Lewy Body Dementia

The second highest cause of dementia is highly variable.

By James E. Galvin, MD, MPH

Introduction

Lewy body dementia (LBD) is an umbrella term that covers 2 closely related diagnoses, dementia with Lewy bodies (DLB)[1] and Parkinson's disease dementia (PDD).[2,3] LBD is the second most common cause of dementia after Alzheimer's disease (AD) affecting approximately 1.4 million Americans.[4] Over the past 2 decades, research has suggested that Lewy bodies (LBs) are found in up to 40% of autopsied brains.[5,6] Although the term LBD covers both PDD and DLB, it is typically used when describing the spectrum of neurodegenerative disease with LB pathology, whereas the terms PDD and DLB are more commonly used when citing specific experimental and clinical conditions.[5]

The precise number of people with LBD remains unclear. The point prevalence of dementia in PD is close to 30%, and the incidence rate is increased at 4 to 6 times relative to controls. The cumulative percentage is very high, with at least 75% of people with PD who survive more than 10 years likely to develop dementia.[7] The mean time from onset of PD to dementia is approximately 10 years. However, there is considerable variation, and some people develop dementia early in the disease course. Age, more severe motor symptoms (in particular, gait and postural disturbances), mild cognitive impairment at baseline, and visual hallucinations are reliably identified as risk factors for early dementia.

Prevalence estimates of DLB range from 0% to 5% in the general population and from 0% to 30.5% of all dementia cases.[8] Very few studies have looked at the incidence rates for DLB with reports suggesting incidence rates of 0.1% in the general population, and 3% for all new dementia cases. A recent review examined 22 studies and reported incidence rates between 0.5 to 1.6 per 1,000 person years, accounting for 3% to 7% of dementia cases.[9] Prevalence estimates ranged from 0.02 to 63.5 per 1,000, increasing with increasing age.

There is no single sign or symptom that definitively distinguishes PDD from DLB.[2-5] Current clinical criteria for DLB distinguish PDD only by the temporal requirement that the dementia manifests more than 12 months after the onset of motor signs; if dementia precedes or is concurrent with parkinsonism, then DLB is diagnosed.[2-5] There is ongoing debate regarding the validity of the 1-year rule between PDD and DLB researchers.[10,11] Further confusing the clinical picture, the signs and symptoms of LBD may resemble the more widely recognized dementia syndrome of AD (particularly in the early stages). However, with careful evaluation, LBD can be distinguished from AD by application of consensus criteria for DLB[1] or PDD[2,3] and use of indicative biomarkers.

Clinical Features

The clinical dementia picture of LBD revolves around the identification of the visuospatial, executive and attentional deficits, rather than marked episodic memory impairment that characterizes AD (Table 1). Additionally, LBD often demonstrates notable improved with cued recall compared with AD. These cognitive symptoms together with evidence of parkinsonism, cognitive fluctuations, visual hallucinations, and rapid eye movement sleep behavioral disorder (RBD) are core features of LBD.[1] Of the all the core features, cognitive fluctuations, while quite specific for LBD, can be difficult to elicit even at specialized centers. A number of scales have been developed, including the Clinical Assessment of Fluctuation and the One-Day Fluctuation Assessment Scale, and the Mayo Fluctuations Questionnaires.[12] The Mayo scale describes 4 features of fluctuations that can reliably distinguish DLB from AD or normal aging. In this composite, 3 or 4 features occurred in 63% of individuals who had DLB compared with 12% of those who had AD and 0.5% of normally functioning people in the same age range. In addition to core features, there are supportive features that may facilitate diagnosis such as depression, apathy, anxiety, hallucinations in other modalities, syncope and frequent falls, transient and unexplained loss of consciousness, and autonomic dysfunction.[1,5]

Neuropsychologic Features

Neuropsychologic evaluation has provided clinicians and researchers with profiles of cognitive strengths and weaknesses that help to define LBD, as well as distinguish LBD from AD (Table 2).[13,14] As a general rule, cognitive symptoms in LBD include a combination of cortical and subcortical impairment; this is contrasted with a classic cortical profile of impairment predominant in AD. LBD is typified by impairments in attention and executive functions.[13,14]

TABLE 1. FEATURES OF LEWY BODY DEMENTIA

Domain	Features
Cognitive	Visual tracking and attention
	Visuospatial and perception
	Episodic memory deficits that improve with cued recall
	Timed attention tasks
	Executive tasks
	Construction tasks
	Verbal and psychomotor initiation
	Cognitive fluctuations
Movement	Bradykinesia
	Rigidity (with or without cogwheeling)
	Festinating gait
	Postural instability with falls
	Rest, postural, or action tremor
Behavioral	Well-formed visual hallucinations (eg, little people, furry animals)
	Delusions (eg, Capgras or misidentification)
	Depression
	Anxiety
	Apathy
	Hallucinations in other modalities
	REM sleep behavior disorder
Autonomic/ constitutional	Orthostatic hypotension
	Loss of smell
	Constipation
	Sialorrhea/rhinorrhea
	Sexual dysfunction
	Urinary incontinence
	Hyperhidrosis
	Seborrheic dermatitis

TABLE 2. NEUROPSYCHOLOGIC DEFICITS IN ALZHEIMER'S DISEASE VS LEWY BODY DEMENTIA

Domain	Alzheimer's disease	Lewy body dementia
Episodic memory		
Free recall	Early, severe	Moderate
Recognition	Early, severe	No impairment
Prompting	Not helpful	Helpful
Intrusions	Early, severe	Early, severe
Semantic memory (naming)	Moderate	Mild
Procedural memory	No impairment	Mild
Working memory	Moderate	Early, severe
Insight	Early, severe	Mild
Attention	Moderate	Early, severe
Executive functions	Moderate in typical disease Early, significant in frontal variant	Early, severe
Visuospatial skills	Moderate in typical disease Early, significant in the posterior variant	Early, severe

Visuospatial deficits are common in LBD and represent a very early and sensitive marker, especially when LB pathology and AD are mixed.[15,16] In terms of memory testing, people with LBD generally perform better than those with AD for any given level of dementia severity, and are more likely to improve with cued recall and recognition than people with AD.[14] Individuals with LBD generally show milder naming deficits than those with AD on measures of confrontation naming, whereas people with LBD may perform worse than those with AD in category and letter fluency tasks.[5,14] This may be due to verbal initiation in timed tasks seen in LBD as well as attentional and executive difficulties.

Behavioral and Neuropsychiatric Features

Hallucinations and delusions are common in LBD, elicited primarily through informant interviews and less so from patient reports or direct observation by clinicians.[17] Visual hallucinations in LBD tend to occur early in the course of the disease, be well-formed, detailed, and most commonly involving anonymous people (often described by the patient as dysmorphic or small), although they may also involve family members, animals, body parts, and machines.[5,17] Visual hallucinations in AD tend to occur later in the disease and be ill-formed and poorly described by patients.[5,17] Hallucinations can occur in other modalities, including auditory, tactile and olfactory.[1] Auditory hallucinations are less common and generally not present in the absence of visual hallucinations.

Delusions tend to be more common in DLB than in PDD or AD.[18] Paranoid, Capgras (believing individuals are replaced by identical imposter), and "phantom boarder" (unseen individuals residing in one's home) symptoms are among the most common content of the delusions.[18] Capgras syndrome almost always accompanies visual hal-

lucinations and anxiety in DLB. Misidentification syndromes appear to be particularly prevalent in LBD occurring in up to 40% of people with DLB, compared with 10% in people with AD. Depression, anxiety, and apathy are common in both LBD and AD.[5,14,19]

Autonomic and Constitutional Features

Autonomic dysfunction is a common clinical sign in LBD.[20] Symptomatic orthostasis is probably the most serious manifestation of autonomic dysfunction, but other features include decreased or increased sweating, excessive salivation (sialorrhea), seborrhea, heat intolerance, urinary dysfunction, constipation or obstipation, erectile dysfunction, impotence, and changes in libido. Interestingly, constipation may precede any cognitive or motor symptoms by more than a decade. Other constitutional features include anosmia and excessive daytime sleepiness.

Improving Diagnosis With Composite Scores

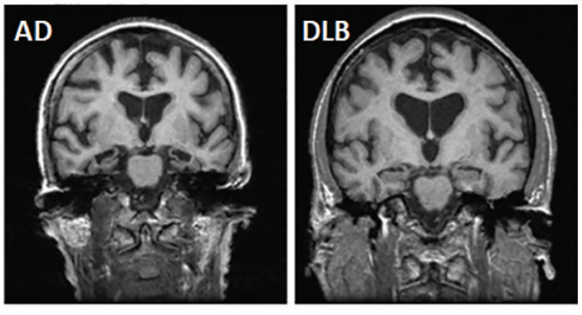
A diagnostic challenge, particularly outside of expert centers, there are long delays in diagnosing LBD leading to significant burden. Although consensus criteria have excellent specificity, there is no standardized way to assess symptoms, reducing sensitivity. We developed the LB Composite Risk Score (LBCRS)[21] from autopsy-verified cases to improve the ability to detect LBD in clinic and research populations (Figure).

The LBCRS was validated in a consecutive series of 256 participants compared with the Clinical Dementia Rating (CDR) and criterion standard measures of cognition, motor symptoms, function, and behavior. Receiver operator characteristic (ROC) curves demonstrated that the LBCRS was able to differentiate: (a) LBD from AD; (b) LBD from all dementias, and (c) mild cognitive impairment (MCI) due to LBD from MCI due to AD. Mean LBCRS scores were significantly different between LBD and AD (6.1 ± 2.0 vs 2.4 ± 1.3, $P < .001$) and between MCI-LBD vs MCI-AD (3.2 ± 0.9 vs 1.0 ± 0.8, $P < .001$). Using a cut-off score of 3, areas under ROC for DLB vs AD were 0.93 ± 0.89-0.98), and for MCI-DLB vs MCI-AD were 0.96 ± 0.91-1.0. Translations of the LBCRS demonstrate similar psychometric properties.[22] Other tools include the Assessment Toolkit for Lewy Body Dementia[23] that corresponds to consensus criteria for DLB and PDD. The use of tools such the LBCRS and the LBD Assessment Toolkit increases diagnostic probability that LB pathology is contributing to a dementia syndrome and should improve clinical detection, diagnosis and treatment, as well as case ascertainment to enhance enrollment for clinical trials.

A

Please rate the following symptoms as being present or absent for at least 3 times over the past 6 months. Does the patient...	Yes	No
Have slowness in initiating and maintaining movement or have frequent hesitations or pauses during movement?		
Have rigidity (with or without cogwheeling) on passive range of motion in any of the 4 extremities?		
Have a loss of postural stability (balance) with or without frequent falls?		
Have a tremor at rest in any of the 4 extremities or head?		
Have excessive daytime sleepiness and/or seem drowsy and lethargic when awake?		
Have episodes of illogical thinking or incoherent, random thoughts?		
Have frequent staring spells or periods of blank looks?		
Have visual hallucinations (see things not really there)?		
Appear to act out his/her dreams (kick, punch, thrash, shout or scream)?		
Have orthostatic hypotension or other signs of autonomic insufficiency?		
TOTAL SCORE		

B



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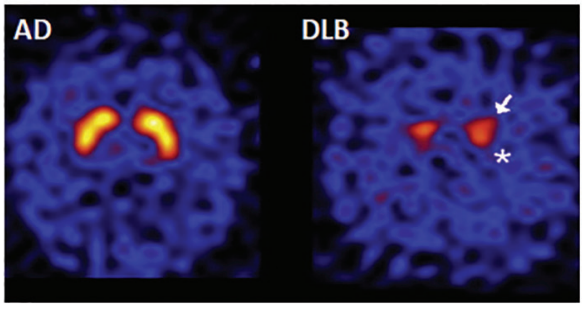

Figure. Diagnostic Tools for Dementia With Lewy Bodies. The Lewy Body Composite Risk Score (LBCRS) is a 10-item questionnaire to capture signs and symptoms associated with Lewy body pathology. A score of 3 or greater represents a high probability that Lewy bodies are contributing to cognitive decline (A). Comparison of MRI in Alzheimer's disease (AD) and dementia with Lewy bodies (DLB) demonstrates less cortical and hippocampal atrophy in DLB (B). Comparison of dopamine transporter single photon emission tomography (DaT-SPECT) in AD and DLB shows decreased dopamine uptake in the basal ganglia in DLB vs normal uptake in AD.

Biomarkers

Although there are no biomarkers specific for LBD, revisions to diagnostic criteria recognize the move to incorporate biomarkers to increase specificity of clinical diagnoses. The most common biomarker used in dementia clinical and research evaluations is MRI. Cortical atrophy is common to many neurodegenerative diseases, however the relative preservation of medial temporal lobe structures in DLB may help distinguish it from AD (Figure).[1] Another biomarker is fluorodeoxyglucose positron emission tomography (FDG-PET).[24,25] AD is characterized by hypometabolism in posterior parietal and temporal lobes. DLB, particularly those with visual hallucinations will additionally demonstrate reduced occipital activity.[24] Relative preservation of FDG uptake in the posterior cingulate in LBD leads to the cingulate island sign.[25]

Low dopamine uptake in the striatum on dopaminergic imaging (Figure) was a suggestive feature of DLB in the third consensus report, but has been upgraded to an indicative biomarker in the fourth consensus report.[1] Other indicative biomarkers include evidence of REM sleep without atonia during polysomnography (PSG) supporting the presence of RBD,[26] and abnormal (low uptake) cardiac MIBG (^{123}I-MIBG myocardial scintigraphy) imaging.[27] Abnormal MIBG imaging results from the reduction in noradrenergic innervation of the myocardium in LBD[27]; however this may also be seen in other conditions that affect the autonomic nervous system such as diabetes mellitus. The fourth consensus report advances the previous consensus criteria by incorporating biomarker presence along with redefining the core features to allow the diagnosis of probable DLB. Abnormal biomarker evidence alone, in the absence of a core clinical feature is not sufficient to diagnosis probable DLB.[1]

Therapeutic Approaches

There are limited approved therapies specifically for LBD; however there is ample evidence in the literature regarding the use of medications approved for other disorders for the treatment of the various symptoms of LBD (Table 3).[5,28,29]

Cognitive Symptoms

Acetylcholinesterase inhibitors (AChEIs) may be especially useful in the treatment of LBD.[29,30] These medications, including donepezil, rivastigmine, and galantamine block the breakdown of acetylcholine within the synapse, thereby prolonging its effect on postsynaptic receptors. AChEIs are generally well-tolerated at their standard dosing. Independent clinical studies of AChEI treatment using donepezil, galantamine, and rivastigmine in persons with LBD suggest that AChEIs improve cognitive and neuropsychiatric measures, with no significant increase in extrapyramidal signs.[28-30] The *N*-methyl-D-aspartate (NMDA) antagonist memantine, approved for use in AD, has not yet been tested in large, randomized, controlled studies in LBD. In small cases series the results have been equivocal.[28,29]

TABLE 3. LEWY BODY DEMENTIA TREATMENT[a]

Domain	Possible Treatment Options
Cognitive symptoms	Cholinesterase inhibitors
	NMDA receptor antagonists
Motor symptoms	Carbidopa/levodopa
Behavioral symptoms	Antidepressants
	Atypical antipsychotics
Sleep symptoms	Melatonin
	Clonazepam
Autonomic symptoms	Fludrocortisone
	Midodrine

[a]Treatments are generally off-label with exception of donepezil in Japan and Philippines for dementia with Lewy bodies and rivastigmine in US and Europe for Parkinson's disease dementia.

Motor Symptoms

The staple of treating extrapyramidal signs in PDD is levodopa combined with carbidopa. Although there are no controlled clinical trials evaluating the treatment of motor features in DLB, studies suggest improvement of motor symptoms with levodopa.[31] Dopamine agonists are associated with more side effects, especially drug-induced psychosis, even at low doses. Other PD medications such as amantadine, catechol-*O*-methyltransferase inhibitors, monoamine oxidase inhibitors, and anticholinergics tend to exacerbate cognitive impairment and should ideally be avoided.[5,29]

Behavior Symptoms

Behavioral symptoms frequently accompany LBD.[5] Clinical experience suggests that nonpharmacologic treatment approaches should be considered first, including evaluating for physical ailments that may be provoking behavioral disturbances (eg, fecal impaction, pain, or decubitus ulcers). Avoidance or reduction of doses of other medications that can potentially cause agitation should also be attempted.[5]

There are no approved medications for the treatment of behavioral symptoms in LBD. Antidepressants, particularly serotonin reuptake inhibitors are gaining traction to treat agitation and irritability in addition to depression. Classical neuroleptics (such as haloperidol) are best avoided in DLB as they may worsen motor function and even potentially result in life-threatening neuroleptic sensitivity. Experience with atypical antipsychotics in LBD has been mixed, but drugs with higher dopamine blockage (ie, risperidone) or greater anticho-

linergic activity (ie, olanzapine) may be poorly tolerated.[5,28,29] Pimavanserin, an inverse agonist of serotonin $5HT_{2A}$ and $5HT_{2C}$ receptors is approved for the treatment of psychosis in PD[32] but no studies are yet available for efficacy in DLB.

Treatment of RBD typically focuses on 2 options: melatonin or alprazolam. Melatonin doses between 3 to 10 mg daily is a reasonable first choice as it may help up to 50% of people with RBD and the side effects are few.[33] Clonazepam doses between 0.5 to 2.0 mg daily will often control symptoms in the remainder.[34] (See also *Sleep and Alzheimer's Disease* in this issue.)

Conclusions

Lewy body disorders are a common cause of dementia in the elderly, characterized by varying degrees of cognitive, behavioral, affective, movement, and autonomic dysfunction in older adults. LBD are associated with the accumulation of LBs in subcortical, limbic, and neocortical regions and are characterized clinically by progressive dementia, parkinsonism, cognitive fluctuations, visual hallucinations and RBD. Whether or not PDD and DLB reflect the same underlying disorder whose differences in symptom presentation are merely the end product of the underlying brain region(s) affected earlier or later in the disease course, is the subject of much controversy.[10,11] For now, the 1-year rule should still be applied while the debate continues between the PDD and DLB research groups. From a neuropsychologic perspective, PDD and DLB are more readily distinguished from AD than from each other. Continued phenotypic characterization of prodromal stages of disease (RBD, autonomic dysfunction, anosmia) may improve our understanding of the earliest clinicopathological changes associated with LBD. Use of composite risk scores and assessment toolkits should help improve diagnosis in the clinical setting and could potentially be used for inclusion/exclusion criteria for LBD clinical trials. The expanding use of indicative biomarkers will enable clinicians and researchers to diagnose these disorders earlier, as well as aid in the prediction and monitoring of treatment response and development of more selective therapeutic agents. Public awareness campaigns, such as those led by the Lewy Body Dementia Association[4] that specifically address LBD may aid in generating increased awareness, foster new research collaborations, and the development of new therapies to benefit people with LBD and their families ■

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James E. Galvin, MD, MPH
Professor of Neurology
Director, Comprehensive Center for Brain Health
Director, Lewy Body Dementia Research Center of Excellence
Charles E. Schmidt College of Medicine
Florida Atlantic University
Boca Raton, FL

Disclosure

JEG reports no disclosures.