Diffuse Lewy Body Disease

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Current Science Inc. ISSN 1092-8480
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Opinion statement

• Diffuse Lewy body disease (DLB) is a neurodegenerative disorder characterized by dementia, fluctuations in mental status, hallucinations, and parkinsonism. Diffuse Lewy body disease is the second most common cause of dementia, following Alzheimer's disease. The treatment of DLB includes cholinergic therapy for cognitive impairment, atypical neuroleptics to alleviate hallucinations, and levodopa/carbidopa to improve parkinsonism.

• The recognition and diagnosis of DLB has critical treatment implications.

• Centrally acting cholinesterase inhibitors, such as rivastigmine, donepezil, and galantamine partially reverse decreased cortical cholinergic activity and may improve cognition and neuropsychiatric symptoms in DLB. Rivastigmine has been demonstrated to improve cognition and neuropsychiatric symptoms in patients with DLB without worsening parkinsonian features. Due to the potential adverse events associated with neuroleptics in this population, treatment with cholinesterase inhibitors is currently considered first-line therapy in the treatment of hallucinations and mental status fluctuations in DLB.

• Exquisite sensitivity to neuroleptic medications is a hallmark of DLB and life-threatening complications have been reported. Caution should be exercised when implementing antipsychotic therapy for the treatment of behavioral disturbances of DLB. When required, atypical neuroleptics with the least extrapyramidal side effects, such as quetiapine, should be used.

• The parkinsonian features of DLB may respond to dopaminergic therapy with levodopa. If parkinsonian symptoms result in clinical disability, a trial of levodopa is warranted. Unfortunately, dopaminergic medications may worsen hallucinations. Because dopamine agonists have a greater tendency to induce hallucinations and somnolence, levodopa is the treatment of choice for parkinsonism in DLB.

• Rapid eye movement (REM) sleep behavior disorder (RBD) is now recognized as a feature of DLB. Awareness of the presence of this symptom in patients with DLB is important and treatment with low dose clonazepam may help. Cholinergic augmentation may also improve these symptoms in patients with DLB.

Introduction

Diffuse Lewy body disease (DLB) is a neurodegenerative disorder characterized by cognitive dysfunction, fluctuating mentation, psychiatric disturbances, and parkinsonism. In contrast to Parkinson's disease (PD), which was described in 1817 [1], DLB has only recently been recognized as an entity distinct from PD and...
Alzheimer’s disease (AD). It is now estimated that DLB accounts for roughly 20% of cases of senile dementia, second in prevalence only to AD [2,3]. A pathologic hallmark of Parkinson’s disease is the Lewy body, described by Friedrich Lewy in 1912 [4] as an eosinophilic intra- or extracellular aggregate located in the brainstem nuclei. Almost 50 years later Okazaki [5] described two cases of parkinsonism and dementia associated with the presence of cortical Lewy bodies. Not until the 1980s did Kosaka and colleagues [6] publish their clinicopathologic series of dementia with Lewy bodies and propose this as a “new disease,” distinct from AD and PD.

The discovery of a mutation in the gene encoding α-synuclein in a rare familial form of PD [7] and the recognition of α-synuclein as the major protein component of Lewy bodies [8] have created a shift in the nosologic paradigm of these diseases. Parkinson’s disease, DLB, and Lewy body variant AD may represent a clinical paradigm of these diseases. This paradigm suggests a common etiopathologic mechanism related to α-synuclein. However, it is possible that these are separate diseases with distinct pathogenesis, and Lewy body deposition may be a nonspecific epiphenomenon. This article will review the diagnostic criteria, clinical features, neuropathology, neurochemistry, neuroimaging, and treatment of DLB.

**DIAGNOSTIC CRITERIA**

Diffuse Lewy body disease (also known as dementia with Lewy bodies) is a newly recognized disease with evolving clinical criteria. In 1996, the consortium on dementia with Lewy bodies proposed the clinical criterion of dementia with associated major and minor criteria [10]. Dementia is defined as progressive cognitive decline, severe enough to result in impairment of social or occupational functioning. Memory deficits may not be present initially, but are common with progression of the disease. The three major clinical criteria of DLB are the following: 1) visual hallucinations; 2) fluctuating mental status; and 3) parkinsonism. The six minor criteria are repeated falls, syncope or loss of consciousness, sensitivity to neuroleptic medications, delusions, and sensory hallucinations other than visual (i.e., olfactory, auditory, sensory, and others). During the second international workshop, two more minor criteria were added, rapid eye movement (REM) sleep behavior disorder and depression [2]. The diagnosis of possible DLB requires the coexistence of one major criterion and two or more minor criteria. The presence of two major criteria suggests a diagnosis of probable DLB.

Several investigators have evaluated the validity of these criteria [11–13]. In a retrospective clinical review, Verghese et al. [14] assessed the sensitivity, specificity, and predictive value of combinations of these clinical criteria, and concluded that a combination of any three major and minor criteria had a positive predictive value of 0.75 and a negative predictive value of 0.96 when applied to patients with mild or moderate dementia. A recent prospective study of 50 cases of AD, vascular dementia, and DLB undergoing autopsy evaluation demonstrated a sensitivity and specificity of 0.83 and 0.95 respectively when the consensus criteria for probable DLB (two major criteria) are applied [15]. These data yielded a positive predictive value of 0.96 and a negative predictive value of 0.80. However, this study was heavily weighted toward DLB, with over 50% of patients demonstrating cortical Lewy bodies on pathology. When applied to the prevalence estimated in clinical practice (15%), the positive predictive value is 0.75. Overall, the specificity of applying clinical criteria for probable DLB approximates the acceptable sensitivities of applying the diagnostic criteria of AD or PD. Lower sensitivity and difficulty in assessing the clinical relevance of milder fluctuations in cognition remain potential pitfalls. Development of additional tools, including detailed neuropsychologic testing and electrophysiologic methods for evaluating fluctuations in mental status, will likely improve diagnostic accuracy [10].

**CLINICAL FEATURES**

**Cognitive decline**

The clinical features of cognitive dysfunction in DLB include impairments in memory, attention, executive function, verbal fluency, and visuospatial performance. In Byrne’s [16] series of 15 patients with pathologically confirmed DLB, dementia was characterized by cortical dysfunction including memory loss, language disturbance, visuospatial abnormalities, apraxia, and dyscalculia. Retrieval of memory appears to be impaired in DLB in contrast to the difficulty in encoding new memories seen in AD. In addition, memory impairment may not be a prominent feature of DLB early in the course of the illness. Tests such as the Folstein Mini-Mental State [17] exam, routinely used in clinical practice, evaluate short-term memory, and, therefore, may not be sensitive enough to pick up memory disturbances in DLB [18]. Attentional deficits appear to be more common in DLB than AD [19]. Social interaction is also affected, sometimes early in the disease process [18].

Del-Ser et al. [20] noted an intriguing temporal relationship between urinary incontinence and cognitive decline in patients with DLB compared with patients with AD. Urinary incontinence, a frequent reason for admission to nursing home facilities, appeared to precede the development of severe intellectual compromise in patients with DLB, whereas patients with AD developed urinary incontinence in later stages of dementia [21].