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Review

Dementia with Lewy Bodies: Clinical Review

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Summary

The aim of this article is to review the diagnosis and management of Dementia with Lewy Bodies. Dementia with Lewy bodies (DLB) is considered the second most common cause of dementia in the elderly after Alzheimer's disease. Diagnostic criteria for DLB is categorised into central feature (progressive dementia), core features(fluctuating cognition, recurrent visual hallucinations and parkinsonism), suggestive features(rapid eye movement sleep behaviour disorder, increased sensitivity to neuroleptics and low dopamine transporter uptake in the brain's basal ganglia) and supportive features(repeated falls , transient loss of consciousness, hallucinations in other modalities, visuospacial abnormalities and autonomic dysfunction). DLB patients have the diffuse presence of Lewy Bodies in both sub cortical and cortical areas of the brain. Patients with DLB also have more severe dopamine and acetylcholine loss as compared to Alzheimer's disease. Cholinesterase inhibitors can be used for the treatment of neuropsychiatric symptoms. Treatment with levodopa-carbidopa combinations should be considered when parkinsonian symptoms cause functional impairment. Antipsychotics should be used with great caution due to increased extra pyramidal adverse reactions. Clonazepam can be helpful to manage REM sleep behaviour disorder.

Clinicians need to be aware of the diagnosis of DLB in order to provide appropriate pharmacological and nonpharmacological treatment for its cognitive, neuropsychiatric, motor and sleep disturbances without causing distressing side effects due to inappropriate drug prescription.

Abbreviations

DLB=Dementia with Lewy Bodies, AD=Alzheimer's disease, PD=Parkinson's disease, REM=Rapid eye movement, SPECT=Single-photon emission computed tomography, PET=positron emission tomography.

INTRODUCTION

Dementia with Lewy bodies (DLB) is considered the second most common cause of dementia in the elderly after Alzheimer's disease. DLB is a progressive neurological disorder characterized by core features of cognitive impairment, psychosis and Parkinsonism. The disease is commonly referred to by a number of names, such as Lewy Body Disease, Lewy Body dementia, dementia with Lewy Bodies, *or* diffuse Lewy Body Disease. Prevalence estimates of DLB, depending on case criteria, range from 0 to 5% with regard to the general population, and from 0 to 30.5% of all dementia cases [1]. It is claimed that DLB accounts for 20% of late onset dementia [2, 3] .Most studies suggest that DLB is slightly more common in men than in women. DLB is a disease of late middle age and old age. DLB has been described in Asian, African, and European races.

Friederich Lewy discovered abnormal proteins called Lewy Bodies in early1900's These Lewy Body proteins are spherical intraneuronal cytoplasmic inclusions 15-30um in diameter and are found in the brainstem of patients with Parkinson's disease. In DLB, these abnormal proteins are found diffusely throughout other areas of the brain including midbrain and the cerebral cortex. The brain chemical acetylcholine is depleted, causing disruption of perception, thinking, and behaviour. Lewy body dementia shares characteristics with both Alzheimer's disease and Parkinson's disease. This can lead to difficulty or delay in reaching the right diagnosis of DLB.

CLINICAL FEATURES

First consensus guidelines for diagnosis of DLB were published in 1996 [4] and reviewed in 1999 [5].The latest consensus diagnostic criteria for DLB was agreed in the third report of the DLB consortium in 2005 [6].

COGNITIVE IMPAIRMENT

Prominent memory impairment may not be evident in the early stages. Cognitive features distinguishing DLB from AD are more prominent impairment of attention, executive functioning (e.g., planning, prioritizing, sequencing), and visuospatial problems (such as problems in following an unfamiliar route) [8, 9]. Mental inflexibility, perseveration, and intrusion are more likely with DLB than with AD [10]. Patients with DLB have more difficulties in clock drawing or figure copying as compared to patients with Alzheimer's disease who have more prominent memory changes on mini mental state examination [8, 11-13].

A core feature of DLB is the fluctuation in cognitive performance, which can occur early in the illness. By way of example, one day a patient may be able to hold a sustained conversation, the next they may be drowsy, inattentive and almost mute.

Diagnostic criteria for Dementia with lewy bodies [4-7]

Central feature

- Progressive dementia - deficits in attention and executive function are typical. Prominent memory impairment may not be evident in the early stages.

Core features:

- Fluctuating cognition with pronounced variations in attention and alertness.
- Recurrent complex visual hallucinations
- Spontaneous features of Parkinsonism.

Suggestive features:

- REM sleep behaviour disorder (RBD), which can appear years before the onset of dementia and Parkinsonism.
- Severe sensitivity to neuroleptics occurs in up to 50% of LBD patients who take them.
- Low dopamine transporter uptake in the brain's basal ganglia as seen on SPECT and PET imaging scans.

Supportive features:

- Repeated falls and syncope (fainting).
- Transient, unexplained loss of consciousness.
- Autonomic dysfunction.
- Hallucinations of other modalities.
- Visuospatial abnormalities like depth perception, object orientation, directional sense and illusions
- Other psychiatric disturbances like systematized delusions, aggression and depression.

A probable LBD diagnosis requires either:

- Dementia plus two or more core features, or
- Dementia plus one core feature and one or more suggestive features.

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Data from [4-7]

VISUAL HALLUCINATIONS

Visual Hallucinations are another core feature distinguishing DLB from AD. In DLB, hallucinations are typically recurrent, well formed, and complex and are usually detailed. Patients may see images of people or animals that they recognise. Some patients see coloured patterns or shapes. Presence of hallucinations with substantial fluctuation in attention can lead clinicians to diagnose delirium. Hallucinations are not always distressing to patients and many learn to distinguish between real and unreal images: some people actually come to enjoy them. In many patients visual hallucinations are accompanied by delusions which tend to be persecutory in nature.

PARKINSONISM

Spontaneous features of Parkinsonism are another core feature of DLB. Patients usually present with rigidity, bradykinesia, gait changes, masklike faces [14], reduced arm swing and a tendency to falls. Resting tremor is less common in DLB than in PD. Development of dementia within 12 months of extrapyramidal signs suggests DLB, whereas late development of dementia makes PD with dementia more likely [4]. Patients who have dementia with Lewy bodies tend to respond less favourably to levodopa with carbidopa as compared to patients who have Parkinson's disease with dementia [11, 15].

OTHERS CLINICAL FEATURES

Severe sensitivity to antipsychotics occurs in up to 50% of DLB patients who take them, developing Parkinsonism even if they have not shown such signs before drug administration. The associated Parkinsonism is often prolonged, profound and may even be fatal. REM sleep behaviour disorder occurs in about one half of these patients. REM sleep behaviour disorder usually presents with vivid dreams associated with simple or complex motor behaviour during REM sleep [11]. Diagnosis of DLB is also supported by repeated falls and syncope, transient loss of consciousness hallucinations in other modalities, visuospacial abnormalities and autonomic dysfunction.

PATHOGENESIS

The pathology of DLB closely resembles that of Parkinsonism disease. Patients with DLB are characterised by the diffuse presence of Lewy Bodies in both subcortical and cortical areas of the brain whereas Parkinson's disease patients have lewy bodies in the subcortical areas of the brain mainly substantia nigra and locus cerules [11, 16]. Both DLB and Parkinson's disease are associated with abnormal aggregation of alpha-synuclein which is a nerve terminal protein that is a better marker of lewy bodies than ubiquitin. Biochemically, numerous neurotransmitters, including acetylcholine and dopamine are diminished in DLB. The decrease in acetylcholine may be more severe than in Alzheimer's disease.

Pathological features in DLB [17, 18]

- Diffuse Lewy bodies - Essential for diagnosis of DLB
- Lewy neuritis
- Senile Plaques (all morphological types)
- Neurofibrillary tangles
- Neuronal loss in substantia nigra
- Neuronal loss in locus coeruleus
- Meynert nucleus neuronal loss
- Microvacuolation and synapse loss
- Neurochemical abnormalities and neurotransmitter deficits e.g. Ach, Dopamine

Data from [17, 18]

DIFFERENTIAL DIAGNOSIS

DLB can be easily confused with Alzheimer's disease (AD) and Parkinson's disease (PD).It is important to differentiate between DLB, AD and PD due to differences in treatment approaches. As compared to AD, patients suffering from DLB more frequently show signs of frontal lobe dysfunction, more prominent visual and auditory hallucinations, fluctuating cognitive performance, greater sensitivity to neuroleptics [19] and parkinsonian symptoms. Patients with DLB also have more severe dopamine and acetylcholine loss as compared to AD. DaT FP-CIT scan can be useful to differentiate between DLB and AD. Other diagnoses which can be confused with DLB include delirium and psychiatric illnesses.

Differential Diagnosis of DLB [20]

- Alzheimer's Disease
- Parkinson's Disease
- Dementia in Parkinson's Disease
- Psychiatric illnesses like mania and psychotic depression
- Vascular Dementia
- Delirium

INVESTIGATIONS

It is important to do dementia screen to rule out any reversible causes of cognitive impairment.

Blood tests

Laboratory studies should include those usually ordered in a dementia evaluation [21], including the following:

- FBC, ESR, CRP, biochemical screen
- Urea and creatinine
- T4 and TSH
- Glucose
- B12 and folate
- Clotting & albumin
- Syphilis serology
- HIV - if in young person
- Caeruloplasmin

Urine tests

Perform a midstream urine test if delirium is a possibility.

Imaging studies

- Structural imaging can be used to exclude other cerebral pathologies and help establish the subtype of dementia. Imaging studies may help to identify treatable causes such as subdural haematoma, normal pressure hydrocephalus, and cerebral tumours.
- Brain MRI is indicated to distinguish DLB from vascular dementia. Patients with vascular dementia often have white matter lesions on MRIs, whereas patients with DLB do not.
- Regionally distinct patterns of hypoperfusion on single-photon emission computed tomography (SPECT) or hypometabolism on positron emission tomography (PET) can help differentiate Frontotemporal Dementia, AD and Vascular Dementia, and dopaminergic loss in the basal ganglia can differentiate DLB from AD [22].
- Reduced dopamine transporter activity in the basal ganglia is seen with positron emission tomography (PET) scanning or single-photon emission CT (SPECT) scanning.
- DaTSCAN (Ioflupane, 123-I FP-CIT) SPECT imaging.DaTSCAN contains Ioflupane labelled with radioactive iodide in an ethanolic solution. DaTSCAN is a drug used as part of a diagnostic procedure called SPECT imaging. DaTSCAN SPECT is indicated for detecting loss of functional dopaminergic neuron terminals in the striatum. The sensitivity of the FP-CIT scan for the diagnosis of DLB is 88% and specificity is 100 % [23].It helps to differentiate probable dementia with Lewy bodies from Alzheimer's disease.

MANAGEMENT

There is limited evidence about specific interventions but available data suggests a role for cholinesterase inhibitors, atypical antipsychotics, levodopa and clonazepam. For the treatment of agitation and hallucinations associated with DLB, acetyl cholinesterase inhibitors are the drugs of choice. In a small minority of patients, motor features are worsened with cholinesterase inhibitors. Most experts recommend atypical neuroleptics when cholinesterase inhibitors are ineffective. Levodopa/carbidopa may improve motor function in some patients with DLB; however, in many patients this combination has no effect and may exacerbate psychiatric symptoms or confusion. Depression is frequent in DLB patients and may result from damage in the dorsal raphe and locus ceruleus and/or as a psychological response to impaired function. Selective serotonin reuptake inhibitors are the drugs of choice.

PHARMACOLOGICAL TREATMENT

Acetyl cholinesterase inhibitors

Cholinergic deficits in DLB are even more severe than in AD [24]. Patients with DLB are more likely to improve with cholinesterase inhibitor therapy. Encouraging results have been obtained with Rivastigmine, Donezepil and galantamine. Double-blinded, placebo-controlled studies [25-27] have demonstrated that rivastigmine may decrease neuropsychiatric symptoms associated with DLB, particularly apathy, anxiety, hallucinations, and delusions. There is also some evidence from several case reports, open label trials and case series about the use of acetyl cholinesterase inhibiters including Rivastigmine and Donepezil in DLB [28-32].

Atypical neuroleptics

Due to increased sensitivity to antipsychotics, clinicians are generally cautious about the use of these drugs in patients with DLB. There have been multiple studies about the use of atypical antipsychotics like risperidone, olanzapine and quetiapine in DLB patients for the management of neuropsychiatric symptoms [33-37]. Patients with DLB frequently have distressing neuropsychiatric symptoms. When these symptoms are mild, no medical treatment may be necessary. Acetyl cholinesterase inhibitors should usually be tried first to treat neuropsychiatric symptoms [38]. Atypical antipsychotics appear to be better tolerated by DLB patients [39]. Most experts recommend atypical neuroleptics when cholinesterase inhibitors are ineffective. Neuroleptics should be reserved for situations where the psychosis is causing serious distress or putting the patient or others at risk. Very slow titration of the neuroleptic medication is indicated.

Anti-Parkinson's Medications

Patients with DLB can have troublesome parkinsonian symptoms which might need treatment. Treatment with levodopa-carbidopa combinations should be considered when symptoms cause functional impairment. Most of the evidence for benefit comes from case series [40, 41].

Benzodiazepines

Clonazepam can be helpful in treating REM sleep behaviour disturbances in DLB patients [42, 43].

Antidepressants

Patients with DLB have increased frequency of depression and anxiety. Selective serotonin reuptake inhibitors (SSRI's) are the drugs of choice.

NONPHARMACOLOGICAL TREATMENT

Nonpharmacological management mainly involves education of the patient and carers to deal with specific symptoms of the illness as well as general issues of caring for a patient with dementia [20].Various interventions including education of patient and family, structuring of environment, teaching behavioral skills and improving sensory impairment have been found useful in other types of dementias and might also be useful in patients suffering from dementia with lewy bodies [44-48].

COMPETEING INTERESTS:
None declared

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