

Cognitive and Psychiatric Disturbances in Parkinsonian Syndromes



Richard M. Zweig, MD*, Elizabeth A. Disbrow, PhD,
Vijayakumar Javalkar, PhD

KEYWORDS

- Parkinson • Dementia with Lewy Bodies (DLB) • Parkinsonian
- Progressive Supranuclear Palsy (PSP) • Multiple System Atrophy (MSA)
- Corticobasal degeneration (CBD)

KEY POINTS

- Executive dysfunction is often measurable in newly diagnosed Parkinson's disease.
- Treatment with dopaminergic medications, particularly dopamine agonists, has been associated with hallucinations and impulse control disorder.
- While sharing many pathological features with Alzheimer's disease, distinguishing clinical features of Dementia with Lewy bodies include episodic fluctuations of cognition, early hallucinations, and REM behavior disorder symptoms.
- Quetiapine appears to be effective for hallucinating patients, without worsening parkinsonism at lower dosages. Clozapine is also effective. The promising 5-HT_{2A} inverse agonist pimavanserin is awaiting FDA approval.
- The neuropsychiatric profile of progressive supranuclear palsy may closely resemble that of the frontotemporal lobar degenerations.

INTRODUCTION

As is the case with all of the neurodegenerative disorders, the subset comprising the parkinsonian syndromes of Parkinson disease, dementia with Lewy bodies, progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and multiple system atrophy (MSA) are considered proteinopathies. In these disorders, disease-associated proteins accumulate in the wrong cellular or extracellular compartments, and are often

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Department of Neurology, Louisiana State University Health Sciences Center - Shreveport, 1501 King's Highway, Shreveport, LA 71103, USA

* Corresponding author.

E-mail address: rzweig@lsuhsc.edu

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glycosylated, phosphorylated, ubiquitinated, and misfolded, initiating or otherwise contributing to neuronal dysfunction and death. Moreover, misfolded proteins likely spread to other neuronal populations that are neighboring or networked, acting as prion-like templates corrupting native proteins, resulting in specific patterns of neuronal cell loss, with gliosis and atrophy.¹

Patients with these syndromes also share certain clinical signs including akinesia/bradykinesia and rigidity, which are the hallmark clinical consequences of pathologic involvement of dopaminergic neurons of the substantia nigra pars compacta. These cells normally fire regularly, in pacemaker-like fashion, releasing dopamine in the striatum. Released dopamine is quickly taken back up by the presynaptic terminal through the dopamine transporter and stored in presynaptic vesicles, thus allowing for tight regulation of extracellular, synaptic dopamine. Based on the well-established direct/indirect pathway model of basal ganglia function,² this dopaminergic tone is necessary for the proper gain setting of this system, facilitating desired movement, without excessive inhibition of movement or excessive, unwanted movements.

During movement, neurons in normal basal ganglia modulate activity to specific parameters including velocity, direction selectivity, force, amplitude, and active versus passive movement,³ and are organized somatotopically.⁴ These patterns of specific movement-related modulation of activity have been described at multiple subcortical levels (for review, see Ref.⁵). In Parkinson disease, this level of specificity is lost, and inhibitory output from basal ganglia to thalamocortical circuitry seems to be increased. Thus, electrophysiologic recording data from humans and MPTP nonhuman primate animal models indicate that the relative number of pallidal cells showing movement-related activity is increased,⁶ and the ratio of inhibited to activated cells in this basal ganglia outflow nucleus drops from 0.22 to 0.03.⁷ Furthermore, somatotopy breaks down with an increase in kinesthetic cells responding to multiple joints or body parts and ipsilateral (in addition to contralateral) limbs.^{4,8} Moreover, direct recording from the motor cortex of Parkinson disease patients undergoing deep brain stimulation therapy has demonstrated neuronal population spiking that is excessively synchronized to oscillations of subcortical basal ganglionic networks, which is reversed with successful deep brain stimulation.⁹

In 1923, the pathologist Fredrick Lewy described the characteristic target-shaped cytoplasmic inclusions found in dopaminergic and other neuronal populations affected in Parkinson disease. Following the identification of mutations in the gene encoding the protein α -synuclein in a small number of families with this disease¹⁰ it was soon discovered that this protein is a component of Lewy bodies.¹¹ Thus, the distribution of these inclusions (and α -synuclein-containing Lewy neurites) could be determined using antibodies raised against this protein. Although the direct contribution of Lewy body inclusions is unclear, these inclusions occur preferentially in brain regions with neuronal dysfunction/death and atrophy. In 2004, using α -synuclein immunocytochemistry in an autopsy series of brains from individuals with Parkinson disease and clinically normal control subjects, Braak and colleagues¹² described six stages of Lewy inclusions. The first three stages were considered presymptomatic, with pathology confined to olfactory bulb/nucleus and lower brainstem, and (in stage 3) inadequate nigral pathology to result in motor symptoms. At the other end of the spectrum, Lewy inclusions were found in the amygdala as early as stage 4, and then in neocortex in the higher Braak stages of disease. However, the course of disease varies widely among patients.

This article discusses aspects of cognitive and psychiatric disturbances in patients with mild/early Parkinson disease without dementia. This is followed by a discussion of dementia in Parkinson disease: its anatomic/pathologic basis, relationship to

dementia with Lewy bodies and to Alzheimer disease, and available treatments of resultant symptomatology. Finally, cognitive and psychiatric disturbances in the other parkinsonian syndromes are discussed.

COGNITIVE AND PSYCHIATRIC DISTURBANCES IN PATIENTS WITH MILD/EARLY PARKINSON DISEASE WITHOUT DEMENTIA

In recent years, there has been considerable study of nonmotor symptoms in patients with mild Parkinson disease, including retrospective review of these symptoms before onset of motor symptoms, presumably reflecting stages 1 to 3, and other early pathology.¹³ Thus, many patients report difficulty with sense of smell and/or rapid eye movement (REM) behavior disorder symptoms while sleeping, starting years before onset of motor symptoms, presumably reflecting olfactory bulb and lower brainstem Lewy-related pathology. Likewise, early constipation presumably reflects Lewy-related pathology in the intestines.¹⁴ A recent study¹⁵ has suggested that the well-known negative relationship between cigarette smoking and risk of Parkinson disease may reflect a greater ease of quitting smoking than normal in presymptomatic patients, rather than a neuroprotective effect of nicotine or other ingredients in tobacco smoke. Whether this behavioral consequence, if verified, reflects early dopaminergic pathology or pathology elsewhere is unclear.

Although estimates vary, the prevalence of cognitive impairment in newly diagnosed Parkinson disease approximates 55%.¹⁶ Affected domains include executive functions, such as memory, cognitive flexibility, and planning, and processing speed, verbal fluency, and visuospatial processing (for review see Ref.¹⁷). For example, task switching, or the ability to modify a plan because of evolving environmental conditions, has been shown to be impaired in Parkinson disease.^{18–20} Patients with this disease show deficits on standard neuropsychological tests with a large task switching component, such as the Wisconsin Card Sort Test.^{21,22} Nondeclarative, or procedural memory has also been associated with basal ganglia function, which is in contrast to declarative memory that is subserved by the hippocampus. There seems to be a relationship between cognitive and motor deficits in Parkinson disease. Producing a movement is a complex interplay between cognitive factors, such as flexibility and planning, and motor execution, and both are impaired in Parkinson disease. Cognitive (bradyphrenia) and motor (bradykinesia) slowing, and cognitive and motor inflexibility and perseveration are noted.¹⁷

The pathophysiology underlying parkinsonian executive dysfunction is not fully understood. However, basal ganglia dysfunction has a far reaching impact because of dense connectivity with the thalamus and cortex. In fact, anatomically segregated basal ganglia–thalamocortical circuits have been described in nonhuman primates that subserve specific functions based on cortical targets.^{2,23} Thus, disruption of the motor circuit underlies motor deficits. In contrast, disruption of the executive control network with cortical targets in prefrontal cortex results in executive dysfunction, and parkinsonian cognitive deficits have been described as frontoexecutive.¹⁷ Like motor dysfunction, executive dysfunction is reportedly dopamine responsive in Parkinson disease.²² These include spatial working memory, planning, processing speed, and switching, which have been demonstrated to improve with dopamine replacement therapy.^{22,24}

Dopaminergic nigral neurons projecting to the putamen are preferentially lost in Parkinson disease, with relative sparing of neurons projecting to the caudate. This is readily demonstrated using dopamine transporter radioimaging.²⁵ Yet in Parkinson disease and in the other parkinsonian syndromes, caudate projecting neurons are

involved with disease progression. Other dopaminergic neuronal populations, such as the neighboring ventral tegmental area, are less consistently affected by the disease processes. Involvement of these “extra” putamenal projections may contribute to some of these cognitive disturbances, and to psychiatric comorbidities discussed later.

Parkinson disease has classically been staged clinically on the one-dimensional, five-level, Hoehn and Yahr scale,²⁶ where the higher scores mostly reflect increasing immobility, irrespective of presence or severity of cognitive impairment. A more comprehensive way of staging Parkinson disease might include two axes, one reflecting severity, with the other axis reflecting how widely distributed is the disease process (Fig. 1).

Thus, a typical patient with onset in the late 40s or 50s, presenting with levodopa-responsive asymmetrical resting tremor and perhaps micrographia, but few additional symptoms, would have mild, focal disease. Over the years, if this patient developed increasing levodopa-responsive motor symptoms, but also “wearing off” of levodopa benefit between dosages (sometimes with unpredictable response or rapid wearing off) and levodopa-induced dyskinesias, but without significant cognitive disturbances, he or she would have severe, focal disease. Pathology would likely be severe Braak Stage 4 disease.

Although by this scenario the patient would not have dementia, he or she might have one or more psychiatric/behavioral disturbances related either to the underlying disease state or side effects of medications used. These include depression, with or without anxiety, and possibly resulting from or worsened by a disturbance of sleep and/or daytime sleepiness. Psychiatric comorbidities, such as depression, anxiety, and apathy, are difficult to identify in Parkinson disease because of symptomatic overlap with the associated movement disorder (for review, see Ref.²⁷), thus it is not surprising that estimates of prevalence vary wildly. A large study by Aarsland and colleagues²⁸ evaluated neuropsychiatric symptoms in 537 Parkinson disease patients. They reported depression in 58%, apathy in 54%, anxiety (sometimes with associated internal tremor) in 49%, and hallucinations in 44% of participants. A community-based prospective study noted that of 137 individuals with Parkinson disease, 60% developed hallucinations or delusions by the end of the 12-year study (many also with dementia).²⁹

Treatment with dopaminergic medicates, and in particular dopamine agonists, has been associated with hallucinations.³⁰ Although more common in patients with frank dementia, visual hallucinations can occur as a complication of dopamine agonist use in otherwise cognitively intact patients, particularly at higher dosages. These may be fleeting, and are sometimes described as “off the corner of the eye,” just out of view. Other patients may have recurrent, vivid, visual hallucinations, which may or may not

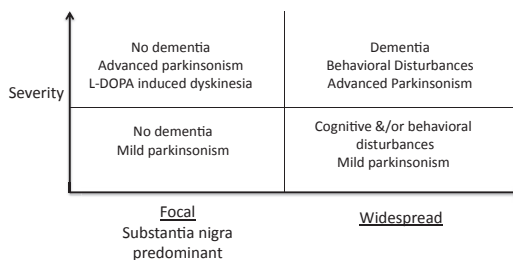


Fig. 1. The spectra of Parkinson disease and dementia with Lewy bodies. L-DOPA, levodopa.

be troublesome to the patient or family. These typically subside with reduction of dopamine agonist dosage. In addition, treatment with dopamine agonists can result in the development of impulse control disorders (ie, compulsive behaviors) that can be problematic.³¹ This has also been described with the drug amantadine.³² These can occur at any dosage of medication, sometimes improving with dosage reduction, but not always. Common compulsive behaviors include compulsive gambling, shopping, and compulsive interest in sex. It is imperative that these complications be screened for regularly during office visits, and their absence be corroborated if possible by the patient's spouse or others accompanying the patient.

DEMENTIA IN PARKINSON DISEASE AND DEMENTIA WITH LEWY BODIES

When clear cognitive impairment begins within 1 year after the onset of parkinsonian motor symptoms, or precedes the onset of motor symptoms, the diagnosis of dementia with Lewy bodies is used rather than Parkinson disease.³³ This distinction between Parkinson disease (with later-onset dementia) and dementia with Lewy bodies is arbitrary, but useful clinically (eg, dopamine agonists should be used with great caution, or not at all, in patients with dementia with Lewy bodies). Nevertheless, with few exceptions, autopsy series have failed to distinguish pathologically patients with dementia with Lewy bodies from Parkinson disease patients with dementia early in the course of disease.³⁴

A major determinant of early widespread Lewy body deposition, and early dementia, seems to be presence of Alzheimer disease–related pathology: amyloid plaques and tau-containing neurofibrillary tangles. For example, of 87 patents coming to autopsy from the prospective Sydney Multicenter Study of Parkinson disease,³⁵ 83% of those meeting clinical criteria for dementia with Lewy bodies and 80% of patients with Parkinson disease with dementia dying within 10 years of disease onset had significant amyloid plaque formation. Patients with dementia living longer than 10 years had an increasingly lower percentage with amyloid plaques. By contrast, none of the patients with Parkinson disease dying within 15 years of disease onset and without dementia had amyloid plaque formation. In another study of 56 pathologically confirmed Parkinson disease cases,³⁶ including 29 who had developed dementia, a combination of cortical Lewy body score, amyloid plaque burden, and Braak Alzheimer tau stage³⁷ was better than any of the individual measures in predicting presence of dementia. However, of the three measures, higher Braak tau stages correlated best with severity of dementia within the last year of life (as is also seen with Alzheimer disease). Of note, amyloid scores and age at death were tightly correlated, and both predicted a faster progression to dementia, whereas carriers of the Alzheimer disease genetic risk factor APOE-4 also had higher amyloid scores. Thus, it seems that older age, presence of APOE-4 gene, and/or other factors result in amyloid plaque deposition that, in turn, accelerates cortical Lewy body and tau pathology, linking dementia with Lewy bodies and Parkinson disease dementia (particularly early in the course) with Alzheimer disease.

Despite the pathologic link between dementia with Lewy bodies and Parkinson disease with dementia (especially early in the course) on the one hand, and Alzheimer disease on the other hand, there are clinical distinctions between these conditions. A “core” clinical feature of Dementia with Lewy Bodies is episodic fluctuations of cognition or clouding of consciousness, sometimes resembling delirium. Though this sign can be quite alarming to family and physicians, it has been difficult to define formally or measure. Another core feature, visual (and less often, other) hallucinations, tends to occur early in the course of dementia with Lewy bodies, often before the start of

dopaminergic medications, which can worsen this symptom. In an autopsy series of patients with dementia with Lewy bodies and Parkinson disease with and without dementia,³⁸ dementia with Lewy body cases had highest Lewy body densities in the parahippocampal gyrus, amygdala, and particularly in the inferior temporal cortex, which was also associated with the presence of well-formed visual hallucinations early in the course of disease. Of note, no pathologic correlates of fluctuating cognition were found. In another study of Parkinson disease patients that included a large autopsy series, hallucinations typically occurring late in the course of disease were also associated with temporal lobe Lewy body deposition, and Lewy bodies in the middle frontal and anterior cingulate gyri.³⁹ However, in a more recent MRI study controlling for dementia, hallucinations were associated with cortical atrophy in visual perceptual pathways rather than mesial temporal lobe.⁴⁰ Clinical correlates of presence of hallucinations, in addition to cognitive impairment, included sleep disorders (including REM behavior disorder and excessive daytime sleepiness), depression, higher age at disease onset, and duration of disease (for review, see Ref.⁴¹).

Although not originally considered a core feature of dementia with Lewy bodies, REM behavior disorder is a common, distinguishing feature of the α -synucleinopathies, including MSA, and in Parkinson disease, is a marker for earlier onset of dementia.⁴² Other nighttime sleep disturbances occur commonly in Parkinson disease including restless leg syndrome, obstructive sleep apnea, and insomnia. Other patients have motor “wearing off” during the night, associated with difficulty turning and sometimes with pain, including from dystonic posturing (often in the more symptomatic foot). Patients often have low back pain and urinary frequency at night, aggravating the sleep disturbance. Daytime sleepiness is also very common, sometimes caused by or aggravated by medications (dopamine agonists in particular, but also levodopa in some patients). Sudden, narcolepsy-like sleepiness may occur, and may be particularly problematic in patients still driving.⁴³

As in Alzheimer disease, there is a profound cholinergic deficit in dementia with Lewy bodies and in Parkinson disease with dementia, even in patients with minimal Alzheimer-related pathology.⁴⁴ Treatment with cholinesterase inhibitors has been shown to be efficacious in these patients, with best evidence for rivastigmine.⁴⁵ However, the effect seems to be modest and some of the potential side effects are particularly problematic in this group of patients. These include gastrointestinal (diarrhea, weight loss); sleep disturbances including daytime sleepiness; increased drooling; and worsening of parkinsonian motor symptoms, including tremor. There is also some evidence for benefit from the *N*-methyl-*D*-aspartate receptor antagonist memantine⁴⁵; however, the potential side effect of confusional episodes may mimic the episodic fluctuations of cognition from the disease state.

Treatment of hallucinations in Parkinson disease with dementia and in dementia with Lewy bodies can be challenging, particularly because most neuroleptics, including so-called “atypical” neuroleptics, greatly worsen parkinsonism in these patients. Although sometimes relatively benign (with insight and/or where the patient can be easily redirected), hallucinations are often problematic, particularly if the patient becomes delusional and agitated. Psychotic symptoms in Parkinson patients often contribute to nursing home placement.⁴⁶ The first steps in management include screening for underlying stressors, such as medical illness (including dehydration and infection), worsening depression or anxiety, worse sleep, or others. Parkinson and other medications must be reviewed: the dosage of dopamine agonist should be reduced or the medication should be stopped, with increase in levodopa dosage as needed for control of parkinsonian symptoms. Elimination of amantadine and probably monoamine oxidase-B inhibitors should be considered. Anticholinergics,

including quaternary formulations, which are less likely to cross the blood-brain barrier, can cause or worsen hallucinations, and should be eliminated if possible. Although often helping sleep, benzodiazepines can also trigger hallucinations in some vulnerable patients.

The usual first-line atypical neuroleptic used in this group of patients is quetiapine, which seems to be effective in many patients, even at a low dosage (although there is no class 1 or 2 evidence of efficacy available). In an open label series of Parkinson patients with hallucinations, the average dosage used was 54 mg nightly,⁴⁷ with a typical range from 12.5 mg nightly to, in some patients, well over 100 mg daily in divided dosages. This medication typically worsens parkinsonism only to a small degree, and only at higher dosages. Clozapine is also effective in many patients, and does not worsen parkinsonism.⁴⁸ However, the requirement for frequent white blood count assessments (including weekly for the first 6 months), has undoubtedly dampened use of this medication. In addition, both of these medications (and other neuroleptics) can be oversedating. The 5-HT_{2A} receptor inverse agonist pimavanserin is currently awaiting Food and Drug Administration approval for Parkinson disease psychosis, and should be a welcome addition when it is available. In clinical trials, this medication effectively reduced psychotic symptoms, and improved nighttime sleep, without daytime sedation.⁴⁹

Various selective serotonin reuptake inhibitor or serotonin-norepinephrine reuptake inhibitor antidepressants have also been shown to be beneficial for depression, which occurs commonly in Parkinson disease, with class 1 evidence for patients without dementia.⁵⁰ Benefit for depression and other nonmotor symptoms may be enhanced when treatment also includes the monoamine oxidase-B inhibitor rasagiline.⁵¹ There is also evidence that aerobic exercise may improve not only motor function, but additionally mood and executive control in Parkinson disease,⁵² reflecting the neuroplasticity of basal ganglia circuitry.⁵³

NEUROPSYCHIATRIC MANIFESTATIONS IN MULTIPLE SYSTEM ATROPHY, PROGRESSIVE SUPRANUCLEAR PALSY, AND CORTICOBASAL DEGENERATION

Cognitive impairment, and in particular executive dysfunction, occurs in patients with the other α -synucleinopathy, MSA. These patients can also have some impairment of memory and spatial skills.⁵⁴ This may occur early in the course of disease. In one study, about 22% of patients with early stages of MSA had cognitive impairment.⁵⁵ The type of cognitive impairment may vary between the types of MSA. In one study,⁵⁶ patients with a parkinsonian presentation (ie, MSA-P) showed involvement of visuospatial, constructional, verbal fluency, and executive skills, whereas those with a cerebellar presentation (ie, MSA-C) demonstrated visuospatial and constructional dysfunction only. The same study also showed that patients with MSA-P have more severe and widespread problems with cognitive dysfunction than patients with MSA-C. The cognitive deficits in MSA may correlate with frontal atrophy and duration of the disease.⁵⁷ The pathologic basis of cognitive impairment in this disease is not clear. In one report there was no difference in the severity of MSA-related pathologic finds (eg, glial and neuronal cytoplasmic inclusions) in patients with, versus those without, cognitive impairment.⁵⁸ However, another study noted that in patients with MSA, cortical thickness was reduced in the same areas as observed in Alzheimer disease and in Parkinson disease with dementia.⁵⁹ Similarly, a PET study showed reduced glucose metabolism in frontal, temporal, and parietal cortices in patients with MSA.⁶⁰

Patients with MSA can have anxiety and depression in addition to executive dysfunction. The severity of anxiety and depression may differ between the two

subtypes of MSA. In one study, patients with MSA-P reported abnormally increased levels of depression and anxiety, whereas patients with MSA-C reported higher anxiety levels than healthy adults. The authors correlated this with reduced executive regulation, abstract reasoning, and episodic learning.⁶¹ Other behavioral changes reported in patients with MSA include emotional incontinence, panic attacks, and suicidal ideation.⁶²

PSP and CBD are two of a family of tauopathies that also includes tau variants of the frontotemporal lobar degenerations (FTD). In patients with PSP, cognitive slowing, executive impairments, and inefficient memory recall have been identified in most patients.^{63,64} The neuropsychiatric profile may closely resemble that of FTD.^{63,65} For example, the prevalence of antisocial behavior in PSP may be comparable with those with FTD.⁶⁵ The pattern of cortical atrophy may also be similar between PSP and the behavior variant of FTD (bvFTD), with decrease in gray matter volume in widespread frontal areas and in the temporal uncus in bvFTD, and decrease in the frontal and temporal lobes and in the thalamus (and brainstem) in PSP.⁶⁶ Other neuropsychiatric manifestations observed in PSP include apathy and disinhibition.⁶⁷ Apathy has been associated in PSP with executive dysfunction.⁶⁸ Depression also occurs commonly in patients with this disease.⁶⁹ Patients with PSP may have deficits in emotion recognition and this has been correlated with the severity of other cognitive disturbances rather than duration of disease.⁷⁰

Patients with CBD also demonstrate impairments in executive functions and memory, but more distinguishing are deficits in language, visuospatial dysfunction, such as apraxias and “alien hand,” and social cognition difficulties (for review, see Ref.⁷¹). Depression (73%) and irritability (20%) were noted to occur more commonly in patients with CBD than with PSP. Apathy and agitation was also common, with anxiety, disinhibition, delusional activity, or aberrant motor behaviors (eg, pacing) noted less commonly with CBD.⁷²

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