Cognitive and Psychiatric Disturbances in Parkinsonian Syndromes

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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-HT2A 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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glycosylated, phosphorylated, ubiquinated, 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 disease[10] 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 colleagues[12] 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