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Neuropsychiatric Symptoms in Parkinson Disease and Dementia with Lewy Bodies: What Geriatric Psychiatry Can Learn

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In an examination of the history of psychiatric and cognitive research in Parkinson disease (PD), it was noted that in the first year of publication of *Movement Disorders* (1986), none of the issues contained primary manuscripts that pertained to the psychiatric and cognitive complications of PD.¹ The neuropsychiatric symptoms (NPS; defined here as psychiatric and cognitive complications) of PD received scant attention at that time, although there was an appreciation, present since James Parkinson's legendary quote about the melancholic features of his defining case, that depression was common. In addition, ever since levodopa was introduced as the first dopamine replacement therapy in the 1960s, studies have documented the occurrence of psychotic symptoms in treated PD patients. In general, it was thought that the "senses" were mainly preserved, in part because the shortened life span of PD patients at that time precluded the development of dementia. When dementia (PDD) did occur, it was considered most often to represent the co-occurrence of Alzheimer disease (AD). Other psychiatric and cognitive complications in PD either were not commonly recognized or were not frequent due to the limited prevailing treatment options available. Beyond a very limited understanding of the epidemiology of these disorders, very little research was conducted on assessment, diagnosis, impact, course, neuropathophysiology, or treatment.

Fast forwarding 25 years, although PD is still considered a movement disorder and is diagnosed on that basis, the high prevalence of NPS suggests it is more accurately conceptualized as a neurocognitive-psychiatric disorder. In addition to the most commonly studied aforementioned disorders, other relatively common psychiatric complications include impulse control disorders, anxiety symptoms, disorders of sleep and wakefulness, and apathy. The emergent focus on the NMS of PD over the past 25 years is exemplified by the nonlinear increase in the number of published manuscripts devoted to this topic¹ and by quality improvement efforts that increasingly stress the nonmotor features of the disease.^{2,3}

The original lack of focus on cognition in PD, particularly early in the disease course, led astute clinicians to recognize patients who presented with concomitant dementia and parkinsonism, giving rise to the new diagnosis of dementia with Lewy bodies (DLB), now considered the second most common dementia diagnosis in the developed world after AD.⁴

The clinical features of PDD and DLB are very similar (i.e., presence of dementia plus triad of parkinsonism, fluctuating cognition, and visual hallucinations), as is their neuropathology, and it is controversial whether they are distinct illnesses or simply the same disease with different time courses for the presentation of cognitive deficits relative to parkinsonism. When considering the diseases together, the term Lewy body disease (LBD) is typically used, because Lewy bodies and neurites (intraneuronal aggregates of misfolded α -synuclein) are the pathologic hallmarks of both diseases.

LBD MANUSCRIPTS IN CURRENT ISSUE

Visuoperceptual disturbance are common in LBD. In “Testing visual perception in dementia with Lewy bodies and Alzheimer’s disease,” Wood et al.⁵ piloted a new computerized neuropsychological assessment for visuoperceptual abilities, the Newcastle visuoperception battery, which is independent of motor function and has minimal global cognitive load. In a sample of 28 AD and 26 DLB patients as well as 35 healthy elderly control subjects, the Newcastle visuoperception battery was used to test angle, color, and form discrimination and motion perception, ultimately generating a composite visuoperception score. DLB patients performed significantly worse than AD participants on the composite score, with visuoperceptual deficits present in 71% of DLB group. Visuoperceptual performance was significantly related to global cognitive performance in DLB patients, potentially raising questions about the specificity of the Newcastle visuoperception battery.

The results highlight how common visuoperceptual disturbances are in DLB, show that they can be used to help distinguish it from AD at a group level, and help introduce a computerized cognitive battery that may be useful for clinical research in LBD. Given how common visual hallucinations are in LBD, it would have been helpful to know if visuoperceptual disturbances in the DLB patients were associated with the severity of visual hallucinations or other visual perceptual symptoms (e.g., presence or passage phenomena), as this might provide additional insight into the neural substrate of hallucinations in this population. The authors hint at this latter point by noting that the Newcastle visuoperception battery tests visual function in both the dorsal and ventral visual pathways that have been shown to be altered in functional magnetic resonance imaging activation studies in LBD patients with visual hallucinations.

Another common neuropsychologic deficit in LBD is executive impairment, and at times the behavioral manifestations of frontal lobe dysfunction. In “Neuropsychiatric features of frontal lobe dysfunction in autopsy-confirmed patients with Lewy bodies and ‘pure’ Alzheimer’s disease,” Peavy et al.⁶ compared autopsy-confirmed DLB and AD patients on the frequency of frontal lobe behaviors and their association with dementia severity. There was a significant dementia severity by diagnosis interaction on multiple frontal behavior ratings. AD patients showed significant impairment across the range of dementia severity, whereas behavior was relatively preserved for DLB patients in early disease. The authors hypothesized that frontal-subcortical circuits associated with frontal lobe behaviors are affected early in AD but not until later stages in DLB, which may aid in differentiating the two diseases. The results are somewhat surprising, because in early disease executive impairment is more pronounced and overall NPS scores higher in DLB compared with AD.

However, the small sample size of DLB patients precludes drawing definitive conclusions from this study.

In “Pharmacologic treatment of anxiety disorders in Parkinson’s disease,” Pontone et al.⁷ investigated pharmacologic treatment of anxiety disorders in idiopathic PD, examining 250 patients at three community-based movement disorder neurology practices. A current anxiety diagnosis was present in 37% of patients, confirming the high prevalence of anxiety disorders in PD. For those patients with an anxiety disorder(s) only (i.e., no comorbid depression diagnosis), only half were treated with medications effective for anxiety, primarily antidepressants. However, when anxious subjects with comorbid depressive disorders were included, close to three-fourths of patients were on medications that might treat anxiety symptoms. Thus, clinicians are more likely to recognize and treat depressive symptoms compared with anxiety symptoms, not surprising given the longstanding focus on depression as the major psychiatric disorder in PD. However, this indicates a significant clinical problem, because anxiety in PD is also very common and often more distressing and disabling than depression.

In “Prevalence of Parkinson’s disease and Parkinson’s disease dementia in community nursing homes,” Hoegh et al.⁸ estimated the prevalence of both PD itself and PDD specifically in three community nursing homes in the St. Louis metropolitan area, with dementia ascertained by assessing patients directly. Fifty-five of 714 nursing home residents (8%) met criteria for PD, a prevalence higher than in the general elderly population, not unexpected given that advanced PD is a risk factor for nursing home placement. Of those patients who agreed to undergo additional cognitive testing, approximately half met criteria for PDD, a frequency of dementia consistent with the cumulative prevalence rate reported in recent longitudinal studies. It was noteworthy that not a single dementia patient carried a diagnosis of PDD in their medical record, and only about 10% were on U.S. Food and Drug Administration–approved treatment for PDD. Given that both PD and dementia are overrepresented in institutional settings, the prevalence findings are not surprising, but the fact that PDD patients are undiagnosed and may be receiving suboptimal care is concerning.

UNANSWERED QUESTIONS IN LBD NEUROPSYCHIATRY

The four articles pertaining to LBD published in this issue of *The American Journal of Geriatric Psychiatry* together make a significant contribution to increase our understanding of the epidemiology, clinical presentation, and treatment of LBD. Additional research is needed to address our incomplete understanding of the epidemiology, phenomenology, risk factors, neuropathophysiology, and optimal management strategies for all NPS that occur in LBD. Despite the increasing recognition of DLB as a common dementing illness, research into it still pales in comparison with that done in PD.

There are several high priority areas for future research. First, observational studies are needed in large LBD cohorts to examine predictors, development, course, and impact of NPS. Second, sophisticated statistical techniques should be incorporated to refine the classification of NPS in LBD and to account for the significant comorbidity, heterogeneity, and variability in symptoms that occur. Third, recognition and diagnosis could be improved

through continued development and validation of LBD-specific diagnostic criteria and assessment tools for NPS. Fourth, we need to improve our knowledge of the neural substrate of NPS, through examination of neuropathology, biomarkers, neurotransmitters, brain structure, and neural circuitry. Fifth, a better understanding is needed of the psychiatric and cognitive benefits versus risks of deep brain stimulation, increasingly used as a treatment for PD. Sixth, the ongoing DLB versus PDD debate needs to be resolved, given the extensive overlap between the two diseases, with additional research and expert consensus needed to determine if maintaining separate diagnostic categories for these two disorders is still indicated. Finally, large-scale, controlled, clinical trials need to be conducted to determine the efficacy of different interventions for NPS in LBD, including use of disease-modifying agents (when available) to delay or prevent development of NPS in advanced disease.

RELEVANCE OF LBD TO GERIATRIC PSYCHIATRY

Beyond being a common disease with numerous, highly prevalent, and clinically significant NPS, LBD is important to the field of geriatric psychiatry for its ability to help inform our understanding of the etiology and treatment of numerous psychiatric disorders of late life. This statement is based on the following observations.

First, if one examines the psychiatric disorders listed in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*, a large number of them occur commonly in the context of LBD, including depression, anxiety, psychosis, dementia, impulse control disorders, apathy, and disorders of sleep and wakefulness. Second, different NPS are commonly comorbid in LBD, suggesting shared risk and pathophysiology for different clinical syndromes, which potentially can help link seemingly disparate disorders. Third, these NPS occur in the context of relatively common diseases, with approximately 2 million people in the United States being affected by either PD or DLB, making it a population that is relatively easy to study.

Additional insights can be gained from the study NPS in LBD. The neural substrate of synucleinopathies is relevant to psychiatry, with neuropathologic changes concentrated in monoamine-producing regions (i.e., significant deficits in dopamine, norepinephrine, serotonin, and acetylcholine), affected brain regions of psychiatric importance (e.g., the basal ganglia and prefrontal cortex), and impairments in neural pathways implicated in psychiatric disorders (e.g., corticostriatal-thalamic circuitry). Given that the primary neuropathology for LBD is known, once imaging biomarkers for α -synuclein are developed, it will be possible to correlate NPS with a specific disease biomarker in living patients.

Other intriguing aspects of NPS in LBD are that many of them (e.g., impaired olfaction, depression and anxiety, and rapid eye movement behavior disorder) can predate the onset of motor or cognitive symptoms. This strongly suggests a neurobiologic underpinning to many of these NPS, along with an ordered disease progression in the brain, which may be of relevance to other diseases that can have a prodromal state, including AD. Additionally, because some NPS in PD are induced by treatments for the motor aspects of the disease, such as dopamine agonists leading to the development of impulse control disorders, an advantage to studying these disorders in PD is the opportunity to induce remission and study

patients in both affected and unaffected states, which is not as easily done with psychiatric disorders in the general population.

The crossover between neurology and psychiatry is longstanding and extensive, including neurologic treatments being tested for the treatment of various psychiatric disorders. Recent examples include use of deep brain stimulation for depression, obsessive-compulsive disorder, and substance dependence, and the use of dopamine agonists for the treatment of depression. The ongoing study of NPS in LBD in particular can help the field of geriatric psychiatry continue to mature.

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