Dementia with Lewy bodies

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Abstract

Dementia with Lewy bodies (DLB) is the second most common cause of neurogenerative dementia in elderly people, accounting for 10–15% of all cases of dementia. It occupies part of a spectrum of disorders that includes Parkinson's disease and primary autonomic failure, all of which share a neuritic pathology based on abnormal aggregation of the normally occurring synaptic protein α-synuclein. It is important to identify DLB patients accurately because they have specific symptoms, impairments and functional disabilities that differ from other common dementia syndromes, including Alzheimer's disease, vascular cognitive impairment and fronto-temporal dementia. Recently revised clinical diagnostic criteria for DLB have been refined in an attempt to identify a substantial minority of cases with atypical presentations that are often due to the presence of mixed pathology. Newly developed rating scales for the core features of DLB (fluctuation, visual hallucinations and Parkinsonism) promise to improve clinical diagnostic accuracy, as does the use of structural and functional neuroimaging, particularly of dopamine transporter activity in the basal ganglia. DLB patients frequently have severe neuroleptic sensitivity reactions, which are associated with significantly increased morbidity and mortality. Cholinesterase inhibitor treatment is usually well tolerated and substantially improves cognitive and neuropsychiatric symptoms. Virtually unrecognized 20 years ago, DLB may, within this decade, be one of the most treatable neurodegenerative disorders of late life.

Keywords α-synuclein; cholinesterase inhibitor; Parkinson's disease

Dementia with Lewy bodies (DLB) is a common disorder accounting for 10–15% of all cases of dementia in elderly people.[1] Accurate diagnosis is important because of extreme sensitivity to the side effects of neuroleptics and good responsiveness to cholinesterase inhibitors. Unfortunately, many clinicians have great difficulty in recognizing DLB, partly because of lack of experience of the condition, and also because of the variable pattern of clinical presentation. The demand for accurate recognition of DLB is increasing as awareness of the disorder grows, together with the establishment of caregiver associations specifically for DLB patients and their families.[2,3] This article summarizes some recent information about improved methods for the assessment, diagnosis and management of DLB.

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What's new?

- New criteria have recently been published for the clinical and pathological diagnosis of DLB, including guidelines for patient management
- The 2006 NICE dementia guideline recommends that people with DLB who have non-cognitive symptoms, causing significant distress to the individual, or leading to behaviour that challenges, should be offered an acetylcholinesterase inhibitor
- FP-CIT SPECT imaging of the dopamine transporter has been licensed in the EU for use in the differential diagnosis of DLB from AD
- DLB is leading to increased interest in and better understanding of dementia in Parkinson's disease (often indistinguishable from DLB)

Neuropathology

DLB occupies part of a spectrum of clinical presentations that also includes Parkinson's disease (PD). Both syndromes are underpinned by similar pathological changes, including Lewy body (LB) and Lewy neurite (LN) formation, which are the result of abnormal aggregation of a normally occurring synaptic protein called α-synuclein, which plays a role in synaptic vesicle formation (Figure 1). Neither severity nor duration of dementia is directly correlated with cortical LB density, so neurotransmitter deficits and the disruptive effects of LN on axonal function are suggested as more likely causes of clinical symptoms. Most DLB cases also show some characteristics of Alzheimer's disease (AD) at autopsy, predominantly in the form of amyloid plaques. Tau-positive inclusions and abundant neocortical neurofibrillary tangles occur in up to 20% of cases. The presence of these neocortical tangles modifies the typical clinical presentation of DLB to one more closely resembling AD and makes such cases harder to differentiate on clinical grounds alone.

Clinical criteria for DLB

The core clinical features of DLB are fluctuating cognitive impairment, recurrent visual hallucinations and Parkinsonism.[4] The specificity of a clinical diagnosis of 'probable DLB', defined by two or more of these core features being present, is high at more than 80%, but only about 50% of cases are identified by this approach alone. In clinical practice it is advisable to have a higher index of suspicion by using the presence of only one core feature for 'possible DLB' to increase case detection rates. Recently revised clinical diagnostic criteria[5] describe three additional features 'suggestive' of DLB, which occurring alone or in combination in a person with dementia should alert the clinician to a diagnosis of possible DLB. If present with one or more core features they are sufficient for a diagnosis of probable DLB. These suggestive features, rapid eye movement sleep behaviour disorder (RBD), severe neuroleptic

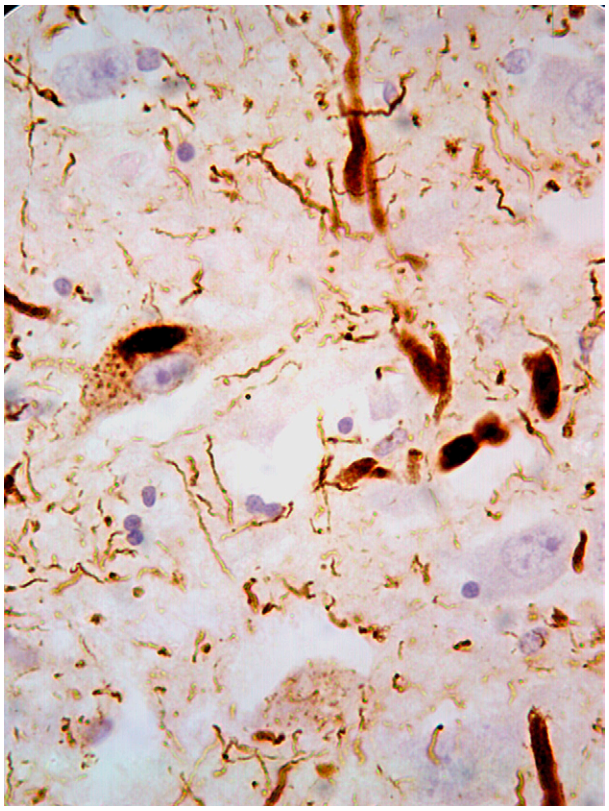

Figure 1 Lewy bodies and Lewy neurites staining (brown) with α-synuclein antibodies. X63 in CA2 region of hippocampus in patient with DLB. (Image courtesy of Dr E Jaros.)

sensitivity and low dopamine-transporter uptake in basal ganglia demonstrated by SPECT or PET imaging are included in Table 1, which outlines the new diagnostic criteria.

There is considerable debate regarding the relationship between DLB and dementia occurring as a late manifestation of Parkinson's disease (PDD). An arbitrary '1-year rule' is frequently used to 'separate' them by proposing that onset of dementia within 12 months of Parkinsonism qualifies as DLB and more than 12 months of Parkinsonism before dementia qualifies as PDD.[6] This is helpful in individual clinical case diagnosis and management, but is hard to justify from a neurobiological point of view because there do not seem to be any major neuropathological or neurochemical differences between DLB and PDD.

Pointers to a diagnosis of DLB

- Presence of at least one of the core features: visual hallucinations, fluctuation or Parkinsonism
  or
- One of the suggestive features: REM sleep behaviour disorder, severe neuroleptic sensitivity or low dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET imaging
- Attentional deficits, daytime somnolence and apathy
- Relative preservation of episodic memory
- Disproportionate executive and visuo-perceptual impairment
- Dysautonomia: early urinary incontinence, dizziness and falls
- Lack of medial temporal lobe atrophy on CT/MRI
- Good cholinesterase inhibitor response

Table 1

Clinical presentation and course of DLB

Generally, the onset of DLB tends to be insidious, although reports of a period of increased confusion, the onset of hallucinations or a significant fall, may give the impression of a sudden onset. The main differential diagnoses of DLB are AD, vascular dementia, PDD, atypical Parkinsonian syndromes such as progressive supranuclear palsy (PSP), multi-system atrophy (MSA), corticobasal degeneration (CBD), and also Creutzfeldt–Jacob disease (CJD).[4] The course of DLB is progressive, with cognitive test scores declining about 10% per annum (similar to AD). Cognitive fluctuations may contribute to large variability in repeated test scores (e.g. 5 MMSE-point difference over the course of a few days or weeks) making it difficult to be sure of the severity of cognitive impairment by single examination. Survival times from onset until death are generally similar to AD, although some DLB patients seem to have a more rapid disease course.

The clinical diagnosis of DLB rests on obtaining a detailed history of symptoms from the patient and an informant, mental state examination, appropriate cognitive testing and neurological examination. Systemic and pharmacological causes of delirium need to be excluded. There are as yet no clinically applicable electrophysiological, genotypic or cerebrospinal fluid markers to support a DLB diagnosis,[1] but neuroimaging investigations may be helpful in supporting the clinical diagnosis. Changes associated with DLB include preservation of hippocampal and medial temporal lobe volume on MRI and occipital hypoperfusion on SPECT. Other features such as generalized atrophy, white-matter changes and rates of progression of whole-brain atrophy seem to be unhelpful in differential diagnosis. Dopamine transporter loss in the caudate and putamen occurs in DLB as a consequence of nigro-striatal dopaminergic degeneration, but not in AD, making it a potential biomarker for distinguishing between the two disorders. A recent multicentre study demonstrated a high sensitivity (78%) of dopamine-transporter SPECT imaging for identifying probable DLB cases, with an accompanying specificity of 90%. The images are easily read (Figure 2), and the technique is now licensed in the EU for this indication. It should be used to support a clinical diagnosis of probable DLB when the clinician is not fully confident on clinical grounds alone, and in cases of possible DLB (only one core or suggestive feature present) when an abnormal scan will upgrade the level of diagnostic certainty.[7]

Fluctuating cognition

The profile of neuropsychological impairments in patients with DLB differs from that of AD and other dementia syndromes, reflecting the combined involvement of cortical and subcortical pathways and relative sparing of the hippocampus. Patients with DLB perform better than those with AD on tests of verbal memory, but less well on visuo spatial performance tasks and tests of attention (Figure 3). Fluctuations in cognitive function, which may vary over minutes, hours, or days, occur in 50–75% of patients and are associated with shifting levels of attention