THE MICHAEL J. FOX FOUNDATION
FOR PARKINSON'S RESEARCH

DEMENTIA WITH LEWY BODIES: IN THE NEWS AND IN THE CLINIC

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ABSTRACT

Dementia is a global issue with implications for both individual families and society as a whole. Estimates hold that approximately 65 million people worldwide will be diagnosed with dementia by the year 2030. Dementia with Lewy bodies (DLB) is the second most common cause of neurodegenerative dementia. Primary care providers and general neurologists often are the initial contact for diagnosis; they then either manage patients and families independently or support them in conjunction with movement disorder or cognitive specialists. Regardless of their role on the health care team, all clinicians should be familiar with the nuances of this complicated disease.

The Scope of the Problem

Dementia with Lewy bodies (DLB) has been in the news since it was revealed that Robin Williams suffered hallucinations, paranoia and parkinsonism secondary to the condition. Dementia has also been in the spotlight given that November was National Caregivers Month. With widespread reporting on these topics by television media and Internet sources, clinicians are spending a lot of time correcting or clarifying information for patients and families who wonder whether they, too, will be robbed of their memories and ability to carry out activities of daily living by dementia. Physicians must be prepared to face these concerns and present a realistic, but not hopeless, picture of this disease.

DLB affects more than 1 million people in the United States and is second only to Alzheimer's dementia (AD) on the list of neurodegenerative causes of dementia. With the aging population, that number is expected to grow exponentially in accordance with what some have referred to as the "silver tsunami." Dementia will continue to upend the lives of even more patients and families, and our nation and current health care system must prepare to absorb the additional stress.

This article provides general guidelines regarding diagnosis and management of DLB, particularly in relation to idiopathic Parkinson's disease (PD) with associated dementia (sometimes referred to as PDD). Family and caregiver issues are addressed and ongoing research in Dementia with Lewy bodies is briefly covered.

Maintain a High Index of Suspicion for Dementia with Lewy Bodies

Dementia with Lewy bodies can present acutely or subacutely. Minor surgical procedures; illnesses, particularly those requiring hospitalization; or medications, such as narcotics, might trigger delirium, characterized by agitation, confusion and possible psychosis. Reflecting then on the preceding months to years, families will frequently identify mild cognitive problems that had previously

been attributed to aging or other conditions. Sometimes a spouse recognizes short-term memory issues or personality changes of which the patient is unaware or in denial. In other cases, a physician witnesses the unfolding of disease over time, from subtler concerns of difficulty multitasking or following directions along a continuum to fulminant dementia.

The central features of DLB are parkinsonism (bradykinesia, rigidity or tremor) and cognitive dysfunction. The latter develops prior to or within one year of motor symptoms and primarily influences attention, executive function and visuospatial domains. Consistent with dementia of any type, more than one aspect of cognition is impaired to a level that interferes with the patient's daily, occupational or social functioning. While it is a progressive illness, DLB is characterized by fluctuations in cognition and levels of consciousness. A person can be nearly lucid one moment and completely confused the next. Spontaneous visual hallucinations (i.e., not necessarily precipitated by medication) are very common in DLB, and delusions, agitation or other behavioral disturbances may also occur. Autonomic impairment is not uncommon and may include urinary dysfunction and orthostatic hypotension. Patients with DLB may experience falls early in the disease course.

As with most neurodegenerative diseases, DLB is thought to result from a constellation of genetics, environmental factors and aging.

The differential diagnosis of DLB is broad. Reversible causes of cognitive impairment—vitamin B12 deficiency, thyroid hormone abnormalities, syphilis, pseudodementia secondary to depression, structural lesions or normal pressure hydrocephalus—must be ruled out. Other possible etiologies of dementia to be considered include AD, PDD, vascular dementia, frontotemporal dementia (FTD) and prion-related disorders such as Creutzfeld-Jakob disease.

Differentiating Dementia with Lewy Bodies from Parkinson's-Associated Dementia

Because of the parkinsonism seen in dementia with Lewy bodies, PDD is usually high on the list of other possible causes. Separating the two can be difficult but relies on:

- the temporal correlation between onset of motor symptoms and cognitive deficits,
- the presence of spontaneous or severe hallucinations early in the disease course,
- and a tendency toward earlier falls and more significant autonomic dysfunction.

In PDD, significant cognitive deficits follow motor symptoms by several years—10, on average. An estimated 50-80% of people with PD will be afflicted with dementia. Although visual hallucinations and autonomic disturbances may be present in both conditions, they tend to be more prominent and present earlier in DLB.

Diagnosing Dementia with Lewy Bodies

TThe diagnosis of DLB—obviously serious and life-changing—rests on clinical expertise. The lack of confirmatory testing understandably makes everyone a bit uneasy. A formal neuropsychological evaluation can provide supportive data regarding the degree and pattern of cognitive dysfunction. Unfortunately the duration and intensity of testing, along with cost, can serve as deterrents. Brain PET or SPECT perfusion imaging are sometimes contemplated, but financial and geographic constraints—and the fact that results don't change management—limit their utility. In addition, DAT scanning does not at present distinguish among the various neurodegenerative parkinsonian conditions. The Mini Mental Status Examination (MMSE) can monitor progression of disease when repeatedly administered over time, but, for screening purposes, The Montreal Cognitive Assessment (MoCA) is a more appropriate tool.

DLB can be verified only at autopsy. Lewy bodies—aggregates of abnormally folded alpha-synuclein, ubiquitin and other proteins—are widely distributed throughout the brain but are densest in the cortex. Of note, these pathological clusters are present in idiopathic PD and PDD as well but to a different degree and dissemination. The brains of patients with DLB also demonstrate loss of neurons, vascular abnormalities and basal forebrain cholinergic deficits. Interestingly, the beta-amyloid plaques and phosphorylated tau protein tangles of Alzheimer's disease are seen in all of these conditions as well.

Treatment Is Symptomatic and Supportive

No disease-modifying agent is available for DLB. Cholinesterase inhibitors—rivastigmine or donepezil—may provide a modest improvement in cognition and lessen hallucinations. Memantine has demonstrated benefit in small trials. Medications that can exacerbate mental status symptoms, such as anticholinergics, are best avoided or minimized. Neuroleptics—even atypicals—should be used cautiously, if at all. Patients with DLB are particularly sensitive to these agents and may experience worsening of parkinsonism and cognition. If antipsychotics are absolutely necessary, quetiapine is commonly used because it has the fewest extrapyramidal side effects. Clozapine is an option as well, but the risk of agranulocytosis

limits its use. Newer therapies with a better side effect profile may be on the horizon. Pimavanserin, a selective serotonin inverse agonist, is currently under review by the FDA for the treatment of Parkinson's disease psychosis. Wakefulness promoting agents—modafanil or armodafanil—have been employed to increase alertness and limit daytime sleepiness but may worsen confusion and psychosis. SSRIs or SNRIs may be used to treat associated depression and anxiety. Levodopa can be prescribed for parkinsonism, but patients do not generally experience a robust response. In addition, levodopa may be more likely to induce psychosis or confusion in DLB patients. Dopamine agonists are rarely, if ever, used. For sleep disturbances and REM sleep behavior disorder (RBD), low doses of as-needed benzodiazepines could be considered, taking into account the inherent risks of sedation and falls. Many clinicians have begun to try melatonin first for insomnia and RBD as it is less likely to precipitate delirium or imbalance.

Active Research Is Ongoing

Many clinical trials surrounding the diagnosis and management of DLB are under way. European studies are recruiting patients for deep brain stimulation of the nucleus basalis of Meynert. One U.S. study is looking to examine whether treadmill walking can improve mobility and decrease falls. Another is attempting to repurpose nilotinib—a tyrosine kinase inhibitor currently approved for chronic myelogenous leukemia—to clear Lewy bodies and slow disease progression.

Participation in clinical trials allows patients, families and friends to take a proactive approach to a disease that may otherwise feel hopeless. Fox Trial Finder is a great resource to match patients, based on a de-identified medical profile, to available recruiting studies. Post-mortem brain donation is a possibility as well but needs to be considered before death; many centers require office visits and examinations so that autopsy findings can be correlated with clinical symptoms.

Dementia with Lewy Bodies Touches an Entire Family

In the course of the disease, a significant other switches from partner to primary caregiver and family members are called upon for ancillary physical, financial and emotional aid. Everyone involved must adapt to the patient's progressive disease and changing needs.

A person with DLB is apt to require some level of supervision around the clock, but this depends on the stage of disease. The home environment and caregivers should remain familiar. Hearing loss or visual impairment must be remedied so as not to aggravate confusion and hallucinations. Driving is unlikely to be safe, but patients may argue for their privileges, even just to get to church or the local store. In these cases, an independent driving assessment, as offered by a rehabilitation center or AAA, is beneficial.

To minimize confusion and agitation, patients should adopt a regular daily routine and sleep schedule. Keeping a drowsy person awake by day and calm in bed despite hallucinations or REM sleep behavior disorder at night is definitely easier said than done. Planned daytime activities, like exercise or social interaction at a senior center, and limitation of daytime napping may help. Bed alarms, which sound when a patient gets up at night, can alert a sleeping care partner.

Doors must remain locked at all times to prevent outside wandering. An identification bracelet should be worn. To ensure patient and family safety, weapons, power tools and toxic chemicals need to be locked up or removed from the home.

Therapists are a necessary part of the professional care team. Physical and occupational therapists manage motor symptoms, gait instability and falls. They recommend adjustments and adaptations to improve home safety—removal of loose rugs and cords that can cause tripping; a bedside commode to prevent unsteady nighttime ambulation; and a hospital bed, chair lift or bathroom grab bars for ease of transfer and increased stability. They may suggest appropriate walking aids (taking into consideration that cognitive dysfunction will restrict use) and teach exercises to improve strength and range of motion. Speech therapists can attend to dysphagia by completing a swallowing evaluation and modifying diet and mealtime postures.

Difficult Conversations Early Can Ease Later Transitions

As dementia progresses, the patient will require more intensive care and assistance with all activities of daily living. Dysphagia elevates risk of aspiration pneumonia; falls can lead to head trauma and hip fracture; and immobility may result in deep venous thrombosis, urinary tract infection or decubitus ulceration. Eventually, a caregiver may become unable to safely and adequately support the patient at home due to his or her own physical and/or mental limitations. This possibility should be discussed sooner rather than later so that choices can be made before an urgent situation necessitates a pressured decision.

Social workers can educate families on long-term care options, insurance issues and financial considerations. They can also serve as liaisons to support groups and services.

Palliative care physicians offer extremely valuable input on symptom management in the advanced stages of dementia. Hospice care can be incorporated when the expected duration of life is six months or less.

Average survival time is five to eight years from determination of dementia, but, of course, this varies. A patient and family should be encouraged to complete advance directives—a living will and health care power of attorney paperwork—shortly after diagnosis. This topic is often overlooked but can be framed in a positive manner—advance directives give a patient power in a disease that otherwise strips control. Patients can be confident that their wishes for the later stages of life and death will be honored. Families can be comforted knowing they are fulfilling these desires.

Don't Overlook a Caregiver's Needs

Clearly a clinician's primary focus is his or her patient. With this disease, however, ensuring the well-being of caregivers is a priority. They should be regularly asked about their own health, encouraged to schedule their own activities and remain socially active, and instructed to enlist the help of others for short-term respite or an uninterrupted night of sleep. Other family members can be invited to participate in doctor visits so that they can be informed about the disease and how they can assist their loved ones. Education is invaluable; physicians should direct families to appropriate online and print resources.

Caregiver participation in support groups, even online, is crucial for preventing isolation, validating struggles and learning coping strategies. The Lewy Body Dementia Association website is a good resource for both families and physicians. While Parkinson's-specific, the Partners in Parkinson's initiative from The Michael J. Fox Foundation and AbbVie may be beneficial in identifying and connecting with local and online support and resources.

In a disease in which symptomatic drug therapies leave much to be desired, the office visit becomes a major component of management. Gently leading a patient into the exam room and listening with an empathetic ear can relay powerful messages of care and concern. This alone may ease the burden of disease more than any prescription ever could and that might spark even a small bit of hope necessary for patients and families to continue the daily fight against dementia.

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The Michael J. Fox Foundation is the largest nonprofit funder of Parkinson's disease research worldwide. The Foundation is dedicated to finding a cure for Parkinson's disease through an aggressively funded research agenda and to ensuring the development of improved therapies for those living with Parkinson's today. Because patients are vital partners in this process, the Foundation works to mobilize volunteer engagement in research by providing education and direct research-related services to Parkinson's clinicians, researchers, patients and families.