A 74-Year-Old Woman with Anxiety and Paranoid Delusions

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A 74-year-old single, retired, white female was admitted to the inpatient geriatric psychiatry unit for evaluation and treatment of increasing anxiety and agitation over the previous 5 months. She had recently moved out of her own apartment to an assisted living facility due to difficulty with activities of daily living. Since then, frequent anxiety episodes and panic-like attacks had resulted in repeated emergency department visits.

At other times, the patient experienced variable combinations of paranoid delusions and perceptual disturbances. Her delusions involved beliefs that her apartment was occupied by witches; her perceptual disturbances included visual hallucinations of bugs and illusions of distorted forms and shadows.

A sense of overwhelming dread often accompanied her symptoms. Between episodes, she was described as lucid and insightful. Recently, her nocturnal fearfulness and agitation had become so severe that she required 24-hour supervision.

The patient’s medical history was significant for Parkinson’s disease (PD), major depressive disorder, breast cancer (in remission following a mastectomy 25 years prior), hyperlipidemia, and osteoporosis. She had a history of alcohol abuse that at the time of presentation had been in full sustained remission for over 10 years.

Family medical history was significant for bipolar disorder in her mother. Medications on admission included carbidopa-levodopa (25/100 mg x 2.6 times daily), nortriptyline (10 mg at bedtime), and rivastigmine patch (4.6 mg/24 hours). The carbidopa-levodopa dose recently had been increased due to frequent on-off episodes, which are dramatic changes in motor function due to dopaminergic fluctuations.

The patient was initially diagnosed with Parkinson’s 8 years prior when she presented with a left-sided resting tremor. Although she had a clear history of syndromal depression antedating her Parkinson’s diagnosis, her psychiatric symptoms were noted to have worsened in the previous 7 months, coincident with the advancement of her Parkinson’s disease. Her only other psychiatric hospitalization occurred approximately 5 months ago, in the context of hallucinations and agitation.

Neuropsychological testing performed at that time revealed deficits in executive function and visuospatial processing. During the year prior to admission, her behavioral dysfunction had progressed to a point requiring formal designation of a relative for decision-making regarding personal finances, living arrangements,
and medical care. Around that time, she was started on transdermal rivastigmine.

At the time of her present hospital admission, she endorsed symptoms of depression, sometimes punctuated by episodic sobbing, as well as intense periods of anxiety throughout the day, every day, variably associated with difficulty breathing and intense phobia of falling.

Upon admission, the patient was noted to be a thin, elderly female with a slow, shuffling gait, and moderate rigidity, but minimal tremor. There were no dyskinesias; her speech was hypophonic; and her mood was anxious and fearful. The patient’s expressive linguistic function was fluent and her thought processes were circumstantial and perseverative.

She had paranoid ideations about being kidnapped by her roommate or given poison by the nurses; this paranoia occasionally reached delusional intensity. She experienced visual hallucinations and confusion that were most prominent at night, although none was evident upon admission using a mental status examination. The patient’s insight and judgment were fair. On Mini-Mental Status Examination (MMSE), she scored a 29 of 30 with impairment in visuospatial ability.
Dementia Associated with Parkinson’s Disease

Diagnostic formulation included several etiologic components, including her PD (see Sidebar 1, page 472).

For an illustration of a systematic approach to the etiology and management of agitation in dementia associated with Parkinson’s disease (PD-D), see Figure 1 (page 472).¹⁻⁴

On admission, complete blood count, chemistries, thyroid function tests, and urinalysis were normal. Rapid plasma reagin was nonreactive, and serum B12 was normal with normal homocysteine and methylmalonic acid levels. An electrocardiogram showed normal rate and sinus rhythm with a corrected QT interval (QTc) of 426.

Neuroimaging was performed to evaluate for cerebrovascular disease, subdural hematoma, and cortical and hippocampal atrophy (as markers of cognitive decline in PD-D).⁵ Non-contrast magnetic resonance imaging (MRI) revealed periventricular white matter ischemic changes and a small focus of increased signal intensity in the right deep frontal white matter, but it otherwise showed ventricles and sulci of normal configuration for age.

A routine 30-minute electroencephalogram revealed diffuse slowing and disorganization of the background rhythm, reflecting diffuse cerebral dysfunction, and runs of symmetrical bifrontal delta range activity that reflected her underlying PD-associated fronto-striatal impairments. There were no focal or epileptiform characteristics.

**DISCUSSION**

This case illustrates a number of typical features of PD-D. As shown in Figure 2, PD-D involves a multi-neural system dysregulation and typically presents with a complexly layered and interacting neuropsychiatric phenomenology.⁴ Consequently, PD-D poses challenges to both the neurologist confronted with the patient’s worsening psychiatric features, as well as to the consulting psychiatrist’s attempts to manage symptoms that become increasingly complex in their pathogenesis and management as the disease progresses.

As multifactorial neuropsychiatric symptoms evolve in the setting of an
SIDEBAR 2.

Differential Diagnosis of Dementia Associated with Parkinson’s Disease

**Neurodegenerative**
- Dementia with Lewy bodies
- “Parkinson’s plus” syndromes:
  - Progressive supranuclear palsy
  - Multiple system atrophy
  - Olivopontocerebellar atrophy
  - Shy–drager syndrome
  - Striatonigral degeneration
  - Corticobasilar degeneration
- Frontotemporal dementia (FTDP-17)
- Fahr’s disease

**Vascular**
- Vascular dementia with vascular parkinsonism

**Drug/toxin-related**
- Dopamine receptor antagonists (eg, antipsychotics)
- Carbon monoxide poisoning
- 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)
- Wilson’s disease
- Phenylketonuria (off-diet)
- Hemochromatosis
- Aceruloplasminemia
- Wilson’s disease
- 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)

**Hereditary disorders/inborn errors of metabolism**
- Gaucher’s disease (glucocerebrosidase deficiency)
- Wilson’s disease
- Aceruloplasminemia
- Mitochondrial disease (MELAS, LHON)
- Hemochromatosis
- Phenylketonuria (off-diet)

**Infectious**
- HIV
- Viral encephalitis
  - Japanese encephalitis
  - Influenza A
  - Encephalitis lethargica
  - Epstein-Barr virus, arboviruses, enteroviruses
- Neurocysticercosis
- African trypanosomiasis

**Metabolic**
- Uremia
- Liver failure, acquired hepatocerebral degeneration

**Autoimmune/antibody-mediated**
- Hashimoto’s encephalopathy
- Paraneoplastic syndromes
- Sjogren’s syndrome
- Neuro-Behçet’s disease
- Celiac disease

**Other**
- Normal pressure hydrocephalus
- Anoxic brain injury

LHON = Leber’s hereditary optic neuropathy; MELAS = mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke.

Source: Aloysi and Aron

**TABLE 1.**

Differentiating Features of Alzheimer’s Dementia, Dementia with Lewy Bodies, and Dementia Associated with Parkinson’s Disease

<table>
<thead>
<tr>
<th></th>
<th>AD</th>
<th>DLB</th>
<th>PD-D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of cognitive symptoms in</td>
<td>Initial symptom is</td>
<td>Cognitive symptoms develop simultaneously</td>
<td>Onset of cognitive symptoms occurs in</td>
</tr>
<tr>
<td>relation to motor features:</td>
<td>impaired memory;</td>
<td>or within 1 year of motor symptoms.</td>
<td>the setting of established PD with a mean</td>
</tr>
<tr>
<td></td>
<td>motor symptoms</td>
<td>Marked fluctuations in cognition/level of</td>
<td>of 10 years after initial diagnosis.</td>
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<td></td>
<td>usually absent until</td>
<td>arousal may occur.</td>
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<td></td>
<td>late stages of the</td>
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<td></td>
<td>disease when</td>
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<tr>
<td></td>
<td>parkinsonism may</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>occur (rigidity,</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>bradykinesia, tremor)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuropsychiatric testing profile:</td>
<td>Impairment in episodic</td>
<td>Striking deficits in visuospatial abilities,</td>
<td>Impaired executive functioning, attention,</td>
</tr>
<tr>
<td></td>
<td>memory, with or</td>
<td>as well as impairment of attention, executive</td>
<td>and visuospatial abilities predominate.</td>
</tr>
<tr>
<td></td>
<td>without deficits in</td>
<td>functioning, memory, language.</td>
<td></td>
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<tr>
<td></td>
<td>other cognitive</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>domains.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imaging:</td>
<td>Medial temporal lobe</td>
<td>Nonspecific findings. Diffuse cerebral atro-</td>
<td>Nonspecific or normal.</td>
</tr>
<tr>
<td>Structural MRI</td>
<td>(MTL) atrophy and</td>
<td>phy, relative sparing of MTL compared with AD.</td>
<td></td>
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<td></td>
<td>volume loss in the</td>
<td></td>
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<td></td>
<td>hippocampus, entorhinal</td>
<td></td>
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<tr>
<td></td>
<td>cortex, or amygdala.</td>
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<tr>
<td></td>
<td>Diffuse cortical atrophy</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>over time.</td>
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<td></td>
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<tr>
<td>Functional</td>
<td>Bilateral temporo-</td>
<td>Decreased occipital activity on perfusion</td>
<td>Reduced glucose metabolism in the frontal</td>
</tr>
<tr>
<td>or SPECT</td>
<td>parietal and posterior</td>
<td>SPECT and 18F-FDG PET.</td>
<td>and parietal cortex (18F-FDG) PET</td>
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<td></td>
<td>cingulate cortex</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>hypometabolism on</td>
<td></td>
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<tr>
<td></td>
<td>SPECT and 18F-FDG PET.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DAT-SPECT:</td>
<td>Normal</td>
<td>Decreased uptake in the basal ganglia.</td>
<td>Decreased uptake in the basal ganglia.</td>
</tr>
<tr>
<td>Dopamine transporter binding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potential CSF biomarkers:</td>
<td>↓ alpha-synuclein</td>
<td>↑ alpha-synuclein</td>
<td>↑ alpha-synuclein (↓ beta-amyloid 1-42 may be a marker for progression in PD-D)</td>
</tr>
<tr>
<td></td>
<td>↓↓ beta-amyloid 1-42</td>
<td>↓↓ total tau and phosphorylated tau</td>
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<td></td>
<td>↑ total tau and</td>
<td></td>
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<td></td>
<td>phosphorylated tau</td>
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</tbody>
</table>

AD = Alzheimer’s dementia; CSF = cerebrospinal fluid; DAT = dopamine transporter; DLB = dementia with Lewy bodies; MRI = magnetic resonance imaging; PD-D = dementia associated with Parkinson’s disease; PET = positron emission tomography; SPECT = single photon emission computed tomography.

Source: Aloysi and Aron
illustrates mechanisms implicated in the conversion of Parkinson’s to PD-D.4

Cognitive dysfunction emerging within Parkinson’s predominantly involves executive impairment. This patient’s high MMSE score may simply reflect the insensitivity of that screening measure to Parkinson’s-related cognitive failure. Inventories that assess executive function (eg, Montreal Cognitive Assessment [MoCA]) may better evaluate for emerging cognitive dysfunction in Parkinson’s. However, the practice parameters recommended by the American Academy of Neurology (AAN) include screening for dementia in Parkinson’s using the MMSE or the Cambridge Cognitive Exam (CAMCog).1 The Movement Disorder Society (MDS) characterizes the dementia of Parkinson’s by impairment in at least two of the following: attention; executive functioning; visuospatial functioning; and free recall memory.3

The differential diagnosis of PD-D is wide (see Sidebar 2, page 474). Additionally, PD-D can be complicated by comorbidities typical of older patients, including other neurodegenerative and cerebrovascular processes. Neurodegenerative conditions with symptomatic and/or neuropathological overlap with PD-D include dementia with Lewy bodies (DLB) and other historically grouped “Parkinson’s plus” syndromes. Clinical features, neuroimaging, and CSF biomarkers may distinguish common de- mencias (see Table 1, page 474).3-12

Treatment of PD-D begins with searching for reversible comorbidities, optimizing environmental factors, adjusting dopaminergic medications, and attempting to preserve cognitive function. AAN practice parameters1 and an analysis in a recent Cochrane Review13 support using cholinesterase inhibitors such as rivastigmine or donepezil in PD-D, as they lead to modest improvements in global assessment, cognition, behavior, and activities of daily liv- ing (ADLs). Rivastigmine remains the only Food and Drug Administration-approved agent for PD-D.

Although there is no clear evidence-based support for the use of memantine in PD-D, some data suggest it is well-tolerated, can improve overall quality of life, and can lead to amelioration of REM sleep behavior disorder (RBD), which is prevalent in Parkinson’s patients and can even long precede the onset of the disease or other neurodegenerative disorders (or can occur on its own).3

Management of noncognitive symptomatology is a primary target in the treatment of patients with PD-D. While treatment of mood symptoms can be relatively straightforward, other neuropsychiatric issues are more nuanced. For example, what may seem to be panic attacks may actually be nonmotor “off” phenomena, and may resolve with agents that prolong levodopa action (eg, COMT-inhibitors).2,4

Nocturnal agitation may reflect RBD, which may respond to clonazepam, melatonin, gabapentin, or memantine. Treatment of psychotic features is typically challenging, in that the use of dopamine antagonists is relatively constrained by the parkinsonian motor context.

With the advance of additional available treatments for the motor aspects of Parkinson’s (eg, deep brain stimulation), management of the neuropsychiatric features of the disease requires increasingly sophisticated diagnostic assessments and innovative treatment designs.

REFERENCES