Dementia with Lewy bodies: Diagnosis and clinical approach

**ABSTRACT**

Dementia with Lewy bodies (DLB) is a common form of dementia that is being increasingly recognized. This paper reviews this disorder, emphasizing how it is different from other causes of dementia.

**KEY POINTS**

The clinical criteria for the diagnosis of DLB are specific, but their sensitivity is low. Underdiagnosis (usually misdiagnosis as Alzheimer disease) remains common, and current research is focused on ways of enhancing detection.

Hallucinations, mild executive dysfunction, visual perceptual or spatial deficits, disturbance of the dreaming phase of sleep, and parkinsonian rigidity are perhaps the most useful clinical signs and symptoms.

The differential diagnosis varies with the presentation, which may resemble a psychiatric disturbance, dementia, or a movement disorder.

Treatment is complicated by susceptibility to both hallucinations and parkinsonism, but cholinesterase inhibitors may offer meaningful benefits in DLB-related symptoms such as attention fluctuations and executive dysfunction.

**NOT A VARIANT OF ALZHEIMER DISEASE**

Lewy bodies—eosinophilic inclusion bodies found within the cytoplasm of neurons in the cerebral cortex and limbic system (FIGURE 1)—are named after the German pathologist Friedrich Lewy, who first described them. They are composed of proteins derived from neurofilaments as well as alpha-synuclein and ubiquitin.

Although at autopsy Alzheimer-type senile plaques are commonly seen along with Lewy bodies in the brains of patients of DLB, neurofibrillary tangles are unusual, and differences in clinical presentation suggest that DLB is a unique entity and not simply a variant of Alzheimer disease. Why Lewy bodies accumulate and how they cause dementia remain unknown.
The current diagnostic term “dementia with Lewy bodies” came from a consensus conference convened to simplify and organize a variety of competing diagnostic classifications, including Alzheimer disease-Parkinson disease complex, Lewy body variant of Alzheimer disease, and diffuse Lewy body disease, among others. The conference also adopted clinical and neuropathological criteria for the diagnosis of DLB. Although the criteria are controversial and they share the limitations of any clinical criteria for dementia diagnosis, the consensus terminology has proved useful in fostering improved understanding of this fascinating disease.

SECOND MOST COMMON CAUSE OF DEMENTIA

DLB is the second most common form of degenerative dementia after Alzheimer disease, accounting for 15% to 25% of dementia cases at autopsy. In a recent population-based series of 601 adults aged 75 or older, DLB accounted for 22% of 137 cases of dementia. This was about half the rate of Alzheimer disease (47%), and about the same as the rate of vascular dementia (23%).

The prevalence of dementia is difficult to interpret in studies published before the consensus criteria were adopted, because patients now classified as having DLB would have been classified as having any of several other diseases, especially Alzheimer disease or Parkinson disease with dementia, with considerable variability among studies.

DIAGNOSTIC CRITERIA

According to the consensus criteria, patients with DLB must exhibit dementia. In addition, the core features of DLB are:

- Fluctuations in cognitive function, attention, and alertness
- Visual hallucinations
- Motor signs of parkinsonism (these features are discussed in detail below).

Other findings that support the diagnosis are:

- Repeated falls, syncope, and transient losses of consciousness
- Neuroleptic (antipsychotic) drug sensitivity
- Systematized delusions or hallucinations in other sensory systems.

These criteria are very specific (> 90%), but their sensitivity is much lower (< 25%). This pattern of high specificity and low sensitivity suggests that DLB is significantly underdiagnosed in both research and clinical settings.

Key clinical features of DLB are listed in Table 1. The onset of DLB before age 55 to 60 is rare. Men are affected slightly more often than women.

Fluctuations in alertness

The criteria for DLB particularly emphasize fluctuations in alertness and attention, which are more frequent and more variable than in patients with Alzheimer disease of comparable severity.

Clinicians who see relatively few cases of dementia may find it very difficult to assess whether the fluctuations are sufficient to meet the criteria, however. Clinical scales to measure fluctuation have been reported, but are not in widespread use, and much of the research on fluctuation uses complicated computerized measures of attention and reaction time.
Hallucinations

For the clinician, one of the most useful identifying features of DLB is the early emergence of hallucinations and delusions. Although these also occur in patients with Alzheimer disease, they occur earlier in the course of DLB and may be the presenting symptom.

One study suggested that in patients with relatively mild cognitive deficits, hallucinations are the symptom that best distinguishes DLB from other diseases. In another study, 15 of 25 mildly affected DLB patients (with Mini-Mental State Exam [MMSE] scores > 20) had visual hallucinations vs only 1 of 19 similarly impaired patients with Alzheimer disease. In the same series, 10 of the patients with mild DLB had auditory hallucinations vs none of the Alzheimer patients.

The visual hallucinations in DLB are usually benign, well-formed, and nonthreatening visions of people or animals. The character of the hallucinations suggests that they may be linked to deficits in processing complex visual information. For instance, the hallucinated elements are commonly perceived as inappropriately small (micropsia).

Not surprisingly, there is a strong association between early visual hallucinations in DLB and the neuropathological observation of a high density of Lewy bodies in the limbic system (amygdala) and visual association cortex of the inferior temporal lobe.

Parkinsonism

Parkinsonian motor dysfunction is a part of the clinical expression of DLB, but it should appear within 1 year of cognitive or behavioral symptoms. Parkinsonism occurring more than 1 year before the rest of the syndrome suggests the alternative diagnosis of Parkinson disease with dementia, or one of the other parkinsonian disorders.

Tremor is not a major feature of the parkinsonism in most cases of DLB at the time of presentation. In contrast, facial hypokinesia (ie, masked facies) is common.

Transient and otherwise unexplained lapses of consciousness, with or without falls, can be part of the pattern of fluctuations, but may also represent orthostatic syncope. Autonomic dysregulation is a part of the Lewy body syndrome, and orthostatic hypotension resulting in syncope was seen in 28% of patients with neuropathologically confirmed DLB in one series.

Constipation, which can also occur early in the course, is typical.

Unsteady gait, postural instability, significant cogwheel rigidity, and dystonia are all unusual in mild DLB, which can help distinguish it from other parkinsonian disorders such as progressive supranuclear palsy. These parkinsonian features may emerge as the disease progresses or in response to antipsychotic drug therapy.

Like those with Parkinson disease, patients with DLB can develop significant bradykinesia and rigidity in response to antipsychotic drugs used to treat hallucinations. Older, typical antipsychotic drugs are the worst offenders, but even the more modern atypical agents can provoke worsened parkinsonism in DLB patients.

Other clinical features

Cognitive dysfunction. Impairment in memory is required for the diagnosis of dementia in commonly used classification schemes, but the nature of the memory dysfunction in DLB appears different from that in Alzheimer disease. In general, DLB patients
recall information better than do Alzheimer patients.9

Disorders of executive function such as planning and initiation of appropriate behaviors are among the earliest cognitive problems seen in DLB.10 These symptoms may magnify the clinical complaint of “memory loss,” because patients have difficulty attending to and prioritizing information that they may subsequently need to recall, and so have poor working memory.11 Other changes include general slowness of thought and action (bradyphrenia or psychomotor slowing). Apathy and depression are also frequent.

Given the pathological findings of Lewy bodies in the visual association cortex of the temporal lobe, it is not surprising that visual and spatial deficits are also common. These often appear early in the disease course.

Mori et al12 found that visuoperceptual tasks, such as size discrimination, form discrimination, overlapping figure identification, and visual counting, were more impaired in DLB patients than in patients with Alzheimer disease. The visual processing deficits extend to spatial and visuomotor realms on neuropsychological testing as well, in which DLB patients performed worse than Alzheimer patients on complex visuomotor and executive tasks, even though the DLB group scored higher on the MMSE and a word recall task.

Sleep disturbances. Nighttime behavioral disturbances such as violent or active dreams may predate other symptoms.13 Normally, muscle tone is suppressed during the dreaming or rapid-eye-movement (REM) phase of sleep, but patients with DLB may develop “REM sleep behavioral disturbance,” in which this normal suppression or paralysis is attenuated. As a result they vocalize and move about vigorously during their dreams. Family members may report that patients are having unusually vivid dreams or acting out their dreams. Patients are frequently unaware of the problem, though they may feel that sleep is less restful.

Acetylcholinesterase inhibitor drugs (used for cognitive enhancement) may provoke sleep disturbances and vivid dreams independently of DLB, although these symptoms often begin before the patient starts this therapy.

Differential diagnosis

The differential diagnosis of DLB is complicated by its variable presentation. Depending on the nature of the complaints, the differential diagnosis will focus on primary psychiatric illnesses, other late-life dementia syndromes, or other parkinsonian disorders (TABLE 2).

Reversible causes of dementia

Reversible causes of dementia are infrequent, and treatment of them is unlikely to fully reverse the dementia,14 but appropriate treatment may reduce excess disability. Therefore, the American Academy of Neurology practice guidelines15 recommend the following as part of the routine workup for dementia:

- Metabolic screening blood work
- Thyroid function testing
- Vitamin B12 level determination
- Cerebral imaging.

Laboratory tests for reversible causes of dementia are particularly pertinent for patients with potential DLB, because the neurological presentation of hypothyroidism can involve psychomotor slowing and cognitive impairment with a dysexecutive character like that seen in DLB. Both hyperthyroidism and vitamin B12 deficiency can be associated with psychosis.

Cerebral imaging is useful to exclude intracranial processes that might cause or contribute to DLB-like symptoms, including strategic infarcts in the basal ganglia, thalamus, or visual association cortex, and surgically correctable disorders such as hydrocephalus, subdural hematoma, and neoplasms (especially meningiomas). Although quite unlikely, intracranial tumors affecting the inferior temporal lobe can present with hallucinosis, visuoperceptual problems, and confusion.

Psychiatric differential diagnosis

Since psychotic features may be the presenting symptom of DLB, the clinician may suspect a psychiatric problem.

Schizophrenia. The much older age at onset of DLB usually differentiates it from schizophrenia. Furthermore, the hallucinations associated with DLB are usually benign and nondirective, ie, patients do not tend to hear voices telling them to harm themselves.
or others. Paranoia is not a common feature in early DLB.

Depression is somewhat harder to differentiate from DLB. Apathy, sleep disturbance, inattentive/dysexecutive cognitive profile, and psychomotor retardation are common to both DLB and depression, and up to 40% of DLB patients experience a major depressive episode in the course of their illness. Since abnormal mood states may also progress to include psychotic features, the presence of hallucinations could be consistent with either, as well. Like patients with depression, patients with DLB may report a depressed mood.

Features that separate DLB from depression:
• Suicidal thoughts, statements of low self-worth, and prominent somatic complaints are much more characteristic of depression than DLB. (Constipation, however, is an exception—it is a somatic complaint that is common among DLB patients.)
• Depression tends to progress over weeks to months, reaching a stable, impaired level of cognitive dysfunction. In contrast, DLB progresses more slowly, but continuously.
• On examination, DLB patients are more likely to show a masked face, bradykinesia, and visuospatial impairments on testing (e.g., difficulty copying two pentagons or drawing a clock face during the MMSE). A depressed patient is more likely to put forth poor effort on cognitive testing, giving up on tasks that require more effort.

Other forms of dementia
When cognitive impairment is the presenting complaint, the clinician needs to evaluate for DLB in the context of other dementias, principally Alzheimer disease and vascular dementia.

Alzheimer disease. Compared with Alzheimer patients, DLB patients with a similar degree of overall cognitive impairment have better memory performance but worse initiation, more perseveration, and worse design-copying. Recall of events (episodic memory) is the
domain in which DLB patients seem to have an advantage over those with Alzheimer disease; semantic memory (knowledge of facts) was similar among Alzheimer patients and DLB patients in a series reported by Calderon et al.11 In the same study, DLB patients had worse working memory, attention, and visuo-perceptual ability compared with the Alzheimer patients.

Qualitative analysis suggests that DLB patients are more likely to show features suggesting acute confusional states during neuropsychological testing than carefully matched Alzheimer disease patients (with MMSE scores of about 15); the observations included higher rates of inattentiveness, distractibility, incoherence, confabulation, and perseveration, among others, for DLB patients.16

For patients with high MMSE scores (>24), poor pentagon-copying or clock-drawing performance makes DLB more likely but does not exclude Alzheimer disease.17,18 A subgroup of Alzheimer patients have prominent visual disturbances; the condition is known as the “visual variant of Alzheimer disease” or “posterior cortical atrophy.” It can be very difficult to differentiate from DLB, but clinical observations suggest that patients with this Alzheimer variant often have a greater degree of language impairment, especially on confrontational naming, like other Alzheimer patients.

Magnetic resonance imaging has been reported to show medial temporal lobe atrophy less often in DLB than in Alzheimer disease, and the absence of medial temporal atrophy therefore strongly suggests DLB rather than Alzheimer disease or vascular dementia.19

Vascular dementia patients are highly variable in their cognitive presentation depending on the location of the cerebral infarcts. Dysexecutive states, apathy, or parkinsonian motor features may be present in vascular dementia, but cerebral imaging should reveal significant areas of ischemic damage. In contrast, DLB has an unexpectedly low rate of cerebrovascular lesions.20

Creutzfeld-Jakob disease. A few cases of DLB have been reported with very rapid progression and electroencephalographic abnormalities suggesting Creutzfeld-Jakob disease (CJD). Myoclonus can be seen in both disorders, and there is a CJD variant characterized by prominent visual disturbances. CJD progresses more rapidly and more relentlessly than DLB, which may plateau in the severe stage. Cerebrospinal fluid assay for the 14-3-3 protein can assist in the differential diagnosis because it has high specificity for CJD, but only brain biopsy or autopsy can definitively confirm this diagnosis.

Movement disorders
When parkinsonian movement disorders are the presenting complaint, the timing in which the symptoms appear is important to the differential diagnosis. For a diagnosis of DLB, the movement disorder and cognitive or behavioral changes should appear within 1 year of each other. If the movement disorder precedes the cognitive and behavioral features by more than 1 year, idiopathic Parkinson disease or one of the other movement disorders is most likely.

Parkinson disease is suggested by prominent tremor at rest with a unilateral predominance, postural instability, and levodopa-responsive motor dysfunction. Other parkinsonian syndromes in the differential diagnosis include:

- Progressive supranuclear palsy, which is best differentiated from DLB by problems with vertical gaze, a greater gait disturbance, and lack of delusions.21
- Corticobasal degeneration, distinguished by unilateral cortical sensory loss. In addition, apraxia is usually more severe than other cognitive or behavioral disturbances.
- Multisystem atrophy, in which dementia is exceptionally rare. It is characterized primarily by executive dysfunction in the context of much more disabling motor and autonomic deficits. In contrast, dementia for more than 1 year prior to expression of the movement disorder suggests Alzheimer disease with secondary parkinsonism.22

Management
The optimal management of DLB is interdisciplinary and incorporates both nonpharmacologic and pharmacologic approaches.
Nonpharmacologic treatments emphasized

Nonpharmacologic treatment strategies for DLB are the same as the ones used in the care of other dementia syndromes and have been well reviewed elsewhere. They focus on ameliorating environmental, medical, psychological, and social factors that may trigger or exacerbate problem behaviors. In DLB, agitation, aggression, depression, resistance to care, sleep disturbance, and wandering may emerge, especially later in the course of the illness, and are reasonable targets for nonpharmacologic therapy.

Caregiver education and support are also important parts of the interdisciplinary management of DLB, and most families can benefit from referral to the Alzheimer’s Association to identify programming and information suitable to their needs.

Hazards of drug therapy

One reason for emphasizing nonpharmacologic approaches is that DLB patients are at heightened risk for complications of drug therapy. They are prone to psychosis triggered by dopaminergic therapies for parkinsonism, as well as parkinsonian side effects of antipsychotic drugs used to treat hallucinations. No drug is currently approved by the US Food and Drug Administration (FDA) specifically for the treatment of DLB.

Antipsychotic agents. Up to 50% of DLB patients treated with antipsychotic agents may experience impaired consciousness, irreversible parkinsonism, or an autonomic dysfunction syndrome resembling neuroleptic malignant syndrome. Atypical agents, such as olanzepine or quetiapine, are not risk-free but are preferred when an antipsychotic drug is necessary. Anxiety and depression are more safely treated with selective serotonin reuptake inhibitors, and REM sleep behavioral disturbance may respond to clonazepam at low doses.

Dopaminergic therapy. Many patients with DLB do not require or respond to dopaminergic therapy, but levodopa-carbidopa is the agent of choice when treatment of the parkinsonism is needed. Dopamine agonists are less preferable because of their propensity to cause hallucinations and somnolence.

Acetylcholinesterase inhibitors, although not FDA-approved for use in DLB, can offer meaningful benefit to some DLB patients, particularly in the realms of apathy, confusion, hallucinations, and somnolence. Their use in DLB is supported by evidence that the cholinergic system is dysfunctional and by a double-blind placebo-controlled trial.

In that study, rivastigmine 6 to 12 mg daily was associated with less apathy and anxiety and as improved psychomotor speed compared with placebo, but the statistical significance was marginal. Neither the MMSE score nor clinician-assessed global function was significantly different between treatment groups. Cholinergic gastrointestinal side effects such as nausea, vomiting, and anorexia were more common among the rivastigmine-treated patients; in contrast to some of the open-label case series of acetylcholinesterase inhibitors, somnolence was also more common in the rivastigmine group.

PROGNOSIS

Like Alzheimer disease and Parkinson disease, DLB is a neurodegenerative disorder resulting in progressive loss of cognitive and functional abilities. As the disease progresses, the features that distinguish mild DLB from other dementing illnesses become less specific. For many patients, immobility due to apathy, hypersomnolence, postural instability, and rigidity becomes a major source of excess disability.

No therapies are known to alter the natural progression of the underlying neurodegeneration or time to death. Average survival is similar to that in Alzheimer disease, about 8 years, with progressively increasing disability.

In the future, more specific treatments will depend upon the success of research to identify the still unexplained basic pathophysiology of DLB.

REFERENCES

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