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Review Article

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Keywords

Lewy bodies: protein aggregates present in neurons afflicted by neurodegenerative diseases

Dementia with Lewy Bodies: a progressive dementia closely resembling Parkinson's disease and Alzheimers disease; characterized by protein aggregates diffused throughout the brain

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Dementia With Lewy Bodies: An Overview

Abstract

Background: Dementia is a neurocognitive disorder that involves multiple cognitive deficits, including memory impairment. Dementia occurs in a variety of disease processes, including Alzheimer disease (AD) and dementia with Lewy bodies, the two most prevalent neurocognitive diseases. This paper reviews the signs and symptoms, neuropathology, diagnosis, prognosis, and treatment of Dementia with Lewy bodies (DLB).

Methods: Terms searched included "Lewy body dementia," "Lewy body disease," "cognitive disorders," and "neurodegenerative diseases." Priority was given to peer-reviewed sources published within the last five years.

Summary: In addition to standard neurocognitive disorder symptoms, patients with DLB present clinically fluctuating cognition, visual hallucinations, and Parkinsonism as well as a variety of other symptoms with lower diagnostic sensitivity. Clinical signs, cognitive assessments, and radiologic imaging are used to diagnose DLB as being distinct from disorders like AD, Parkinson disease dementia (PDD), delirium, and normal aging changes. Interventions for this disease may be pharmacological or non-pharmacological. Pharmacological treatments include cholinesterase inhibitors, Levadopa, and selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors. Non-pharmacological interventions include occupational therapy, cognitive stimulation, and physical activity.

Introduction

Dementia is a devastating diagnosis that significantly burdens those of advanced age. Its incidence is increasing in correlation with the world's increasing mean age; the 2050 projected morbidity for dementia is 60-114 million individuals worldwide. (2) Dementia impacts patients' social and occupational functioning, reasoning, memory, capacity for new learning, self-perception, and interpersonal interactions. (3, 4)

Dementia with Lewy bodies (DLB) is the second most prevalent type of dementia. (2, 5, 6) In addition to dementia, individuals with DLB have a varied symptomatology that ranges from visual hallucinations to Parkinsonism, and from sleep complications to alternating cognizance. (5,7) DLB has a unique clinical picture and treatment regimen, so proper diagnosis and management are integral to patients' well being.

Signs and Symptoms

DLB is progressive in course and insidious in onset. (7-11) Like other types of dementia, it is characterized by memory impairment, significant occupational or social decline, and apraxia, agnosia, and disturbances in executive functioning. (3, 12) The diagnostic characteristics of DLB are defined by the consensus criteria, a set of evidence-based guidelines determined by a panel of medical experts. (7)

Central, core, and suggestive features according to the consensus criteria are used to clinically establish a diagnosis of probable or possible DLB (see Table 1). The central feature, which must be present for any DLB diagnosis, describes patients with cognitive decline that interferes with normal social or occupational activities; deficiencies in attention, executive function, and visuospatial abilities; and memory impairment evident upon progression. (7, 8) Core features are specific characteristics that help identify probable or possible DLB. Suggestive features are diagnostically significant signs and symptoms that occur commonly but with lower specificity than the core features. A probable diagnosis of DLB can be made if two or more core features are present or if one core feature and one or more suggestive features are present. A possible diagnosis of DLB can be made if one core feature is present or if one or more suggestive features are present. (7,8)

Patients may also present with supportive features, which lack diagnostic specificity. Table 1 catalogs an inclusive list of diagnostically significant signs and symptoms.

Core Features

The core features of DLB are fluctuating cognition, visual hallucinations, and features of Parkinsonism. Fluctuating cognition involves changes in attention and alertness, daytime lethargy, more than two hours of daytime sleep, staring into space, and disorganized speech. (7-9, 13) Fluctuations from coherence to confusion can occur in the span of a moment, or across several weeks. (13)

Visual hallucinations may be the most useful symptom in diagnosing DLB because they rarely occur in other types of dementia. (7, 13) Hallucinations are often visual, intricate, and recurrent, but may less frequently manifest in the auditory, tactile, gustatory, and olfactory modalities. (5, 7, 9, 13, 14) Patients with DLB often report complex, "lively and colourful," hallucinations in "scenic sequences". (1)

Parkinsonism, or symptoms of Parkinson's disease, may occur in 60-92% of DLB patients. (5) Parkinsonism presents as spontaneous extra-

Table 1. Clinical diagnostic criteria for DLB[a]

Central feature (must be present for a diagnosis of DLB)*:
Progressive cognitive decline
Impaired social or occupational function
Memory impairment often evident with disease progression
Deficits in attention, executive function, and visuospatial abilities

Core features:
Varied attention and alertness in fluctuating cognition
Detailed, recurrent visual hallucinations
Parkinsonism

Suggestive features:
REM sleep behaviour disorder
Severe antipsychotic sensitivity
Low dopamine transporter uptake in basal ganglia

Supportive features:
Syncope and repeated falls
Loss of consciousness
Severe autonomic dysfunction
Hallucinations in other modalities
Systematized delusions
Depression
Certain radiologic signs

Table 1: Table adapted from "Diagnosis and management of dementia with Lewy bodies: third report of the DLB consortium"[7] Abbreviation: DLB, Dementia with Lewy Bodies. *One central feature or one or more core features indicates possible dementia. Two or more core features or one core feature and one or more suggestive features indicate probable dementia.

pyramidal symptoms, abnormal motor symptoms thought to result from a dopaminergic deficiency. (5, 7, 9) Patients often move rigidly, take small, slow, shuffling steps, and have a blank, emotionless expression. (5) Patients also tend to have a stooped posture, gait changes, and facial immobility. (7, 9, 13) Cogwheeling (ratcheting muscle tremors), bradykinesia (moving in slow motion), and fine-movement apraxia (inability to plan and execute movements) may also signify Parkinsonism in DLB. (9, 13)

Suggestive Features

The three suggestive features of DLB are REM sleep behavior disorder (RBD), severe sensitivity to typical antipsychotic medications, and low dopamine transporter uptake in the basal ganglia. (5, 7)

In RBD, individuals act out their dreams by moving around or vocalizing. (5, 7, 13) Bed partners can provide the history, or RBD can be confirmed by polysomnography. (7) RBD can be present years before other symptoms of DLB manifest. (5, 7-9)

Fifty percent of DLB patients react strongly to typical antipsychotics. (1, 7, 15, 16) Antipsychotics may cause the appearance of extrapyramidal symptoms (that can resemble Parkinsonism) for the first time, increase mortality, and exacerbate confusion and gait imbalance. (5, 7, 16) Neuroleptics, therefore, are contraindicated. (7)

Neuropathology

DLB is an alpha-synucleinopathy, an abnormal precipitation of alpha-synuclein proteins in the brain. (7, 10, 17, 18) DLB is characterized by the histological presence of Lewy bodies, or Lewy neurites. (2, 18) Lewy bodies are presynaptic aggregates of alpha-synuclein protein that occur in cortical and subcortical regions in DLB. (1, 7, 10, 11, 17, 18) It is currently thought that alpha-synuclein aggregates contribute to neurodegeneration, which results in a presynaptic neurotransmitter deficiency. (18) Acetylcholine and dopamine paucity produce the overt clinical symptoms. (5, 18)

Cerebrospinal fluid (CSF) analyses have been suggested to link the presence of alpha-synuclein in the CSF and alpha-synucleinopathies like DLB, but the value of these tests is contentious because of false positives resulting from blood contamination during lumbar puncture and false negatives due to paradoxically lower-than-expected levels of alpha-synuclein in certain DLB patients. (7, 10)

Diagnosis

DLB can be challenging to diagnose due to inconsistency in symptomatic presentation and similarities in presentation to other diseases. (1, 5, 7 ,10, 11, 19, 20) Although autopsy is the only conclusive way to confirm a diagnosis of DLB, patient history, physical examination, lab findings, cognitive assessments, and radiologic exams may help the clinician diagnose DLB. (5, 7)

Rating scales and cognitive assessments

The Mini-Mental State Exam (MMSE) is the most frequently used cognitive functioning evaluation for dementia. (4) The MMSE tests attention, short-term memory, visuospatial functioning, language, and orientation. Cognitive impairment and suspected dementia are signified by a score of 25 or lower (out of a perfect score of 30). (4, 21) While useful for establishing the presence and severity of dementia in the patient, the MMSE has several inherent weaknesses. It does not differentiate different types of dementia. (9, 7, 21) In DLB, memory impairments may not be apparent until later stages of the disease, and therefore may not be initially identified by the MMSE. (5, 7) The MMSE is prone to error when patients start at a high baseline intelligence, have never attained an eighth-grade level education, or are not native English speakers. (4, 15)

Other assessments may help the clinician identify or quantify impairment. The Clock Drawing Test, where the patient is instructed to draw an analog clock on a blank page, is most advantageous as a screening test due to its ease and speed of administration. (4) The Montreal Cognitive Assessment is a screening assessment available in multiple languages and sensitive to initial cognitive changes in highly educated individuals. (4) The Saint Louis University Mental Status Examination is also sensitive to early neurocognitive impairment, and accounts for educational level (whether high or low) in its assessment. (21) The Instrumental Activities of Daily Living assesses an individual's ability to complete tasks that are fundamental to independent living and is often used for functional evaluation prior to admission to long-term care facilities. (21) The Blessed Dementia Scale provides an evaluation of cognitive and behavioral functioning through observation by a caregiver over the duration of 6 months. (21)

Neurological Imaging

New research on neurological scans of patients with DLB may be the future of diagnostic criteria. Functional MRI findings indicate significant connectivity differences between patients with DLB and patients with Alzheimer disease (AD). DLB patients tend to have increased connectivity in the putamen and the inferior parietal cortex but decreased connectivity in the medial prefrontal cortex and the primary visual cortex. (20) MRI also demonstrates hippocampal atrophy in AD patients and preserved hippocampus volume in DLB patients. (6) Grey matter atrophy on MRI in DLB patients is similar to that in AD patients and correlates with cognitive decline. (6) Single photon emission CT (SPECT) scans have advantageous sensitivity and specificity of differentiating DLB from AD and normal individuals compared to clinical diagnosis. A SPECT scan with a greater likelihood of DLB shows decreased semi-quantitative uptake in the posterior putamen. (19) PET scans yield amyloid-β (an abnormal protein that accumulates in AD) deposition in AD and in concomitant AD and DLB, but not in sole DLB. (6) Although these imaging studies may eventually support the clinician in more accurately identifying DLB, there is not presently enough research to establish these tests as a component of the diagnostic criteria. (7)

Differential Diagnosis

Sensitivity in differentially diagnosing dementia is low. (7, 11, 19) DLB must be carefully differentiated from other common types of dementia that present similarly. A diagnosis of DLB should be made over time to best assess its characteristic fluctuating presentation and the full range of manifested symptoms. (8) Accurate diagnosis of DLB has a significant impact on the patient's course of treatment.

Alzheimer Disease

AD and DLB can co-occur in as many as 35-90% of cases. (5, 12) Several characteristics differentiate the two discrete processes. Visual hallucinations occur less frequently in patients with AD as compared with DLB patients. (14) Memory impairment is not as apparent in early-stage DLB as in AD (5, 13). Neuropsychologically, frontal executive function is worse in DLB than AD (11, 13). DLB has more profound cholinergic defects than AD, and as a result, more significant improvements from Cholinesterase inhibitors (ChEIs) in LBD have been hypothesized. (2, 5, 6) Functional MRIs may help differentiate the two diseases. (5, 20)

Parkinson Disease Dementia

DLB and Parkinson disease dementia (PDD) have the same underlying pathology of Lewy body disease. (7, 11, 17) Like DLB, PDD is an alpha-synucleinopathy. (2, 10) The main distinction between the two is an arbitrarily chosen time difference. If dementia develops within well-established Parkinsonism, the patient is diagnosed with PDD. If symptoms of dementia occur one year or more before symptoms of Parkinsonism, the patient is diagnosed with Lewy body disease. (7, 8)

Slight differences have been recorded. Lewy bodies are primarily located in the cortex in DLB and in the basal ganglia in PDD. (1, 8) PDD and DLB have similar global cognitive patterns, but DLB patients may perform worse on tests of attention, verbal memory, and executive function. (11) Rest tremor is less common in DLB patients than PDD patients. (7)

Prognosis

A study of late-life wellbeing found that a cognitive infrastructure with intact executive control processes is crucial to a sense of purpose, relationship quality, and opportunities for growth. (22) Because DLB is marked by a course of progressive and irreversible neurocognitive decline, quality of life is severely diminished. (7, 9, 10) Survival is, on average, 5-7 years after the onset of symptoms. (5, 8)

Treatment

Pharmacological

Cholinesterase inhibitors (ChEIs) are the recommended pharmacological treatment for DLB. (1,2, 6, 7, 10) ChEIs increase acetylcholine (ACh) concentrations at the synapse vis-à-vis inhibition of the enzyme (acetylcholinesterase) that degrades it. (2) This mechanism of action is aimed at correcting the pathologic deficit of ascending cholinergic neurons in DLB, which normally provide a link to higher brain centers in healthy brains. (2, 6) Current treatment provides symptomatic relief through increasing ACh, rather than correcting the underlying pathology of presynaptic α-synuclein aggregates. (1, 18) ChEIs have been shown to improve cognitive and neuropsychiatric symptoms in DLB patients. (5, 7)

There are three commonly used ChEIs: donepezil, rivastigmine, and galantamine. (2, 13) Greater efficacy of one particular ChEI has not yet been conclusively determined, although individuals may respond more favorably to a particular agent than another for several reasons. (2, 5) Donepezil and galantamine are metabolized by the liver, and rivastigmine is metabolized in the serum and excreted by the kidneys. Central action of these medications causes their therapeutic effect, whereas peripheral action at cholinergic receptors is responsible for the dose-dependent side effects. (2) ChEIs may cause adverse effects including nausea, vomiting, anorexia, diarrhea, headache, dizziness, and syncope, which may be severe enough to limit their use. (1, 2) Polymorphisms and epigenetics play a role in the individual's response to therapy, although these factors are too multifarious to guide regimen selection at present. (2)

Other medications may be considered in the treatment of DLB. Levadopa, a dopaminergic agent often used in PD treatment, can be used to mitigate the motor symptoms of Parkinsonism that result from the loss of dopaminergic neurons of both pathologies. (5, 7, 13, 18) Selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors are preferable if antidepressants are necessary because they do not have the anticholinergic side effects associated with other classes of antidepressants and because other classes may worsen hallucinations and cognitive symptoms in DLB patients. (5, 7) Anticholinergics and neuroleptics are contraindicated. (1, 7) Anticholinergics decrease the concentration of presynaptic acetylcholine, which exacerbates the underlying pathophysiology of DLB. DLB patients are more sensitive to the side effects of neuroleptics than the general population, and therefore more likely to experience adverse events (see "Suggestive Features"). (1)

Non-Pharmacological

Non-pharmacological interventions include motor and cognitive stimulation and training in activities of daily living (ADLs), namely, eating, bathing, dressing, using the bathroom, and perambulating. (21) Interventions have been shown to produce improvements in social behavior, ADLs, and night restlessness in patients with mild and moderate dementia. (23) Physical activity decelerates the progression of dementia, even in frail patients. (24) Individualized occupational performance treatments can improve task performance despite progressive cognitive losses. (12) Individuals with dementia may be able to benefit from education about their condition and may be capable of learning despite the degenerative nature of the disease. (12, 15) Further, systematized research of non-drug interventions should be conducted to establish a holistic treatment plan.

Conclusion

DLB is a complex condition to care for clinically. It must first be recognized as dementia, as signified by the individual's progressive cognitive decline, diminishing memory, and impaired social or occupational function. Screening tests like the MMSE or the Clock Drawing Test may aid the clinician in rapidly screening patients. Other cognitive evaluations are more suited for a thorough evaluation of the patient's mental and functional status. Further diagnostic imaging and studies may in the future come to occupy a niche in diagnosing DLB. The next obstacle is differentiating DLB from other neurodegenerative pathologies, such as AD or PDD, and identifying any comorbid conditions, especially when there exists a significant overlap of symptoms. A final stepping stone is selecting an appropriate treatment regimen. This can be done by considering the unique characteristics of the ChEI agents; selecting appropriate adjunctive therapy to manage comorbid symptoms such as Parkinsonism and depression; avoiding contraindicated classes of medications (anticholinergics and neuroleptics); and ultimately adjusting or fine-tuning the medication regimen based on the patient's response. Meticulous attention should be paid to the diagnosis and management of these patients in order to optimize quality and expectancy of life.

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