

LEWY BODY DEMENTIA: THE UNDER-RECOGNIZED BUT COMMON FOE

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Editor's note: After Alzheimer's disease, Lewy body dementia (LBD) is the most prevalent progressive dementia of the many cognitive disorders wreaking unspeakable havoc on millions of lives. LBD is characterized by the presence of Lewy bodies, which are abnormal aggregates of a protein called alpha-synuclein, and are found in regions of the brain that regulate behavior, memory, movement, and personality. Many of the symptoms of Alzheimer's, Parkinson's, and LBD overlap, but LBD is more difficult to diagnose. Underdiagnosis is just part of the reason why LBD is unknown to the public and many health-care providers, and why funding for research lags far behind that for almost every other cognitive disorder.

“He’s no longer the same, nor the person he used to be,” says Mrs. A of her husband of 52 years. Mr. A, a 70-year-old retired professor, looks strangely unaffected as Mrs. A helps steady his way as he cautiously approaches the clinic’s examination table. Until two years ago, his family saw him as perfectly healthy, a talented musician and the doting father of two adult children. But when he started relying on “sticky notes” to keep up with his daily activities and needed help to handle routine tasks, they began to suspect something was wrong. Over time, he became distant and withdrawn and would stare into space, a pale shadow of his once gregarious self.

Mrs. A shows the neurologist the bruise Mr. A sustained the previous night, following another of his terrible nightmares. Mr. A falls asleep during a portion of the interview, as he often does during the day. Mrs. A says there are “good days and bad days” as she recounts the first time her husband talked about seeing “little animals” that she knew did not exist. While he is unable to recall what he had for dinner the previous night, he remembers “fried rice” when his wife reminds him that they enjoyed his daughter’s favorite recipe. As Mrs. A fights back tears, she asks the neurologist, “They say it’s Lewy body dementia. Is that the same as Alzheimer’s?”

The Recognition Factor

Lewy body dementia (LBD) is not rare. According to the Lewy Body Dementia Association (www.LBDA.org), LBD affects approximately 1.3 million individuals in the United States and is the second most common form of dementia, after Alzheimer’s disease (which affects about 5 million).^{1,2} LBD actually encompasses two disorders: dementia with Lewy bodies (DLB) and Parkinson’s disease dementia (PDD); both represent a spectrum of symptoms involving cognition, movement, behavior, and sleep. The difference in diagnosis largely depends on the order of symptom presentation. If the movement disorder begins more than one year before any cognitive symptom, it is usually referred to as PDD, while any other pattern of symptom presentation is usually referred to as DLB. Both are generally referred to as LBD, even in scientific papers.

It is important to first clearly define what is meant by the term “dementia” and how LBD differs from Alzheimer’s. “Dementia” is a general term that describes a progressive decline in cognitive function that represents: (a) a change from previous abilities; (b) interference with everyday functioning; and (c) a condition not caused by another illness. There are many forms of dementia

(more than 100), with Alzheimer's considered the most common. While all individuals with dementia experience decline in memory, thinking, language, problem solving, judgment, and the ability to function independently, as well as changes in behavior, there is wide clinical overlap between the different types of dementia. As the diseases progress, the distinctions blur even further. What may make the distinction even more difficult and confusing is that many cases of dementia are actually "mixed," or due to multiple causes. In the case of LBD, nearly 80 percent of individuals will also have brain changes consistent with Alzheimer's, while almost 40 percent of those diagnosed as having Alzheimer's are found to have features of LBD.^{3,4} This overlap probably contributes to the difficulty in making a clinical diagnosis of LBD and helps to explain why so many patients and caregivers find the diagnostic experience so frustrating.⁵ Not only is there overlap between the separate and distinct LBD and Alzheimer's, but awareness and understanding of LBD are generally lower among both the public and the medical community.

The resulting underdiagnosis of LBD has far-reaching implications. In addition to delaying appropriate treatments to alleviate symptoms, the underdiagnosis may expose patients to potentially dangerous adverse reactions to certain medications (such as classic neuroleptic medications like haloperidol). Early and accurate diagnosis helps families prepare for their role in caregiving, specifically the behavioral management and their own emotional preparation in anticipation of the disease course, one that may have its own unique challenges and burdens.^{6,7} The attention to and advancement in research directed at the diagnosis and treatment of LBD significantly lag behind those of Alzheimer's, another consequence of the limited awareness and underdiagnosis.

Drawing Distinctions

Lewy body dementia and Alzheimer's share clinical as well as pathological features, making their separation challenging for even the most seasoned clinician. The presence of mixed forms of the illnesses complicates the picture further. A review of the features of LBD clarifies the picture.² The LBD diagnosis is made when a patient presents cognitive decline (i.e., a dementia) with at least two of the following features: (a) Parkinson's-like movement changes, including slowness, stiffness, tremor, or balance problems; (b) visual hallucinations, often of small people, children, or animals; (c) spontaneous changes in alertness, concentration, and attention, called cognitive fluctuations;

and (d) a sleep disorder causing people to “act out” their dreams, called rapid eye movement sleep behavior disorder (RBD). These symptoms are fairly specific to LBD, and are not present in most cases of Alzheimer’s or other dementias. The challenge for clinicians is to figure out how best to detect these symptoms. In particular, cognitive fluctuations are the most difficult symptoms for the clinician to elicit, unless specific questions are asked, such as those found in the Mayo Clinic Fluctuations Questionnaire.⁸

One clue to proper diagnosis is related to gender. LBD is found more commonly in men, whereas Alzheimer’s has a slight preponderance among females. A research study focusing on caregivers’ reports revealed that LBD’s most common presenting symptoms are memory impairment (57 percent), visual hallucinations (44 percent), depression (34 percent), difficulties with problem solving (33 percent), difficulty with gait (28 percent), and tremor/stiffness (25 percent). In contrast, almost all (99 percent) individuals with Alzheimer’s reported memory impairment as a presenting symptom.⁹ While difficulty with memory is a common presenting complaint in both forms of dementia, the nature of the impairment differs, particularly at the onset. Alzheimer’s affects the ability to encode new experiences into one’s long-term memory, whereas the disorder in LBD can be one that affects retrieval of memory.^{10,11} LBD patients may perform worse on visual-spatial tests than Alzheimer’s patients, while Alzheimer’s patients may perform worse on tests of language function.¹² Neuropsychological testing can help to tease out these differences.

In its early stages, LBD is also more likely to be associated with psychiatric symptoms. The patient not only sees nonexistent people, animals, body parts, or even vehicles, but may describe them in detail. He or she may even respond by talking to the hallucinations.⁷ Paranoia toward caregivers and unshakable false beliefs, such as that family members are being replaced by impostors, are more prevalent among individuals with LBD than among Alzheimer’s patients (this is called Capgras syndrome).¹³ Patients with Alzheimer’s frequently develop psychotic symptoms later in the course of the disease, such that the late stages of LBD and Alzheimer’s may be indistinguishable.¹⁴

Some evidence suggests that the ability to plan and organize complex tasks, known as “executive functioning,” is affected earlier in LBD than in other forms of dementia, although this is not a consistent finding. Patients with LBD are no longer able to perform routine tasks,¹⁵ and are often

found to be withdrawn earlier than those affected by Alzheimer's. This, coupled with partial awareness of their diminishing cognitive abilities, may be associated with higher frequency of depression, apathy, and social withdrawal.¹⁶

LBD also impairs the functioning of the autonomic nervous system, which regulates body functions such as blood pressure, heart rate, sweating, digestion, and bowel and bladder emptying. The clinical symptom of most concern is a decrease in blood pressure upon standing from a horizontal position, which increases the risk of dizziness and falls in about 15 percent of individuals with LBD. Patients are also found to have constipation (which may even pre-date the onset of cognitive symptoms), diarrhea, urinary dysfunction, excess salivation, decreased sweating, heat intolerance, impotence, and erectile dysfunction.^{12,17} Predictably, these symptoms add multiple layers to the care of an individual with LBD, thereby necessitating early and accurate diagnosis.

Neurological Causes

LBD is characterized by the presence of Lewy bodies in regions of the brain that regulate behavior, memory, movement, and personality. Lewy bodies are composed of abnormal aggregates of a protein called alpha-synuclein.² Autopsy findings of individuals with LBD have demonstrated amyloid plaques, which are the key pathological findings in Alzheimer's. However, the other characteristic feature in Alzheimer's, the "neurofibrillary tangles," consisting of aggregates of modified tau protein, are typically not associated with LBD.^{2,18} Scientists are just beginning to understand the steps of protein aggregation in Alzheimer's and LBD.

The knowledge of changes associated with Alzheimer's is far advanced compared with that of LBD. There are several reasons for this. First, the abnormal protein in LBD, alpha-synuclein, was discovered a decade later than the proteins involved in Alzheimer's. Second, the amount of overall pathology associated with alpha-synuclein occurs at lower levels than amyloid and tau proteins in Alzheimer's, which makes it harder to develop lab tests that measure it. Third, there are fewer genetic causes of LBD that can be used to create experimental models than there are of Alzheimer's. Finally, it has been more difficult to develop animal models of LBD that recapitulate both the pathology and the symptoms of the disease.

The brain uses chemicals called neurotransmitters to send messages from neuron to neuron, and multiple neurotransmitter systems are involved in LBD. A consistent finding has been the dysfunction of the cholinergic system. With LBD, it occurs earlier and to a greater degree than in Alzheimer's.¹⁹ It may also be responsible for LBD's earlier onset of hallucinations and fluctuations.¹⁷ It is noteworthy that one of the main groups of medications currently available to delay the progression of the dementia reverses the deficit in the cholinergic system. The dopamine system is also affected, leading to LBD's movement disorder, one that can be treated with the same medications used to treat Parkinson's.¹⁷ Because there does not seem to be an LBD-specific neurotransmitter, it is likely that the many research programs for Alzheimer's and Parkinson's will also provide potential therapies for LBD.

On brain imaging studies, both Alzheimer's and LBD demonstrate neuronal cell loss and shrinkage (atrophy) of the brain. However, volumetric MRI studies of individuals in similar stages of Alzheimer's and LBD reveal that the specific regions of the brain that control memory—namely the medial temporal lobes—are affected early in Alzheimer's but may be preserved until later stages in LBD.²⁰ SPECT scan, a type of nuclear medicine imaging technique using gamma rays, has shown that a transporter for the neurochemical dopamine is affected to a greater degree in LBD when compared to Alzheimer's.^{21,22} This type of imaging (called a DaTScan) has provided the first diagnostic test for LBD approved by the European Union, but it has not yet been approved by the Food and Drug Administration (FDA).

The Many Challenges

With the myriad symptoms that Mr. A experienced—memory impairment, problem solving and executive function impairment, fluctuation in cognition, vivid nightmares (RBD), visual hallucinations, and possible postural hypotension—diagnosing LBD correctly can be akin to solving a jigsaw puzzle. Primary-care providers rarely get it right. In a survey of more than 900 LBD patients and caregivers, 50 percent saw three doctors for more than 10 visits over the course of one year before an LBD diagnosis was established.⁵ First diagnoses given to the patients were most commonly Parkinson's or other movement disorders (39 percent), Alzheimer's or other cognitive disorders (36 percent), and mental illness (24 percent). Neurologists diagnosed most cases (62

percent), while primary-care providers diagnosed only 6 percent of cases.⁵ The remainder of cases (32 percent) are diagnosed by other specialties.

One could only imagine the challenges facing Mrs. A. In a survey, LBD caregivers expressed concerns about fear of future (77 percent), feeling stressed (54 percent), loss of social life (52 percent), and uncertainty about what to do next (50 percent).⁶ Caregivers reported moderate to severe burden; 80 percent felt the people around them did not understand their burden, and 54 percent reported feelings of isolation, with spousal caregivers reporting more burden than nonspousal caregivers.^{6,7} Two-thirds of the caregivers reported medical crises requiring emergency services, psychiatric care, or law enforcement.⁶

Studies of LBD caregivers have demonstrated higher subjective burden compared to that found in studies of individuals caring for those with Alzheimer's.⁷ The caregiving burden affects physical health, emotional health, and relationships with friends and family. A unique feature of the caregiving burden in dementia with Lewy bodies has been that caregivers question their performance in providing care. It has been suggested that the lack of awareness about dementia with Lewy bodies compared to Alzheimer's and other forms of dementia limits the access of caregivers to information and support, leading to emotional isolation and increasing perception of burden.⁷

Even when the diagnosis is made, there are no specific medications approved for the treatment of LBD. Instead, medications for Alzheimer's and Parkinson's are often used to treat individual symptoms. LBD's psychotic symptoms, such as visual hallucinations and behavioral disturbances in dementia, can often be distressing. Antipsychotic medications, often used in other dementias for psychotic symptoms and behavioral disturbances, require special caution in LBD. LBD patients may have an extreme sensitivity to antipsychotic medications, even at low doses, resulting in sudden confusion, worsening of rigidity and immobility, and, in rare cases, a lethal syndrome termed "neuroleptic malignant syndrome," which is accompanied by high fever.²³ LBD patients may also display paradoxical reactions to medications, whereby they become activated and awakened by commonly used sleep aids.²⁴

If medications are employed for LBD patients, a complex and delicate degree of balance is required. Drugs that are commonly used to treat the rigidity and immobility of Parkinson's cannot be used as liberally in dementia with Lewy bodies, since they tend to worsen hallucinations. Similarly, drugs used in treating urinary symptoms tend to cause confusion and worsen memory and attention.

Steps Ahead

Lewy bodies were first described in the early 1900s by Friederich H. Lewy while researching Parkinson's disease. However, the first case of LBD was not described until 1961, with the first set of clinical criteria put forth in 1996. One reason LBD research has lagged behind that focusing on Alzheimer's and Parkinson's for decades is due to an earlier notion that it was a rare disease. It wasn't until the development of a staining technique in the late 1990s that researchers learned how much more common LBD is than previously thought.

There is currently a dearth of drug development in LBD, which is urgently needed because of the limited availability of medications that do not exacerbate symptoms. With fewer unique disease targets identified to date, it is increasingly difficult to secure federal research funding in the current, very competitive climate. Another important problem that delays clinical trials for new medications is the current difficulty in diagnosing LBD. At the present time, it would be difficult to register a clinical trial with the FDA because it is unclear that clinicians could correctly make a diagnosis—this would affect both clinical trial recruitment as well as identifying appropriate patients for therapy.

There is good news on the horizon, though, in that there are some compounds being developed for cognition/dementia in Parkinson's, which is easier to diagnose due to the earlier broad Parkinson's diagnosis. Drugs that become FDA-approved for PD dementia may be ideal candidates for clinical trials in LBD down the road. New Alzheimer's drugs may also hold potential for LBD, due to the strong overlap of Alzheimer's pathology in LBD.

Like Alzheimer's and Parkinson's, LBD is a complicated illness and its mysteries won't be easy to solve. Because all three illnesses have similar symptoms, LBD is frequently misdiagnosed and underdiagnosed. This delays treatment with currently available medications, places individuals with

LBD at risk for exposure to severe medication side effects, and delays testing of promising therapeutics.

One way to improve diagnoses is to use standardized scales that increase the accuracy of detecting LBD, such as the Lewy Body Composite Risk Score,¹² containing 10 items that may accurately and reliably identify LBD as the cause of cognitive impairment. A number of research laboratories are now able to measure alpha-synuclein in cerebrospinal fluid; a clinically available test may be just on the horizon. A number of labs are actively trying to develop imaging markers for alpha-synuclein, similar to what has been done for amyloid imaging in Alzheimer's, but these are probably three to five years away.

These advances in diagnostics, however, hold great promise. For now, it is imperative to establish accurate diagnosis and institute prompt treatment. We also need to raise awareness of LBD for the public and for health-care providers through continuing medical education, increase advocacy for patients and caregivers by supporting groups such as the Lewy Body Dementia Association, and increase research funding to understand the causes and develop the novel therapies needed to address this under-recognized but all too common cause of dementia.

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