Dementia with Lewy Bodies

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Abstract

Dementia with Lewy bodies (DLB) is the second most common diagnosis of dementia after Alzheimer disease (AD). The essential pathologic feature is the Lewy body, a neuronal inclusion containing α-synuclein, found in brainstem nuclei and the neocortex. Clinical features include early fluctuations in attention, hallucinations, and parkinsonism, with progression to a combined cortical and subcortical dementia. To distinguish it from Parkinson disease dementia, a time course of one year from cognitive changes to motor feature onset has been established. There is more severe impairment of verbal fluency, executive function, and visuospatial abilities in DLB patients. Both rapid eye movement sleep behavior disorder and neuroleptic sensitivity are notable in this patient group. Treatment is aimed at symptom management. Cholinesterase inhibitors can be beneficial for behavioral and cognitive issues, whereas dopaminergic agents may help motor symptoms. Survival is equivalent to AD when measured from symptom onset, though diagnosis in DLB may be delayed.

Keywords
- dementia with Lewy bodies
- Lewy body
- synucleinopathy
- dementia
- parkinsonism

Dementia with Lewy bodies (DLB) is an atypical parkinsonian disorder characterized as a synucleinopathy based on the cardinal pathologic finding, the Lewy body, a neuronal inclusion comprised of aggregated α-synuclein. Lewy bodies are found in brainstem nuclei in both Parkinson disease (PD) as well as in DLB, though in DLB there is a concomitant presence of Lewy bodies in the cortex and subcortical white matter. The cortical Lewy bodies may not demonstrate the classic structure of an eosinophilic core with surrounding halo; however, they contain α-synuclein. Clinically, DLB manifests with fluctuating alertness, visual hallucinations, and parkinsonian motor symptoms, and has features of both a cortical and a subcortical dementia.

Epidemiology

Dementia with Lewy bodies is the second most common pathologic diagnosis of dementia, next to Alzheimer disease (AD) and accounts for 25% of all dementias.[1] The prevalence of DLB is estimated to be 0.7% of the population over 65 years of age.[2] Given the challenge of clinical diagnostic accuracy in dementia, there is a wide variation in estimates of the prevalence among dementia patients, ranging from 3 to 26.3% in those over the age of 65 years.[3,4] The incidence of DLB is 3.5 per 100,000 person years and this increases with age.[5] There is a slightly greater male predominance of 1.9:1.[6] Risk factors of DLB include advanced age, hypertension, hyperlipidemia, and carriers of one or more APOE ε4 alleles.[7–9] As in PD, there is overrepresentation of the CYP2D6B allele, and a greater heterozygous frequency of glucocerebrosidase 1 (GBA1) estimated at 3.5% versus 2.9% in Parkinson disease dementia (PDD) and 0.4% in the general population.[10] A separate study also found a significant association between GBA1 mutation carrier status and DLB with an odds ratio of 8.28 versus 6.48 in PDD.[11]

Pathophysiology

Dementia with Lewy bodies is considered a synucleinopathy, along with PD and multiple system atrophy (MSA). It is distinguished pathologically by the presence of Lewy bodies, which are intracellular inclusions with an eosinophilic core

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and marked by a peripheral halo. Structurally, Lewy bodies are composed of filamentous material radiating from an electron dense core. The theory has been proposed that the development of Lewy bodies results from abnormal neurofilament transport from modification of the original cytoskeleton proteins. Lewy bodies were initially noted in PD patients by Lewy in 1912.[12] Within the last few decades, Kosaka identified cortical and subcortical Lewy bodies in DLB, which do not necessarily demonstrate the characteristic halo, but can be identified with staining for α-synuclein and ubiquitin.[13] Staining for these proteins to reveal a diffuse Lewy body distribution cortically and subcortically in DLB has been beneficial in differentiating PD from DLB. In PD, Lewy bodies are found primarily in the substantia nigra and brainstem nuclei, while in DLB they are found not only in the substantia nigra and brainstem nuclei but in the limbic system, parahippocampal cortices, amygdala, and cortex as well.[2] Parkinson disease dementia may also exhibit diffuse Lewy bodies, thus making pathologic diagnosis challenging. Clinical distinction between DLB and PDD is achieved by defining the interval between development of dementia and motor symptoms. This interval must be one year or less to receive a clinical diagnosis of DLB.[14]

Dementia with Lewy bodies can also demonstrate some pathologic features of Alzheimer's disease (AD) including β-amyloid deposits and tau neurofibrillary tangles, though in lower density than AD.[15] Another complicating factor in distinguishing DLB pathologically is the evidence for a Lewy body variant of AD in which neocortical Lewy bodies are identified in the context of clinical and pathologic AD.[15,16]

Lewy body disorders have been associated with α-synuclein gene mutations and multiplications resulting in high concentrations and accumulations of α-synuclein.[17,18] This process is also exacerbated by ubiquitin inhibition, as ubiquitin normally assists in degradation of α-synuclein via proteasomes.[17,19] Dopamine itself also assists in Lewy body formation by binding to α-synuclein thus forming protofibrils and eventually Lewy bodies.[17,19]

The effect of Lewy bodies on the course of the disease remains unclear. It is presumed that both the protofibrils and the Lewy bodies are neurotoxic.[17] Recently, there is evidence that the presence of extracellular α-synuclein may contribute to the symptoms of dementia.[20,21] This is especially interesting given that a connection between cortical Lewy body burden and disease severity has yet to be delineated, though the pattern of distribution of Lewy bodies may have more relevance to symptoms and disease severity.[22]

Dementia with Lewy bodies is characterized by a loss of cholinergic neurons in the nucleus basalis of Meynert, decreased cortical choline acetyltransferase, and depletion of dopamine-containing neurons[23,24]. These neurohistochemical changes potentially account for both the dementia as well as the motor symptoms of the disease. There are also deficits of GABA and serotonin neurotransmission.[23,25]

Signs and Symptoms

Cognitive impairment in DLB is accompanied by fluctuating attention, particularly early in the disease. Other prominent early symptoms include parkinsonism, delusions, hallucinations, and anxiety. Additional cortical features such as anomia, aphasia, and apraxia may develop later in the course of the disease. Concomitant working memory impairment is indicative of subcortical dementia, which allows for greater clinical suspicion of DLB over amnestic disorders.[15,16]

The hallucinations in DLB are classically visual (70%), though other modalities may be experienced as well, and often involve well-formed recurrent hallucinations of small children, people, or animals.[26,27] Visual hallucinations typically develop early in the disease, most often at night making the diagnosis more challenging in differentiating between dreams or hypnogogic hallucinations and true DLB-associated visual hallucinations and delusions. Paranoid delusions and aggressive behavior can be features as well. Additionally, psychiatric features of anxiety, apathy, and/or depression may be seen.[16,22,26–28]

Sleep disturbances are also common, specifically rapid eye movement sleep behavior disorder (RBD), which is thought to precede cognitive and motor features of DLB, sometimes by several years.[22] Neuroleptic sensitivity is also common in DLB at an average rate of 29%, and is thought to be related to low expression of striatal dopamine D2 receptors.[29] This is observed despite using low doses and even with the atypical antipsychotic medications.[29,30]

Bilateral symmetric parkinsonian motor symptoms, especially limb rigidity and bradykinesia are common in DLB.[22] Tremor occurs less frequently than in idiopathic PD, and when present is typically a symmetric postural tremor, rather than an asymmetric rest tremor. Gait disturbance mimics that of PD with shuffling, slow turns, and reduced arm swing. There are more falls in DLB and PDD patients than in AD patients, with an incidence of 9.1 and 19.0 person years respectively versus 2.5 in AD.[31] Falls may be related to dysautonomia, cognitive impairment, motor symptoms, or a combination of these factors.

Autonomic features may also be present including orthostatic hypotension, constipation, and sialorrhea, thought to be due to preganglionic cell loss in the interomediolateral cell column of the spinal cord and is likely exacerbated by loss of cholinergic neurons.[32]

Clinical Course

Dementia with Lewy bodies accounts for 25% of all dementia, and occurs at an older age of onset, generally ages 60 to 90.[16] Dementia with Lewy bodies is characterized by both a subcortical and cortical dementia in addition to motor dysfunction. It begins with a dementia marked by fluctuating cognition. Other key distinguishing features include a more severe visuospatial deficit and relative sparing of memory in earlier stages of DLB.[31,33,34] The visuospatial impairment is seen in performance on copy tasks, shape detection, block design, and clock drawing and copy. By contrast, AD patients tend to improve between the drawing and copying portion of the clock task.[35,36] Other areas of cognitive deficit that are more pronounced in DLB than in AD include verbal fluency, psychomotor speed, and executive function.[35] The verbal

dysfluency has been found to be more severe in DLB than in AD patients, specifically in letter fluency, whereas in AD letter fluency is relatively intact when compared with category fluency.[34,37–39] Attention is also impaired on tests such as reaction time, digit span, and tests of sustained, divided, and selective attention. Similarly, executive dysfunction as measured by tasks such as Trails A and B and card sorting are prominent in DLB.[35,36] These features on testing are consistent with the early clinical symptoms reported in fluctuations in alertness. However, orientation has been observed to be relatively preserved in DLB with respect to AD, as memory loss, particularly episodic and recognition memory, may be less severe early on in DLB than AD and PDD.[31,37,38] Although DLB patients may have more neuropsychiatric features at baseline and at follow-up than AD, and have a greater risk of hospitalization or death secondary to falls or pneumonia in comparison to AD, several studies have found no significant difference in rate of progression between vascular dementia, AD and DLB with respect to functional, cognitive neuropsychiatric decline. However, within DLB patients, apolipoprotein E4 may be an important predictor of more rapid decline.[40–43]

Additionally, as discussed above, visual hallucinations and delusions are present in DLB, as well as parkinsonian motor features. Parkinsonism may be present at onset, or develop later, unlike in PD dementia (PDD) where motor symptoms tend to precede cognitive impairment. It is typically nonmotor features that develop early in DLB, many of which may be subtle including olfactory dysfunction, sleep disorders, autonomic dysfunction, constipation, and sialorrhea. Rapid eye movement sleep behavior disorder (REM sleep behavior disorder) has been shown to precede diagnosis in both PD and DLB.[22]

In terms of survival, higher rates of cerebrospinal fluid (CSF) tau have been associated with earlier mortality in DLB. No differences have been found in age of onset, age at death or disease duration between DLB and AD. Although there is no difference in survival from reported disease onset, the time of diagnosis to death is shorter in DLB than AD. This is more suggestive of a delay in diagnosis of DLB than a true difference in clinical course and overall survival.[44]

Diagnostic Criteria

Criteria for diagnosis of DLB are based upon the triad of fluctuating cognitive impairment, recurrent visual hallucinations, and motor features of parkinsonism. They were established in 1995 and revised in both 1999 and 2005, with estimated sensitivity of 32% and specificity of 95%.[45] The criteria are depicted in the ►**Table 1** and are adapted from McKeith et al.[15] Definitive diagnosis, as in all neurodegenerative diseases, is by brain autopsy and pathologic confirmation.[15,16,22]

Mandatory criteria for diagnosis of probable DLB include dementia plus two out of three core features: fluctuation of cognition or alertness, visual hallucinations, or parkinsonian features. One out of those three are necessary for diagnosis of possible DLB. Supportive features include repeated falls, syncope, loss of consciousness events, neuroleptic sensitivity, systematized delusions, nonvisual hallucinations, depression, and REM sleep behavior disorder. Several of these supportive features may precede or be present at the time of dementia onset.

Studies

Although there are no premortem tests available currently to confirm a diagnosis of DLB, several ancillary studies have been suggested as supplemental tools to differentiate DLB from other dementias such as PD and AD. Magnetic resonance

Table 1 Diagnostic criteria for dementia with Lewy bodies

Central characteristic	Dementia with impairments in daily functioning (may have intact memory function at onset)
Core characteristics	Fluctuation cognition/attention and alertness Visual hallucinations Parkinsonism
Suggestive characteristics	REM sleep behavior disorder Neuroleptic sensitivity Reduced dopaminergic activity in the basal ganglia demonstrated by SPECT or PET imaging
Probable DLB	Central characteristic and At least 2 core characteristics or 1 core and 1 suggestive characteristic
Possible DLB	Central characteristic and 1 core characteristic or 1 or more suggestive characteristic
Supporting characteristics	Repeated falls or syncope, transient impairments in consciousness, autonomic dysfunction (i.e., in the form of orthostatic hypotension or urinary incontinence), hallucinations in nonvisual modalities, systematic delusions, depression, intact medial temporal lobe on anatomic imaging, reduced (particularly occipital lobe) metabolism on metabolic imaging (SPECT or PET), pathologic MIBG-SPECT scan of the myocardium, EEG showing slow activity with intermittent temporal sharp waves

Abbreviations: DLB, dementia with Lewy bodies; EEG, electroencephalogram; MIBG, [I-123] myocardial scintigraphy; PET, positron emission tomography; REM, rapid eye movement; SPECT, single photon emission computed tomography.
Source: Adapted from McKeith et al[15].

imaging (MRI) reveals a pattern of generalized cortical atrophy, with notably less atrophy in the hippocampus than in AD, and with relatively increased atrophy in areas inclusive of the amygdala, striatum, substantia innominata, dorsal midbrain, and hypothalamus.[46–48] Diffusion tensor imaging (DTI) shows diffusely increased mean diffusivity with specifically reduced fractional anisotropy (FA) in the caudate, putamen, pons, left thalamus, corpus callosum, and pericallosal areas as well as frontal, parietal, and occipital white matter tracts being affected, whereas in AD, reduced FA is more widespread. Diffusion tensor imaging has also demonstrated decreased fractional anisotropy (FA) in the precuneus versus both normal controls and AD patients.[49–51]

Fluorodeoxyglucose positron emission tomography (FDG-PET) demonstrates decreased occipital glucose metabolism, which is helpful in distinguishing among other neurodegenerative diseases, with one study showing 71% decrease in occipital metabolism without much asymmetry.[52] Other studies found temporo-parieto-occipital cortical hypometabolism as well as hypometabolism within the basal ganglia and pulvinar of the thalami.[53–55] 99mTc-hexyamethylpropyleneamine oxime (99mTc-HMPAO) single-photon emission computed tomography (SPECT) imaging shows decreased uptake in the striatum in DLB patients compared with AD patients, but does not distinguish well among the other atypical parkinsonian disorders.[56] Electroencephalography (EEG) can show an increase in slow wave activity.[57] Cardiac imaging has also been explored and [I-123] myocardial scintigraphy (MIBG) has been shown to be correlate with decreased postganglionic sympathetic innervation with DLB and PD patients with respect to AD patients.[58]

There are no definitive biomarkers for DLB, though it has been suggested that a relative increase in CSF tau with decrease in Aβ-42 can distinguish between DLB and PD.[59] Additionally, it has been found that the levels of Aβ-42/Aβ-38 can differentiate between DLB and AD.[60]

Treatment

Although there are no medications approved by the Food and Drug Administration for DLB specifically, and no current disease-modifying agents, several symptom-based treatments are commonly employed. Medications for symptomatic treatment in DLB are summarized in ►**Table 2**. Given the predominance of cholinergic deficit, cholinesterase inhibitors, as in AD, can be beneficial for cognitive and behavioral impairments as well as for hallucinations in some cases. Those studied include donepezil and rivastigmine. Donepezil has been shown to decrease visual hallucinations, agitation, apathy, and reduce caregiver burden at highest dose.[61–64] Rivastigmine similarly has been shown to reduce visual hallucinations, delusions, agitation, and apathy and improve sleep.[30,65,66] There is also the suggestion that rivastigmine leads to improvement in cognitive testing.[67] Side effects found include nausea, vomiting, anorexia, and somnolence. Memantine, an NMDA receptor antagonist, has also been suggested to benefit attention and episodic memory in DLB patients, though sedation is a possible adverse effect.[65–68]

In terms of antipsychotic use for behavior and hallucinations, both typical and atypical neuroleptics are not well tolerated, nor effective given the sensitivity in DLB. However, of the atypical neuroleptics available, quetiapine can sometimes be useful and better tolerated.[26,69,70] Use of selective serotonin reuptake inhibitors (SSRIs) for symptoms of anxiety, emotional lability, and depression have also demonstrated benefit, though there is no peer-reviewed evidence.[22,43,71] Tricyclic antidepressants (TCAs) and antispasmotics should be avoided for the potential anticholinergic exacerbations.[70] For REM sleep behavior disorder, clonazepam may be beneficial though it could worsen dementia and alertness.[22,26,72] Melatonin is also beneficial for sleep disorders in DLB.

Although there is no evidence-based support for treatment of motor symptoms in DLB, the parkinsonism found in patients with DLB can be treated with dopaminergic agents.

Table 2 Symptomatic treatments in dementia with Lewy bodies

Medication	Symptoms treated	Common side effects
Cholinesterase inhibitors Rivastigmine Donepezil Galantamine	Visual hallucinations, delusions, agitation, apathy	Diarrhea, nausea, vomiting, somnolence
Selective serotonin reuptake inhibitors	Depression, anxiety, irritability, emotional lability	Sexual dysfunction
Atypical antipsychotics Quetiapine Clozapine	Visual hallucinations, delusions, behavioral symptoms Visual hallucinations, delusions, behavioral symptoms	Worsening confusion agranulocytosis (rare)
Sleep Clonazepam Melatonin	REM sleep behavior disorder	Worsening alertness and/or dementia
Dopaminergic agents Carbidopa/levodopa	Rigidity, bradykinesia, restless legs syndrome	Worsening confusion and psychosis

Abbreviations: REM, rapid eye movement.

Levodopa is preferred to dopamine agonists, but must be carefully titrated to avoid exacerbating cognitive and behavioral manifestations as well as orthostatic hypotension.[73] Dopamine agonists have a greater potential for worsening hallucinations, and less benefit in motor symptom control than levodopa.[74] Restless legs syndrome (RLS) can be treated with low-dose carbidopa/levodopa, pramipexole, or gabapentin.

Orthostatic hypotension can be treated with hydration, salt tablets, compression stockings, avoidance of exacerbating medications, and in resistant cases, with fludrocortisone and midodrine.[26,75]

Overall, despite lack of significant evidence for medications in the treatment of DLB, several agents alone or in combination may be beneficial for symptom management. However, dosing and medication selection must be individualized taking into account degree of functional impact of symptoms being targeted and side-effect thresholds.

Conclusions

Dementia with Lewy bodies is a common pathologic diagnosis of dementia and has the hallmark features of fluctuating attention, visual hallucinations, and parkinsonism, and develops into a combined cortical and subcortical dementia. Clinical differentiation from AD and PDD is important, and can be aided not only by clinical course, but also by diagnostic criteria delineated by McKeith and colleagues.[16] Ancillary studies may prove helpful, inclusive of structural and functional brain imaging and EEG. Currently available therapies are aimed at symptomatic control. However, ongoing research efforts will help to improve the accuracy of clinical diagnosis correlating with final pathologic diagnosis, thus improving not only our understanding of the underlying pathophysiological processes, but guiding current and future therapeutic interventions.

Disclosures

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