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Nonmotor Symptoms of Parkinson's Disease

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INTRODUCTION

Parkinson's disease is generally thought of first and foremost as a disorder of motor control. The cardinal signs of PD are all motor defects, which generally respond favorably to dopaminergic stimulation. While the most obvious pathological change in PD is degeneration of pigmented neurons in the substantia nigra, many other neuronal pathways not involved in motor function (such as the noradrenergic locus ceruleus, the serotonergic raphe nuclei, and the cholinergic nucleus basalis of Meynert) also degenerate in this disease (1). It is not surprising, therefore, that nonmotor symptoms abound in this patient population (Table 1). In this chapter we will consider the most common and important nonmotor symptoms seen in PD and, where possible, discuss therapeutic options for these problems.

TABLE 1 Nonmotor Symptoms of Parkinson's Disease

Dementia
Depression
Anxiety
Psychosis (medication-induced)
Olfactory dysfunction
Pain and sensory disturbances
Autonomic dysfunction
Seborrhea
Sleep disorders

DEMENTIA

Incidence and Prevalence

Estimates of the incidence and prevalence of dementia in PD vary widely due in part to differing operational definitions of dementia and to varying study designs. Cross-sectional studies of clinic or hospital cohorts (2–4) have generally produced lower estimates (around 15–20%) due possibly to a referral bias in which demented patients are seen less frequently in PD follow-up clinics and instead are either institutionalized, lost to follow-up, or treated in Alzheimer's disease clinics. Community-based prevalence studies (5–7) reveal that the proportion of PD patients with dementia ranges from 30 to 40%. The incidence of dementia in a community-based cohort of PD patients was found to be 95.3 per 1000 person-years, which amounted to a sixfold greater risk of dementia in PD versus normal controls (8). Most studies have shown that older age at onset of PD, longer duration of PD, and greater severity of motor symptoms are positive predictors of the development of dementia.

Pathology

The pathological findings in demented PD patients have been quite varied and inconsistent. This variability is due in part to selection bias (clinically unusual cases are more likely to come to autopsy) and in part to varying histopathological techniques used to study these brains. A consistent feature of the older pathological studies of PD dementia is a significant loss of neurons in the nucleus basalis of Meynert associated with extensive reductions of choline acetyltransferase in cortical regions (9,10). These findings suggest that the dementia of PD is in part related to the same cholinergic defect that is seen in Alzheimer's disease. Further supporting a

relationship between the dementia of PD and Alzheimer's pathology are studies showing extensive cortical plaques and tangles in these patients (11,12). However, the plaque and tangle counts did not correlate precisely with the presence or absence of dementia or with the degree of depopulation of the nucleus basalis.

More recent pathological studies have focused on the association of cortical Lewy bodies with dementia in PD. The advent of ubiquitin immunohistochemistry led to the recognition that the number of cortical Lewy bodies correlated positively with the degree of cognitive impairment (13). The discovery of the alpha-synuclein gene mutation in an Italian PD kindred (14) led rapidly to the development of alpha-synuclein immunohistochemistry, which even more reliably identifies both cortical and brainstem Lewy bodies. Recent studies have now shown that cortical Lewy bodies positive for alpha-synuclein are the most sensitive and specific markers for dementia in PD, with amyloid plaques and neurofibrillary tangles being present only inconsistently (15,16). One group has calculated that cortical Lewy bodies (as identified with alpha-synuclein immunostaining) are 91% sensitive and 90% specific for dementia in PD (15).

Apaydin et al. have recently attempted to better characterize the syndrome of PD dementia by reviewing brain autopsy specimens and the clinical histories of patients with PD who later developed dementia (17). They used the Mayo Health Sciences Research Database to identify all patients seen between 1976 and 1997 who had definite PD (defined as two of three cardinal features and a levodopa response) and who later (after at least 4 years from onset of PD) developed dementia. Thirteen such patients had brain autopsy material available; one patient was found to have progressive supranuclear palsy, and the other 12 had findings consistent with diffuse or transitional Lewy body disease. Of great importance, the histories of these patients revealed that while most had a favorable response to levodopa early in the clinical course, the benefit from this drug was later lost as the dementia became severe later in life. The authors have demonstrated that for the most common scenario of PD dementia in which dementia develops late in the clinical course and is associated with a relative diminution of the levodopa response, the pathological substrate is widespread cortical Lewy bodies.

Clinical Presentation

In light of the presence of both Lewy body and Alzheimer pathology in the brains of demented PD patients, some authors have suggested that PD and AD are not really different diseases but merely extremes of a spectrum of neurodegeneration (18). They raised the intriguing possibility that those

patients who are classified as having AD with "extrapyramidal signs" may differ from those diagnosed as PD with dementia only in that the former are followed in AD clinics and the latter in PD clinics. Regardless of whether this view is correct, it is clear that the timing of symptom onset and severity of dementia and parkinsonism factor heavily into the clinical diagnosis assigned during life. At the risk of oversimplifying the situation, patients presenting early with dementia who later develop mild to moderate parkinsonism are usually diagnosed with AD (after other identifiable causes of senile dementia are excluded) while the converse presentation (early prominent levodopa-responsive parkinsonism with later onset of dementia) fits with a clinical diagnosis of Parkinson's disease. Diffuse Lewy body disease (DLB) is diagnosed when dementia and parkinsonism develop together with fluctuating cognitive status and formed visual hallucinations (19).

Classically, the dementia of PD has been described as a "subcortical" dementia in which psychomotor retardation, memory abnormalities, cognitive impairment, and mood disturbances are considered cardinal features (20). A number of studies comparing patients with PD dementia to those with AD matched for dementia severity have suggested important differences in the clinical features of the dementia in these two conditions. Litvan et al. found that semantic and episodic memory were impaired in both groups of patients but that these defects were more severe in AD patients (21). They also reported that demented PD patients were more impaired on executive tasks than AD patients. Cummings et al. compared 16 patients with PD dementia to 10 with AD and found that the AD group had much greater language dysfunction (anomia, decreased speech content), whereas the PD-dementia group had more prominent motor speech abnormalities (22). Others have been less impressed with these differences and have suggested that the dementia of PD has substantial "cortical" features in common with AD (23).

A major problem with such comparative studies is the inherent difficulty in matching the groups for dementia severity. If scores on neuropsychometric testing are used to match the groups, then obviously no differences in the test results will be found. Similarly, it is difficult to match the groups on disability because the motor defects seen in PD patients contribute to disability, making it difficult to tease out the contribution of the dementia per se to the overall disability of the patient. In light of the considerable clinical and pathological overlap between PD dementia and AD with extrapyramidal features, the temporal profile of development of dementia with respect to the onset and severity of parkinsonism remains the most useful clinical criterion for distinguishing between these conditions.

Treatment

While there are no published studies evaluating the effects of cholinesterase inhibitors on the dementia of PD, several recent reports have looked at this class of drugs in patients with diffuse Lewy body disease. Since recent pathological studies now suggest that the dementia in PD is due mainly to diffuse cortical Lewy bodies, these studies might be relevant to the treatment of PD dementia.

Samuel et al. looked at 16 patients prospectively identified as having AD ($n = 12$) or DLB ($n = 4$); both groups were given donepezil 5 mg daily and assessed at 6 months with the mini-mental state examination (MMSE) (24). They found that scores on the MMSE improved to a significantly greater degree in the 4 patients with DLB compared to those with typical AD. They also observed among all study patients that those with "extrapyramidal features" experienced improvement in the MMSE compared to those without signs of parkinsonism, in whom the score declined.

McKeith et al. reported the results of a double-blind, placebo-controlled study of 120 patients with DLB treated with rivastigmine up to 12 mg daily or placebo for 20 weeks (25). They found that the percentage of patients with a 30% or greater improvement in the NPI-4 (a subscale of the neuropsychiatric inventory evaluating delusions, hallucinations, apathy, and depression) was 47.5% in the rivastigmine group and 27.9% in the placebo group in the intent-to-treat population, a difference that reached statistical significance at the $p = 0.03$ level. Of even greater interest was the observation that UPDRS motor scores did not change in either group whether randomized to placebo or rivastigmine. These data argue against the conventional wisdom that cholinergic agents might worsen the motor function of PD patients and suggest that this class of drugs should be considered as a therapeutic option for PD dementia. Clear recommendations for such therapy, however, will require prospective, randomized controlled trials in this patient population.

DEPRESSION

Prevalence

As is the case with dementia, prevalence estimates of depression in PD vary considerably. Slaughter et al. performed a review of the literature and determined an overall prevalence of depression (gleaned from analyzing 45 earlier studies) of 31% (26). In those studies in which DSM-III or DSM-III-R criteria for depression were strictly followed, the prevalence was higher at 42.4%. Dysthymic disorder is even more common, prompting some to suggest that this might be an intrinsic property of PD itself (27).

Pathophysiology

The depression of PD is said to occur in a bimodal distribution, with most depressed patients having either early or advanced disease (28). Those with moderate symptoms of PD have less depression. This observation fits the notion that depression in PD is a reactive depression, which develops when patients find out that they have a degenerative brain disease at the time of diagnosis and again late in the course when disease symptoms are worse. A study comparing the frequency of depression in PD and arthritis showed no difference, which also supports this reactive depression model (29). However, other studies have shown a higher incidence of depression compared to other chronic disabling diseases, calling the reactive depression hypothesis into question (30).

The alternative view is that the neurodegenerative process in PD is the proximate cause of depression through depletion of brain monoamines. Support for this view is found in studies showing that depression is more common among those PD patients with a significant decline in cognitive function in a 12-month period (31) and those studies demonstrating loss of dopaminergic neurons in the ventral tegmental area in patients with parkinsonism, dementia, and depression (32). Maricle et al. showed in a double-blind, placebo-controlled study that intravenous infusions of levodopa resulted in improvement in mood and anxiety in fluctuating PD patients, which supports the concept that endogenous dopamine depletion in PD leads to depressed mood (33). Mayeux et al. reported that the major metabolite of serotonin, 5-hydroxyindoleacetic acid (5HIAA), is reduced in the cerebrospinal fluid (CSF) of PD patients with both major depression and dysthymic disorder, which suggests that the serotonin hypothesis of depression might also be relevant to PD depression (34). However, reduced CSF 5HIAA was also seen in some PD patients without depression, indicating that this biochemical change is not sufficient to cause depression but might create a susceptibility to depressive illness.

Clinical Features

Recognizing the clinical features of depression in PD patients is a challenge, mainly because several key features of depression, such as loss of appetite, concentration difficulties, sleep disturbances, and slowness of movement, are features of PD itself (35). A recent study showed that during the course of routine follow-up visits for PD, neurologists with special expertise in movement disorders correctly made the diagnosis of depression in only 35% of patients who were known to have depressed mood, as shown by a Beck Depression Inventory score (BDI) greater than 10 (36). The routine use of

validated screening instruments for depression in this population may therefore be indicated to improve diagnosis.

PD related depression presents with dysphoria characterized by the presence of hopelessness, pessimism, and decreased motivation. Negative features such as guilt and feelings of worthlessness are not often seen (29). Several studies have shown that dysphoria increases in association with parkinsonian off states (37,38) and that mood and anxiety improve following dopaminergic stimulation (33,37). In spite of the high prevalence of depression in PD, for unclear reasons suicide is no more common in PD patients than in the general population (39).

Treatment

In light of the high prevalence of depression in PD, it is surprising that few well-designed studies of drug therapy for PD depression have been reported. Klaassen et al. published a meta-analysis of therapy trials for depression in PD in 1995, and they concluded that while several small trials of tricyclic antidepressants were positive, methodological limitations of these studies were such that clear recommendations for treatment could not be made (40). In a small study of bupropion in PD, the drug was found to result in a 30% improvement in parkinsonism, while only 5 of 12 depressed PD patients experienced improvement in mood (41).

There have been no properly controlled studies on the selective serotonin reuptake inhibitors (SSRIs) in the depression of PD. One study of 14 nondepressed PD patients treated with 20 mg daily of fluoxetine showed that scores on the Montgomery-Asburg Depression Rating Scale fell significantly after one month of treatment (42). Sertraline was evaluated in an open-label study of 15 depressed PD patients at a dose of 50 mg per day and was found to produce a significant improvement in the BDI without affecting motor scores (43). While several case reports have suggested a potential for SSRI antidepressants to worsen parkinsonism (44,45), these events are considered to be quite uncommon (46).

When data from controlled clinical trials are lacking, expert opinion may be of some use. Richard and Kurlan surveyed 71 members of the Parkinson Study Group (who together followed over 23,000 patients with PD) regarding antidepressant use in depressed PD patients (47). The results were that SSRIs were selected as first-line agents most frequently, with tricyclics being less popular choices. Those who favored initiation with SSRIs considered these drugs more effective and less likely to produce side effects compared to tricyclic antidepressants.

In cases where depression does not remit following appropriate drug trials, electroconvulsive therapy (ECT) should be considered. ECT has long been considered to be effective in drug-refractory cases of depression, and several reports have found an antidepressant effect in depressed PD patients. Douyon et al. showed benefits for mood after ECT in all 7 patients studied, and in those for whom pre- and post-Hamilton Depression Scale scores were available ($n = 4$), a mean improvement of 50% was seen on this measure (48). Additionally, significant improvement in parkinsonian motor function was seen in 5 of 7 patients after only two treatments. Other reports have appeared confirming this finding but have emphasized a particular sensitivity of these patients to ECT-induced delirium (49,50). Most authors noted that this delirium resolves within 2–3 weeks, though they offered varying explanations for this phenomenon ranging from structural changes in the caudate nucleus (49) to dopaminergic psychosis owing to increased permeability of the blood-brain barrier resulting from ECT (51,52). Those advocating the latter hypothesis reported that post-ECT delirium was largely prevented by reducing the dose of dopaminergic drugs by one third to one half of the typical dosage before starting ECT. In light of the powerful antidepressant effects of ECT together with the beneficial effect on parkinsonian motor function, clinicians should consider this treatment modality if several drug trials for depression prove ineffective or poorly tolerated.

ANXIETY

Prevalence

Anxiety is common in PD, occurring about as frequently as depression. Stein et al. found that 9 of 24 patients (38%) with PD suffered from a significant anxiety disorder and that anxiety did not correlate with the severity of parkinsonism or with antiparkinsonian drug exposure (53). Vazquez et al. observed panic attacks in 30 of 131 (23%) PD patients treated with levodopa and stated that 90% of the time, these attacks occurred in the off phase and were relieved by administration of levodopa (54). A comparison of the frequency of anxiety in PD with that seen in other disabling medical conditions showed that anxiety occurred in 29% of PD patients and in only 5% of disabled osteoarthritis patient controls (55). This finding was interpreted as indicating that the anxiety seen in PD is not merely a reaction to the disability inherent in this condition but is more likely related to the underlying neuropathology of the disease.

Pathophysiology

The causes of the various anxiety disorders associated with PD are unknown. While dopaminergic drug therapy could potentially cause anxiety, the observations that anxiety occurs most commonly in the off state (54) and is reversible following a dose of levodopa (37) argue for the opposite conclusion that the dopaminergic deficiency state of PD is in part responsible for anxiety.

Several lines of research support the view that the intrinsic dopaminergic deficiency in PD may be causally related to anxiety. Cash et al. found that in the brains of nondemented PD patients norepinephrine content in the locus ceruleus (LC) was normal while dopamine levels in this region were reduced by 42% (56). Since it is known that dopaminergic projections inhibit the firing of noradrenergic neurons of the LC, and since excess noradrenergic tone correlates with anxiety, Iruela et al. have postulated that the link between anxiety and PD can be at least partially explained by a mechanism in which degeneration of dopaminergic projections to the LC results in disinhibition of LC neurons, which in turn causes anxiety by excess production of norepinephrine (57). Richard et al. showed in a small pilot study that yohimbine (which activates noradrenergic neurons by blockade of the alpha$_2$-adrenergic autoreceptor) triggered panic attacks in three of five PD patients with a history of anxiety, a frequency similar to that seen in psychiatric patients with panic disorder (58). This observation supports the notion that PD is associated with a state of increased noradrenergic sensitivity that could be related to anxiety.

Another possible contributing cause to anxiety seen in PD is autonomic dysfunction. Berrios et al. compared 32 randomly selected PD patients with 32 age-matched healthy controls and found that the PD group had significantly less beat-to-beat variation in heart rate with respiration, a lower Valsalva ratio, and a larger postural drop in blood pressure than the control group, suggesting the presence of autonomic dysfunction in the PD group (59). They also noted a significant correlation between autonomic complaints and anxiety within the PD group. They concluded that anxiety and depression in some PD patients may represent a "behavioral phenocopy" caused by autonomic failure.

Clinical Features

In their review of anxiety in PD, Richard et al. point out that many different anxiety disorders have been reported in this patient population including generalized anxiety disorder, panic disorder, simple phobia, social phobia, agoraphobia, obsessive-compulsive disorder, and anxiety disorder not

otherwise specified (60). No adequate studies exist of sufficiently large populations to establish the relative frequencies of the various anxiety disorders in PD.

Treatment

There have been no randomized controlled clinical trials of pharmacotherapy for the anxiety of PD. Thus, treatment recommendations are based on anecdotal reports and expert opinion. When panic attacks occur coincident with off states, the most rational treatment approach is to modify dopaminergic drugs to reduce the number and duration of off states. This can be accomplished by shortening the interdose interval of levodopa, adding a dopamine agonist, initiating therapy with a COMT inhibitor, or utilizing subcutaneous injections of apomorphine (61).

In those patients with generalized anxiety disorder or panic attacks unrelated to motor fluctuations, benzodiazepines such as alprazolam, lorazepam, or clonazepam are recommended (62). Others have been careful to point out that elderly patients are particularly sensitive to benzodiazepines with regard to sedation and risk of falls and that therefore these agents should be used for short periods only (63). Buspirone at doses of 5–20 mg per day can also be useful (62), but high-dose therapy (100 mg/day) is not recommended due to a worsening of the motor features of PD (64). Patients who do not respond to benzodiazepines may benefit from low-dose tricyclic antidepressant therapy with agents such as nortriptyline, desipramine, and imipramine (62).

Psychological therapies using strategies including cognitive therapy, behavioral training, and relaxation techniques are recommended to help patients cope with stressful elements of the disease (63). One study showed that scores on the Beck Anxiety Inventory diminished significantly following surgery for PD (pallidotomy, thalamotomy, and pallidal deep brain stimulation), indicating that those patients who are candidates for brain surgery on the basis of their motor dysfunction might experience amelioration of their anxiety disorder postoperatively as well (65).

AUTONOMIC DYSFUNCTION

Prevalence

Determining the prevalence of autonomic dysfunction in idiopathic PD is difficult because early in the clinical course, PD can be easily mistaken for multiple systems atrophy (MSA, Shy-Drager syndrome) in which autonomic failure is universal. Generally, as the diseases progress, MSA patients

become less and less responsive to levodopa and their autonomic failure becomes increasingly severe. By contrast, PD patients continue to respond favorably to levodopa throughout their lifetime and autonomic failure is relatively less severe when compared to MSA. Magalhaes et al. retrospectively reviewed clinical records for autonomic symptoms of 33 patients with autopsy-proven MSA for comparison with 135 patients with pathologically proven PD (66). They found that clinically significant orthostatic hypotension was present in 30% of patients with PD and 88% of those with MSA. Other autonomic problems were also less common in PD than in MSA, respectively: bladder dysfunction 32% vs. 82%, constipation 36% vs. 57%, stridor or apnea 2% vs. 42%, and dysphagia 7% vs. 30%. From these data, one can observe that clinically important autonomic failure occurs in about a third of patients with PD.

Clinical Features and Pathology

The autonomic problems seen in PD patients cover the entire spectrum of autonomic dysfunction and include orthostatism, constipation, dysphagia, drooling, excessive sweating, heat intolerance, urinary disturbances, and male sexual dysfunction (67). While levodopa is known to produce an acute hypotensive response, autonomic testing performed before and after clinically effective doses of levodopa in patients chronically taking this drug did not reveal differences in orthostatic, Valsalva's, or cold pressor responses (68), which suggests that the underlying neuropathology of PD, not drug treatment, is the major cause of these problems. Wakabayashi and Takahashi in their review of the neuropathology of autonomic dysfunction in PD point out that Lewy bodies and cell loss are seen in the hypothalamus, intermediolateral nucleus of the spinal cord (sympathetic preganglionic neurons), sympathetic ganglia, dorsal motor nucleus of the vagus (parasympathetic preganglionic neurons), and the myenteric and submucosal plexuses of the gastrointestinal tract from the upper esophagus to the rectum (69).

The major clinical challenge is differentiating between PD with autonomic failure and MSA, which is important for counseling the patient regarding prognosis. Generally, late onset of autonomic signs and mild severity favors a diagnosis of PD over MSA. However, in a large clinicopathological study of autonomic failure in parkinsonism, one third of pathologically confirmed cases of MSA were misdiagnosed as having PD during life (66). In this group of MSA patients, the age at onset of the disease was later and autonomic signs were absent at presentation, features that typically favor a diagnosis of PD rather than MSA. Importantly, however, at the time of death the severity of autonomic failure in this group

of MSA patients was the same as that in the larger group of MSA patients who were correctly diagnosed during life. This suggests that very severe autonomic failure, even late in the clinical course of parkinsonism, should raise clinical suspicion of MSA.

Treatment

Of the various autonomic features seen in PD, orthostatic hypotension is one of the most disabling. Nevertheless, this problem is frequently treatable. Most authorities recommend physical measures first, such as sleeping with the head of the bed elevated 30 degrees, liberalization of dietary salt, and the use of support hose. In patients with mild symptoms of orthostatism these measures may suffice. For more severe cases, fludrocortisone 0.1 mg daily should be added while monitoring potassium levels and supplementing with potassium when needed. Doses greater than 0.3 mg/day do not offer any additional benefit. When these measures fail, therapy with pressors is indicated. Jankovic et al. found that midodrine (2.5–10 mg) produced a 10 mm or greater increase in standing systolic blood pressure one hour after dosing in 11 of 16 (69%) patients (70). The usual recommended dose of midodrine is 10 mg three times daily. Similar beneficial effects on standing blood pressure have been seen with ergotamine/caffeine in a retrospective study of autonomic failure in parkinsonian patients (71). In that study, this agent resulted in long-term improvement in both standing blood pressure and symptoms of orthostatism in four of eight patients.

Other autonomic problems can be treated as well. One study found that the excessive sweating seen in the face and neck of some PD patients could be corrected by dosing with levodopa (68). Constipation can usually be managed by liberalizing fluid intake and adding fiber to the diet. Nocturia and urinary incontinence often respond to agents such as oxybutynin and tolterodine. Excessive salivation, which is due to swallowing dysfunction, not oversecretion of saliva, may respond to administration of glycopyrrolate.

PAIN

Pain is a common problem in PD, affecting as many as 46% of patients, and can be either primary or secondary to motor dysfunction (72). Severe rigidity or off-period dystonia are common causes of secondary pain, which can often be addressed by optimization of dopaminergic medication. Primary pain is poorly understood but is most commonly seen in the off state. Limb burning sensations, lancinating facial pain, abdominal pain, and generalized pain have all been described (73,74). Primary pain syndromes

associated with Parkinson's disease respond poorly to analgesic medications and are best addressed by modifying antiparkinsonian drugs in an effort to reduce or eliminate off time (75). In one case, subcutaneous apomorphine injections were found to be dramatically effective when other dopaminergic agents and a myriad of analgesic drugs failed (73).

OLFACTORY DYSFUNCTION

It has long been recognized that most patients with PD have a diminished sense of smell and that this may be present in very early or undiagnosed patients (76,77). Berendse et al. studied olfactory function in relatives of PD patients and then compared SPECT using a dopamine transporter ligand on 25 hyposmic relatives of PD patients with 23 normosmic relatives used as controls (78). They found a reduction in dopamine transporter binding in 4 of the 25 hyposmic relatives (2 of whom later developed clinical parkinsonism) and in none of the normosmic controls. This study indicated that impaired olfaction can precede the onset of motor symptoms and could conceivably be used to screen patients for presymptomatic PD. The pathological substrate for PD-related anosmia appears to be neuronal loss with Lewy body formation in the anterior olfactory nucleus (79).

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