteration in salivary gland function is, however, still believed to arise from PD-associated changes in the autonomic nervous system and possibly involves the salivary parasympathetic ganglia [11]. Historically, it was also believed that levodopa retarded the salivation rate, but more recent evidence suggests that the medication may actually enhance it [12, 13]. Most researchers now agree that irrespective of the amount of saliva produced, drooling probably occurs because of a PD-related inability to efficiently swallow with normal frequency, an inability to fully close the mouth, and an anterior flexed head position [14]. A full range of treatments for drooling, which is often accompanied by perioral lip and skin irritation and associated odor and embarrassment, have been described. Suggested therapies include administration of anticholinergic medications (e.g., glycopyrrolate, benztropine, etc.), injection of botulinum toxin type-A into the parotid gland and occasionally the submandibular gland at approximately 5-month intervals, parasympathetic denervation via tympanic nerve resection, salivary gland resection, transposition of salivary gland excretory ducts, and irradiation of the salivary glands [15–18]. Selection of the appropriate treatment must be individualized to the specific patient, given the variability in saliva production and the severity of dysphagia, because some individuals previously provided these treatments have gone on to develop xerostomia and a worsening of their dysphagia [14, 19, 20].

Burning mouth is a common complaint of patients with PD. Almost one-quarter of these individuals report discomfort of the tongue, floor of mouth, lips, and cheek. Although the burning sensation has been attributed to a variety of factors (e.g., xerostomia, parafunctional purposeless chewing activity, depression, and levodopa therapy), the exact cause or causes remain obscure [21].

The extent of dental caries in patients with PD is also somewhat controversial. Two studies have noted that the caries rate among patients with PD does not appear to be greater than like-aged individuals [22, 23]. Others, however, have claimed that there is an increased incidence of root caries [24]. Further complicating this issue is the increased craving for sweets and greater frequency of *S. mutans* noted in plaque samples obtained from patients with PD [25]. Almost all researchers have reported that the extent of periodontal disease in patients with PD does appear to be significantly greater than among controls and may arise because of impaired oral hygiene due to compromised manual dexterity resulting from loss of fine motor movements [26]. The extent of edentulism is also significantly greater among those with PD than among controls and may have resulted from the aforementioned advanced periodontal disease [27].

A review of the U.S. Food and Drug Administration (FDA) medication package insert accompanying each of the medications used in treating PD and an analysis of the current medical literature notes that these medications cause numerous adverse orofacial (Table 28.1) [28–31] and systemic reactions that compromise dental health and treatment.

Table 28.1 Adverse orofacial reactions to treat Parkinson's diseasea

Generic name/ Trade name	Xerostomia	Sialadenitis	Dysgeusia	Stomatitis	Gingivitis	Glossitis	Tongue edema	Coated tongue	Bruxism	Miscellaneous
Amantadine	+	0	0	0	0	0	0	0	0	Nasal dryness
Benztropine	+	0	0	0	0	0	0	0	0	Vomiting, throat, and nasal dryness
Cabergoline	+	0	0	0	0	0	0	0	0	Toothache, rhinitis, throat irritation, periorbital edema
Levodopa/ carbidopa	+	0	+	0	0	+	0	0	+	Glossodynia, trismus, sialorrhea, "dark" saliva, pigmentation of teeth, dysphagia, bruxism, trismus
L-dopa/ carbidopa/ entacapone	+	0	+	0	0	+	0	0	+	Sialorrhea, "dark" saliva, pigmentation of teeth, bruxism, trismus
Pergolide	+	+	+	+	+	+	0	0	0	Facial edema, headache, neck pain, perio abscess, jaw pain, moniliasis, dysphagia, dental caries, involuntary mouth/tongue movement
Rasagiline	+	0	0	0	0	0	0	0	0	Neck pain, vertigo, rhinitis, conjunctivitis
Ropinirole	+	0	0	0	+	+	+	0	0	Fall asleep in dental chair (secondary to sedation), toothache, headache, pharyngitis, tinnitus
Selegiline	0	0	+	0	0	0	0	0	+	Sublingual oral ulcerations, burning lips, burning mouth, facial grimacing, supra orbital pain
Trihexyphenidyl	+	0	0	0	0	0	0	0	0	Suppurative parotitis secondary to excessive dryness of mouth

Plus sign (+) indicates "yes"; zero (0), "no"

[a]Physicians Desk Reference. 61st ed. Montvale, NJ: Medical Economics; 2009; McEvoy GK, ed. AHFS Drug Information 2008. Bethesda, MD: American Society of Health-System Pharmacists. 2008; Wynn RL, Meiller TF, Crossley HL, eds. Drug information for dentistry. 9th ed. Hudson, OH: Lexi-Comp; 2003; Anonymous, Prescrire Int 2003;12:179

Within 5 years of treatment, 50–75 % of patients may develop levodopa-induced dyskinesia, which manifests as abnormal, involuntary movements of the tongue (lingual–labial dyskinesia) or sustained abnormal contractions of the muscles of mastication [32, 33]. These movements have been linked to increased severity of bruxism and associated pain in muscles of mastication [34, 35]. The neurologist should query the dentist to determine if their patient's dentition evidences signs of bruxism, that is, an excessive loss of tooth structure. If that is the case, then a change of medication should be considered; if that is not appropriate, the dentist should be asked if it is possible to fabricate a prosthetic appliance to protect the dentition [36].

The ergot-derived dopamine agonist, cabergoline, has been implicated in damaging heart valves and possibly predisposing patients to endocarditis [37]. (Another ergot-derived dopamine agonist, pergolide, has been removed from the market.) People who have had bacterial endocarditis meet the American Heart Association criteria requiring an antibiotic prophylaxis regimen during dental procedures likely to cause a bacteremia [38]. This includes procedures such as dental extractions, periodontal surgery, scaling and root planing of teeth, prophylactic cleaning of teeth or implants where bleeding is anticipated, dental implant placement, and endodontic (root canal) instrumentation or surgery beyond the tooth apex. Patients who are not allergic to penicillin should be given 2 g of amoxicillin orally 1 h before the procedure. For those allergic to penicillin, 600 mg of clindamycin, or 500 mg of azithromycin or 500 mg clarithromycin should be given orally 1 h before the procedure.

It is critically important that the neurologist refer the patient to the dentist as soon as possible because restoration of oral health is best completed early in the PD process because the patient's ability to cooperate during treatment diminishes as functional and cognitive abilities decline [39]. The dentist will take into account the patient's prognosis in relation to immediate vs. long-term dental needs (e.g., giving greater weight to removing a jagged nonrestorable tooth damaging the adjacent mucosa than repairing early recurrent decay about a crown), the patient's desires if expressible and their caregiver's desires, if reasonable. The dentist will ideally schedule the patient for short (no more than 45 min), early morning appointments when the patient usually is least bothered by PD symptoms and when medication often is most effective. The neurologist should advise the dentist that the patient may develop orthostatic hypotension and possibly syncope when the back of the dental chair is raised because of PD associated autonomic dysfunction [40, 41]. Furthermore, the neurologist should advise the dentist if the patient has previously experienced orthostatic hypotension in conjunction with the administration of levodopa, pramipexole, ropinirole, or cabergoline.

The neurologist and dentist should also discuss issues related to potentially significant adverse interactions that may occur when dental therapeutic agents are prescribed to patients receiving medication for PD. Precautions must be taken when administering local anesthetics containing the vasoconstrictor epinephrine to patients being treated with levodopa or entacapone because these individuals may experience an exaggerated effect on blood pressure and heart rate [42]. No more than 0.05 mg of epinephrine (as is found in 3 cartridges of 2 % lidocaine with 1:100,000 epinephrine) per half hour should be administered in such situations, with careful aspiration to avoid intravascular administration. Monitoring of patient vital signs is also recommended [43]. Because entacapone is excreted via bile, caution should be exercised when prescribing erythromycin and ampicillin; medications know to interfere with biliary excretion.

Patients being treated with the monoamine oxidase inhibitor (MAOI), rasagiline, can receive local anesthetic solutions containing levonordefrin or epinephrine, because MAOIs do not potentiate the pressor or cardiac effects of these direct-acting catecholamines [44]. However, the MAOI, selegiline, is unique in that it undergoes extensive first-pass metabolism to L-methamphetamine and L-amphetamines and interactions with levonordefrin or epinephrine may result in severe hypertension. Therefore, it is prudent that the dentist utilize a local anesthetic devoid of a

vasoconstrictor agent. Patients being treated with selegiline and rasagiline should not be prescribed meperidine hydrochloride because of a potentially toxic interaction in which severe hyperthermia, hypertension, and tachycardia may develop [45]. Animal studies have shown that MAOIs also increase the potency of other narcotic analgesics. Therefore, it is also prudent that the dentist prescribe only one-half the usual dosage of narcotic and titrate slowly any additional medication until a symptomatic response is achieved.

In the late stages of PD, the patient may be unable to cooperate during most forms of dental treatment. For these patients, care is best provided in the dental office under intravenous sedation administered by trained anesthesiologists or by using general anesthesia in the operating room of a surgical center or hospital.

Intravenous sedation in elderly patients concurrently receiving other central nervous system depressants should be undertaken with extreme caution. Sedative agents, such as midazolam, may obtund protective airway reflexes; because of impaired swallowing in individuals with PD, the chances for aspiration are enhanced.

The neurologist should emphasize to both patient and caregiver that maintenance of good oral hygiene is very important, but that, in addition to the motor deficits that impair repetitive movements, subtle cognitive deficits, and depression also may impair the ability to perform tooth brushing and flossing [46–48]. The dentist may suggest use of the Collis curved toothbrush, mechanical toothbrushes, and assistance with brushing by caregivers in order to help these individuals maintain their dentition.

The dentist also should provide the caregivers of patients with advanced PD education about techniques that can prevent dental disease. These individuals should receive instructions in proper tooth brushing and flossing methods and how to apply topical sodium fluoride (5,000 parts per million) to the patient's teeth with a toothbrush or sponge applicator. Oral rinse topical agents, such as chlorhexidine gluconate, may not be appropriate given that many patients with PD may not be able to swish and expectorate to minimize ingestion. Lastly, artificial salivary products may also be prescribed for those patients showing signs of xerostomia. It also is very appropriate for the dentist to suggest clinical examination, oral prophylaxis, and application of topical fluorides at 3-month follow-up visits [49]. Defects in the natural dentition or prostheses will also likely be addressed during these recall visits.

PD represents a growing burden on the health care system due to the increasing proportion of elderly individuals in our country. Neurologists familiar with the oral manifestations of the illness and its dental management can confidently discuss these issues with the patient's dental provider and arrive at an enhanced and safe dental treatment plan.

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Index

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