Dementia with Lewy bodies

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Dementia with Lewy bodies (DLB) is the second commonest cause of neurodegenerative dementia in older people. It is part of the range of clinical presentations that share a neuritic pathology based on abnormal aggregation of the synaptic protein α-synuclein. DLB has many of the clinical and pathological characteristics of the dementia that occurs during the course of Parkinson's disease. Here we review the current state of scientific knowledge on DLB. Accurate identification of patients is important because they have specific symptoms, impairments, and functional disabilities that differ from those of other common types of dementia. Severe neuroleptic sensitivity reactions are associated with significantly increased morbidity and mortality. Treatment with cholinesterase inhibitors is well tolerated by most patients and substantially improves cognitive and neuropsychiatric symptoms. Clear guidance on the management of DLB is urgently needed. Virtually unrecognised 20 years ago, DLB could within this decade be one of the most treatable neurodegenerative disorders of late life.

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Dementia is an increasingly common disorder, which affects 7% of the general population older than 65 years and 30% of those aged over 80 years. Alzheimer's disease and vascular cognitive impairment, either alone or in combination, account for most cases[1] but other causes of dementia are not rare. Initially thought to be uncommon, dementia with Lewy bodies (DLB) is now thought to be the second most common type of degenerative dementia in older people, accounting for 10–15% of cases at autopsy.[2] The importance of diagnosing this disorder lies particularly in its pharmacological management, with good responsiveness to cholinesterase inhibitors[3] but extreme sensitivity to the side-effects of neuroleptic drugs.[4,5] DLB has had several diagnostic labels during the past decade, including diffuse Lewy-body disease,[6] Lewy-body dementia,[7] the Lewy-body variant of Alzheimer's disease,[8] senile dementia of Lewy-body type,[9] and dementia associated with cortical Lewy bodies.[10] Close clinical and pathological similarities are now being recognised between DLB and dementia that occurs during the course of Parkinson's disease (PDD),[11] and there are encouraging reports of successful management of these two clinical disorders that were previously characterised by a poor outcome.[12–14]

In an effort to review and clarify current knowledge, concepts, and methods for further inquiry, a specialist meeting was organised by the International Psychogeriatric Association with the participation of the European Movement Disorder Society. Participants were asked to review relevant literature systematically and discuss it. As a product of this international meeting, we have reviewed the current state of scientific knowledge about DLB and identified key issues requiring clarification and research necessary to advance knowledge in this area. Articles for inclusion were selected by the authors as representing the most relevant and important work and supplemented by the personal knowledge of the specialists who attended the meeting.

Diagnostic concepts

DLB and PDD are clinically defined syndromes; although consensus clinical criteria have been validated for DLB,[2] no formal clinical diagnostic criteria have been proposed or validated for PDD (the subject of a recent comprehensive review in this journal).[11] An arbitrary "1-year rule" has until now been used to separate DLB from PDD; onset of dementia within 12 months of parkinsonism qualifies as DLB and more than 12 months of parkinsonism before dementia as PDD. The limitations of this approach are discussed later.

At autopsy, cases of both disorders have Lewy bodies, which are the characteristic pathological feature of Lewy-body disease, but there are as yet no definite pathological criteria that separate the disorders either from each other or

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Consensus guidelines for the clinical diagnosis of probable and possible DLB[2]

Central features

Progressive cognitive decline of sufficient magnitude to interfere with normal social and occupational function. Prominent or persistent memory impairment does not necessarily occur in the early stages but is evident with progression in most cases. Deficits on tests of attention and of frontal-subcortical skills and visuospatial ability can be especially prominent.

Core features (two core features essential for a diagnosis of probable, one for possible, DLB)

Fluctuating cognition with pronounced variations in attention and alertness

Recurrent visual hallucinations that are typically well formed and detailed

Spontaneous features of parkinsonism

Supportive features

Repeated falls

Syncope

Transient loss of consciousness

Neuroleptic sensitivity

Systematised delusions

Hallucinations in other modalities

REM sleep behaviour disorder

Depression

Features less likely to be present

History of stroke

Any other physical illness or brain disorder sufficient to interfere with cognitive performance

from Parkinson's disease without dementia. Moreover, autopsy studies of patients with clinically diagnosed DLB and PDD show heterogeneity in terms of distribution and density of Lewy-body pathology, as well as Alzheimer's and vascular pathology.[8,9,15,16] Because of these diagnostic uncertainties and difficulties in clinical ascertainment, routine sources of information such as death certificates and a limited number of population-based studies leave uncertainty about the relative frequencies of DLB and PDD.

Clinical and pathological criteria for DLB

There is some convergence of agreement on the core clinical features of DLB, which are fluctuating cognitive impairment, recurrent visual hallucinations, and parkinsonism.[17] The clinical distinctions between DLB and Alzheimer's disease are increasingly recognised (panel).[2] The presence of Alzheimer's pathology in DLB modifies the clinical presentation, with the lower rate of visual hallucinations and parkinsonism making such cases harder to differentiate clinically.[18] The specificity and sensitivity of the current clinical criteria for DLB reported by various groups[16,17,19–25] need careful interpretation (table) because of different methods and case mixes.[26] In general, specificity is high but sensitivity of case detection is limited. Case validation is compromised by the lack of defined neuropathological criteria for DLB and the presence of Lewy bodies in a large number of cases at autopsy with non-DLB clinical presentations, such as Lewy bodies limited to the amygdala in advanced Alzheimer's disease.[27]

Other than the temporal course of the disease (ie, the 1-year rule), clinical features in DLB and PDD are similar, including fluctuating neuropsychological function[28] and neuropsychiatric features, predominantly visual hallucinations.[29] Within pathological studies of patients with clinically diagnosed DLB and PDD, there is heterogeneity in terms of Alzheimer's and Lewy-body pathology and vascular abnormalities. There do not seem to be obvious neuropathological differences between DLB and PDD, so a descriptive clinicopathological approach to their classification will probably be most productive, with specificity both about clinical terms (DLB or PDD, largely determined by the temporal order of symptoms) and also about pathological findings (Lewy-body disease, Alzheimer's disease, vascular disease). The latter "categories" will need to be further illustrated by details of lesion density and distribution.

Epidemiology

In population-based clinical studies of people aged 65 years or older, the prevalences of DLB and PDD were reported to be 0·7% and 0.3%, respectively, which suggests that each could account for up to 10% of all dementia cases, a proportion consistent with DLB rates of 10–15% from hospital-based autopsy series. A community study of people aged over 85 years found that 5·0% met consensus criteria for DLB (3·3% probable, 1·7% possible) representing 22% of all demented cases,[30] similar to other clinical estimates[31,32] and consistent with estimates of Lewy-body prevalence in a dementia case register followed up to autopsy.[21] One population-based autopsy study found that Lewy bodies were evenly distributed between demented and non-demented individuals, which could be interpreted as evidence of a substantial pool of preclinical cases.[33] No classic epidemiological studies to investigate age and sex variation and potential risk factors for DLB have yet been reported.

Clinical phenomenology of DLB

Cognitive

Cognitive impairment is the presenting feature of DLB in most, but not all, cases. The disorder typically presents with recurrent episodes of confusion on a background of progressive deterioration. Patients with DLB show a combination of cortical and subcortical neuropsychological impairments[34,35] with substantial attentional deficits and prominent frontosubcortical and visuospatial dysfunction[36] that help to differentiate this disorder from Alzheimer's disease.[37,38] Patients with DLB do better than those with Alzheimer's disease on tests of verbal memory but worse on visuospatial performance tasks. This profile can be maintained across the range of severity of disease but can be harder to recognise in the later stages owing to global difficulties. Fluctuations in cognitive function—which may vary over minutes, hours, or days—occur in 50–75% of patients and are associated with shifting degrees of attention and alertness that can be assessed by carers' reports, observers' ratings,[39] or use of computer-based measures of variation in attentional performance.[40]

Validity and reliability of consensus criteria for DLB[26]

Reference	Number of cases		Diagnostic criteria	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	κ	Comments and recommendations
	DLB	Other							
Mega et al[19]	4	24 AD	Probable	75	79	100	93	F=0·25, H=0·59 P=0·46	Retrospective; suggests 4/6 of H, C, R, B, N, Fl
Litvan et al[20]	14	105 PD, PSP, MSA, CBD, AD	None applied; retrospective clinical diagnosis	18	99	75	89	0·19–0·38	Retrospective; no formal criteria for DLB used; comparison mainly with movement disorder
Holmes et al[21]	9	80 AD, VaD	Probable	22	100	100	91	NA	Retrospective; no specific recommendations; cases with mixed pathology were hardest to diagnose
Luis et al[17]	35	56 AD	Probable	57	90	91	56	F=0·30, H=0·91, P=0·61	Retrospective; suggests H, P, Fl, and rapid progression
Verghese et al[22]	18	94 AD	Probable	61	84	48	90	F=0·57, H=0·87	Retrospective; suggests 3/6 of P, Fl, H, N, D, and F
			Possible	89	28	23	91	P=0·90	
Lopez et al[23]	8	40	..	0	100	0	80		Retrospective; probable DLB not diagnosed once by a team of four raters; no specific recommendations
Hohl et al[24]	5	10 AD	Probable	100	8	83	100	NA	Consensus criteria applied retrospectively; clinician diagnosis without consensus criteria had PPV of 50
			Possible	100	0	NA	NA	NA	
McKeith et al[16]	29	50 AD, VaD	Probable	83	95	96	80	NA	Prospective; false-negative cases associated with comorbid pathology
Lopez et al[25]	13	26 AD	Probable	23	100	100	43		Prospective; met NINCDS–ADRDA criteria for AD, only four met DLB criteria

PPV=positive predictive values; NPV=negative predictive values; AD=Alzheimer's disease; F=falls; H=hallucinations; C=cogwheeling; P=parkinsonism; R=rigidity; B=bradykinesia; N=neuroleptic sensitivity; Fl=fluctuation; NA=not available; PD=Parkinson's disease; PSP=progressive supranuclear palsy; MSA=multiple system atrophy; CBD=corticobasal degeneration; VaD=vascular dementia. *Movement Disorders* © copyright 2003 Movement Disorders Society.

Psychiatric

Psychiatric manifestations are common in DLB—predominantly visual hallucinations, delusions, apathy, and anxiety. They are generally present early in the course of illness and may be the initial reason for referral. They also tend to persist; for example, hallucinations were stable in a placebo-treated DLB group over 20 weeks[13] and in a cohort in which the disorder took its natural course over 52 weeks.[41] The hallucinations are similar to those reported in PDD in that they are vivid, colourful, three-dimensional, and generally mute images of animate objects.[29] Barnes and colleagues[42] suggested that the hallucinations arise from a combination of faulty perceptual processing of environmental stimuli and less detailed recollection of experience, combined with intact image generation. The importance of psychiatric symptoms in the clinical phenomenology of DLB is such that a cluster of hallucinations, delusions, apathy, and depression derived from the neuropsychiatric inventory[43] was used as the primary outcome in the first randomised placebo-controlled study of DLB treatment.[13] Visual hallucinations are associated with greater deficits in cortical acetylcholine[44] and predict better response to cholinesterase inhibitors.[45]

Neurological

Extrapyramidal signs are reported in 25–50% of patients with DLB at diagnosis, and most develop some such signs during the natural course. In up to 25% of autopsy-confirmed cases, however, there may be no record of extrapyramidal signs, which shows that parkinsonism is not necessary for clinical diagnosis of DLB. Indeed, the main reason for "missing" DLB clinically in a prospective clinicopathological study was the absence of extrapyramidal signs.[16] The next most common reason for missing the diagnosis was the suspicion of cerebrovascular disease. Initial suggestions that parkinsonism in DLB is mild have not been supported by studies finding severity equal to that in non-demented patients with Parkinson's disease[46] and similar annual progression rates in motor scores on the unified Parkinson's disease rating scale.[47,48] The pattern of extrapyramidal signs in DLB shows an axial bias—eg, greater postural instability and facial impassivity, with a tendency towards less tremor, consistent with greater "non-dopaminergic" motor involvement. The parkinsonism phenotype of postural instability–gait difficulty[49] is over-represented in DLB, as it also is in PDD, whereas tremor-dominant and postural-instability-gait-difficulty subtypes were evenly distributed in a non-demented group with Parkinson's disease.[50] Extrapyramidal signs in Parkinson's disease, PDD, and DLB may thus be on a continuum, with a shift towards greater non-dopaminergic motor-system involvement through Parkinson's disease to DLB. This idea is consistent with findings that motor features mediated by

non-dopaminergic pathways (speech, posture, and balance) are more closely associated with incident dementia in Parkinson's disease than tremor, rigidity, and bradykinesia.[51]

Sleep

Rapid-eye-movement (REM) sleep behaviour disorder is a parasomnia manifested by vivid and frightening dreams associated with simple or complex motor behaviour during REM sleep. The disorder is frequently associated with the synucleinopathies, DLB, Parkinson's disease, and multiple system atrophy, but it rarely occurs in amyloidopathies and tauopathies.[52] The neuropsychological pattern of impairment in REM sleep behaviour disorder/dementia is similar to that reported in DLB and qualitatively different from that reported in Alzheimer's disease.[53] Neuropathological studies of REM sleep behaviour disorder associated with a neurodegenerative disorder have shown Lewy-body disease or multiple system atrophy.[54] REM sleep-wakefulness dissociations (REM sleep behaviour disorder, daytime hypersomnolence, hallucinations, cataplexy), characteristic of narcolepsy can explain several features of DLB as well as Parkinson's disease.[55] Sleep disorders could contribute to the fluctuations typical of DLB, and their treatment can improve fluctuations and quality of life.[56]

Autonomic failure

Autonomic abnormalities including orthostatic hypotension and carotid-sinus hypersensitivity are more common in patients with DLB than in those with Alzheimer's disease or in age-matched controls.[57] Clinical presentation of DLB is commonly with "dizziness," presyncope, syncope, and falls,[58,59] and autonomic dysfunction is a risk factor for falls in 65% of these cases, through either orthostatic hypotension or carotid-sinus hypersensitivity. Urinary incontinence has been reported early in the course of DLB compared with Alzheimer's disease.[60]

Disease progression and survival

There is conflicting evidence from comparative studies with Alzheimer's disease about both symptom progression and survival in DLB. Most data have been obtained retrospectively. The most parsimonious explanation from the available findings is that there is no difference in progression between DLB and Alzheimer's disease,[61] but mean values from large studies could conceal disease heterogeneity, and some patients with DLB have a very rapid disease course.[62,63] The conclusion is that either there is no difference between DLB and Alzheimer's disease in survival from onset until death, or that survival is worse in DLB.[64,65] Whether there are any specific features, such as more severe extrapyramidal signs or frequent falls, that are associated with more rapid disease progression or poorer survival is not yet known.

Clinical diagnosis of DLB

DLB can initially present to general practitioners, geriatric psychiatrists, movement-disorder specialists, or emergency services. As with all dementias, accurate clinical diagnosis can only be made after a thorough clinical assessment including a detailed history (from the patient and an informant) and full mental-state, cognitive, and physical (including neurological) examinations.[2] There should be particular emphasis on eliciting the core diagnostic features of fluctuating cognitive impairment, parkinsonism, and recurrent visual hallucinations and the supportive features of falls, depression, other hallucinations, and REM sleep disorder. Diagnosis should be made on the basis of the consensus diagnostic criteria for DLB (panel), which are the most widely accepted and have been the best validated by autopsy. The main differential diagnoses are Alzheimer's disease, vascular dementia, PDD, atypical parkinsonian syndromes (such as progressive supranuclear palsy, multiple system atrophy, and corticobasal degeneration), and Creutzfeldt-Jakob disease.

Several retrospective and two prospective studies have examined the predictive accuracy of clinical criteria for probable DLB[16,17,19–25] (table). They show that sensitivity is variable and, although high in one prospective study,[16] was unacceptably low in several other studies. By contrast, specificity is generally high. There is, therefore, a need to develop ways of improving the sensitivity of the diagnosis of DLB without loss of specificity, which may ultimately require a biological test.

Consistent application and greater inter-rater reliability of the consensus criteria would be facilitated by more detailed definitions of the quality, frequency, and severity of core and supportive features. The assessment of fluctuating cognitive impairment poses substantial difficulty to many clinicians, and newly proposed rating scales could be particularly helpful in this regard.[39] The best way to take advantage of supportive diagnostic features (panel) in improving diagnostic accuracy also needs to be identified. Repeated falls, syncope, transient loss of consciousness, and depression are common in older people with cognitive impairment and can serve as "red flags" to a possible diagnosis of DLB. By contrast, neuroleptic sensitivity and REM sleep behaviour disorder can be highly predictive of DLB, but their detection depends on the clinician's having a high index of suspicion and asking appropriate screening questions.

Since PDD is common and typically shares the features of DLB,[11,66] there is much debate about the relation between the two disorders.[67] There are at present no specific operational clinical criteria to diagnose PDD. The criteria in Diseases and Statistical Manual IV are incomplete and descriptive and do not describe several core clinical features associated with dementia in Parkinson's disease. The arbitrary 1-year rule used to separate DLB from PDD is helpful in individual case diagnosis but is increasingly hard to justify from a neurobiological point of view. Current DLB criteria therefore need to be revisited with respect to their relation to PDD; this process would be facilitated by improved operational criteria for PDD. The need for a collaborative research effort by specialists in movement disorders and dementia is apparent and is already being addressed by interdisciplinary task groups.

Laboratory and neuroimaging investigations

Systemic and pharmacological causes of delirium need to be excluded. The standard EEG may show early slowing, epoch-by-epoch fluctuation, and transient temporal slow-wave activity.[68–70] There are as yet no clinically applicable genotypic or CSF markers to support a diagnosis of DLB.[71–77] There have been, however, sufficient studies to allow the conclusion that neuroimaging investigations can be helpful in supporting the clinical diagnosis. Changes associated with DLB include preservation of hippocampal and medial temporal lobe volume on MRI[78,79] (figure 1) and occipital hypoperfusion on SPECT.[80,81] Other features such as generalised atrophy,[79] white-matter changes,[82] and rates of progression of whole brain atrophy[83] are not helpful in differential diagnosis. Dopamine transporter loss in the caudate and putamen, a marker of nigrostriatal degeneration, can be detected by dopaminergic SPECT[84] and can prove helpful in clinical differential diagnosis. A sensitivity of 83% and specificity of 100% has been reported for the association of an abnormal scan with an autopsy diagnosis of DLB[85] (figure 2).

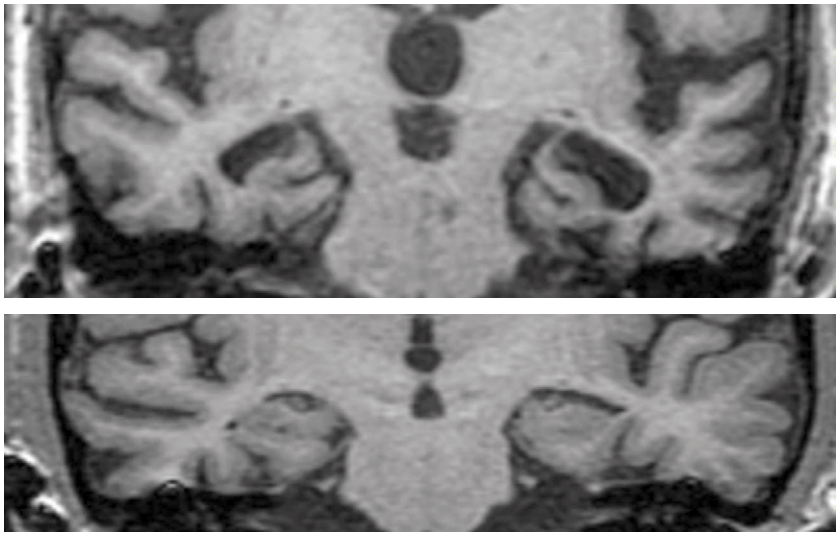

Figure 1. Coronal MRI of patients with Alzheimer's disease and DLB matched for clinical severity of dementia. Medial temporal lobe (particularly hippocampal) atrophy is less pronounced in DLB, consistent with autopsy findings. Images courtesy of Dr Emma Burton.

Pathophysiology of DLB

Consensus criteria for DLB include ubiquitin immunohistochemistry for Lewy-body identification[2,16] and staging into three categories (brainstem-predominant, limbic, or neocortical) depending on the numbers and distribution of Lewy bodies. The recently developed α-synuclein immunohistochemistry is a better marker[86,87] that visualises more Lewy bodies and also shows previously under-recognised neuritic pathology, termed Lewy neurites (figure 3). Use of antibodies to α-synuclein moves the diagnostic rating for many DLB cases from brainstem and limbic groups into the neocortical group. An additional very severe pathological category may therefore now be required. α-synuclein is a normal synaptic protein that has been implicated in vesicle production. In an aggregated and insoluble form it constitutes the main component of the fibrils that are a major constituent of the Lewy bodies in DLB and other synucleinopathies.[15] In most patients with DLB, there are no genetic mutations in the α-synuclein gene or other Parkinson's disease genes. Pathological upregulation of normal, wild-type α-synuclein due to increased mRNA expression is a possible mechanism,[88] or Lewy bodies may form because α-synuclein becomes insoluble or more able to aggregate for some reason.[89] Another possibility is that α-synuclein is abnormally processed, for example by a dysfunctional proteosome system, and that toxic "protofibrils" are therefore produced. Sequestering of these toxic fibrils into Lewy bodies could reflect an effort by the neurons to combat biological stress inside the cell, rather than their simply being neurodegenerative debris. Whether Lewy bodies are "friend or foe" remains to be discovered.

The number of cortical Lewy bodies is not robustly correlated with either the severity or the duration of dementia,[90,91] although associations have been reported with Lewy bodies and plaque density in midfrontal cortex.[92] Lewy neurites and neurotransmitter deficits are suggested as more likely links with clinical symptoms.[91,93] There seems to be no significant cortical pathology that is associated with fluctuating cognition; however, increased numbers of Lewy bodies in the anterior and inferior temporal lobe are associated with the presence and onset of well-formed visual hallucinations.[94,95] These areas are particularly implicated in generation of complex visual images, and their pathological involvement perhaps

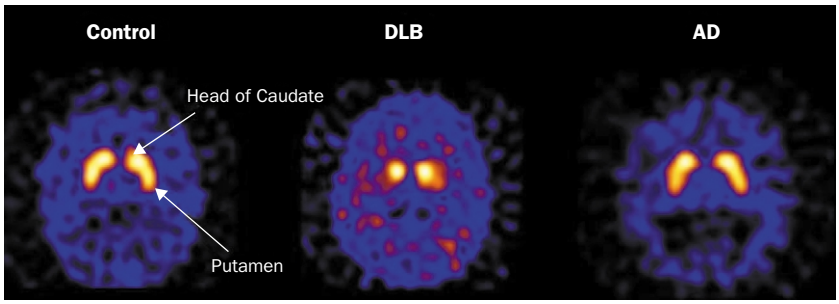

Figure 2. SPECT images of the dopamine transporter at the level of the striatum by use of fluoropropyl-CIT show striking reduction of activity in DLB compared with normal activity in Alzheimer's disease and normal ageing. Images courtesy of Prof J T O'Brien.

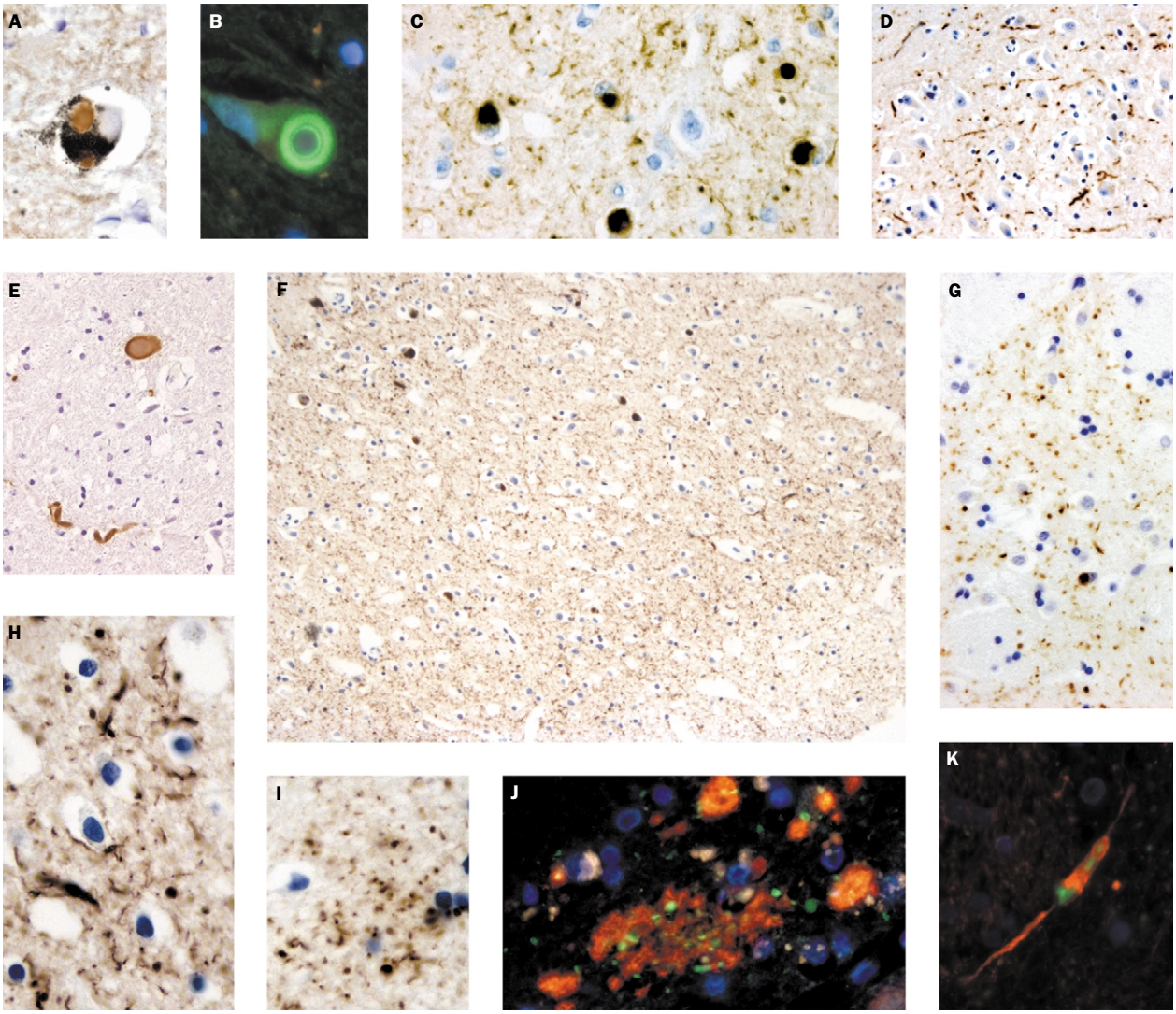

Figure 3. Neuropathology of DLB. Pathological α-synuclein (α-syn) aggregates assume many forms in DLB including typical classical Lewy bodies (LBs) in the pigmented nuclei of the brainstem (A,B), cortical LBs in the neocortex (C) and amygdala, dystrophic or Lewy neurites (LNs) in the CA 2/3 subfield of Ammon's horn (D) and neuroaxonal spheroids (E). The burden of α-syn aggregates in the neocortex (F) can be extreme with cortical LBs in the deeper layers (top left) and LNs throughout the cortical mantle to the pial surface (bottom right). The striatum is also affected (G) with primarily LNs (H) and dot-like aggregates (I). LNs tend to cluster around ß-amyloid plaques (J), which are also common in DLB, and are primarily axonal in location (K). Antibodies: α-syn in A, C-I, and J,K (green); tyrosine hydroxylase in B; β-amyloid in J (red); neurofilaments light chain in K (red). Images courtesy of Dr John E Duda.

contributes to the vivid and complex character of hallucinatory experiences in DLB, contrasting with the very simple visual symptoms (lines and colours) associated with occipital-lobe lesions. Parkinsonism is related to the degree of cell loss and pathology in the nigrostriatal pathway.

Most patients with DLB also have Alzheimer's disease pathology, including cortical amyloid plaques and neurofibrillary tangles. Most have sufficient plaques to meet CERAD criteria for Alzheimer's disease,[8] but only a few meet the tangle-based Braak stages V and VI for Alzheimer's disease. The additional neuritic pathology affects the clinical presentation. DLB patients with few tangles show more core clinical features of DLB, whereas those with many tangles show a pattern more like Alzheimer's disease.[18,89] Lewy bodies also occur in up to two-thirds of patients with early-onset familial Alzheimer's disease caused by mutations of presenilin-1, presenilin-2, or amyloid precursor protein, as well as in sporadic Alzheimer's disease, Down's syndrome, and Pick's disease.[27,96,97] Tau aggregates particularly increase the likelihood of Lewy-body formation in susceptible brain regions, like the amygdala. However, the substantial cortical dysfunction found clinically in patients with limited cortical-cell loss, negligible tangle counts, but numerous cortical Lewy bodies and neurites suggests that they themselves are associated with much functional neuronal impairment. Elucidation of the pathophysiology of DLB will guide future therapeutic strategies.

Management of DLB

A four-stage approach to the management of DLB has been described: accurate diagnosis; identification of target symptoms with patient and carer; non-pharmacological interventions; and pharmacological interventions.[98] Target symptoms can include extrapyramidal motor features, cognitive impairment, neuropsychiatric features (including hallucinations, depression, sleep disorder, and associated behavioural disturbances), or autonomic dysfunction. Patients, carers, and clinicians can differ in their prioritisation of which symptoms "need" treating, and all must understand the potential for gains in one domain may be at the expense of losses in another.

Non-pharmacological interventions are a humane way of treating people with dementia and have the potential to address most of the areas in which there are management difficulties in DLB. They require a general set of caregiving skills as well as tailoring of interventions to the patient, carer, and environment. A systematic analysis of non-pharmacological approaches to DLB and evaluation of the system changes and costs that are needed to support them in clinical practice have yet to be done.

The evidence base for pharmacological management of DLB is also limited, but there is general agreement that if antiparkinsonian drugs are prescribed, the clinician should aim for the lowest acceptable dose of levodopa monotherapy. The effectiveness of levodopa on motor symptoms in DLB has not been established but is probably less than in uncomplicated Parkinson's disease, possibly because there is additional intrinsic striatal pathology and dysfunction.[99] D2-receptor antagonists, particularly traditional neuroleptic agents, can provoke severe neuroleptic sensitivity reactions in up to 50% of DLB patients with an increase in mortality of two to three times.[4] New atypical antipsychotic drugs used at low dose are safer in this regard, but sensitivity reactions have been documented with most and they should be used with great caution.[100–104]

There is consistent evidence that cholinesterase inhibitors are more effective in DLB than in Alzheimer's disease, for which they were originally developed.[105,106] Fluctuating cognitive impairments, visual hallucinations, apathy, anxiety, and sleep disturbance are significantly improved with cholinesterase inhibitors used in the typical dose range for Alzheimer's disease. In addition to the usual gastrointestinal side-effects associated with this class of drug, increased cholinergic activity may cause hypersalivation and exacerbate postural hypotension and falls in patients with DLB.[107] Cholinesterase inhibitors are deemed by some to be first-line treatment for the cognitive and psychiatric symptoms of DLB, although there have been only two double-blind placebo-controlled studies that addressed their symptomatic effects[3,14] and very limited open-label data on long-term effects.[108] No information is yet available about their use in combination with antiparkinsonian or atypical antipsychotic agents, although these are both common clinical situations.

Disease-modifying strategies developed for either Alzheimer's disease or Parkinson's disease will be candidates for use in DLB but none have been attempted so far. DLB is a particularly attractive target for neuroprotection owing to the presence of significant neuronal dysfunction but no striking cortical neuronal degeneration. In vitro and animal models of α-synuclein aggregation and its relation to amyloid deposition will be useful tools for developing novel disease-modifying therapies for DLB.

Trial designs and regulatory issues

There are no treatments licensed for DLB. Regulatory authorities seem prepared to accept DLB as an indication for regulatory approval of a pharmacological treatment on condition that its existence is widely accepted by experts, that it can be operationally defined by reliable and valid criteria, and that outcomes for studies use validated and standardised outcome measures. The US Food and Drug Administration has considered DLB as an indication and initially has suggested that there be dual primary outcomes, namely global and a specified measure of cognition. Cognitive outcome measures from clinical trials of Alzheimer's disease that are predominantly memory based need not necessarily be used in DLB studies, and more appropriate instruments should be considered. The acceptability of a primary behavioural outcome measure in DLB clinical trials has not yet been clarified. Potential confounding factors for global and functional scales in DLB include the additional disabilities arising from motor disability and, for all outcome measures, the inherent fluctuations of the untreated illness.

Trial designs

Few DLB treatment trials have been reported, partly because the disorder was only recently described, but also because of restricted expertise in clinical diagnosis. The current approach is to address DLB and PDD separately, but the close relation of these disorders and the logistics of recruitment provide the opportunity for both populations of patients to enter into a single clinical trial with a harmonised set of entry criteria. Post-hoc subanalysis could be used to assess for differential responses. Recruitment of patients into such trials will require specialised movement disorder and dementia referral clinics to participate, with an anticipated slower accrual if only patients with DLB are recruited. In view of the small number of randomised controlled trials in either DLB or PDD, the use of placebos is still judged ethical, but we note that cholinesterase inhibitors are already in widespread use in some countries.

Outcome measures

Specific measures of attention and cognitive fluctuation, which are both part of the clinical profile of DLB and PDD, are sensitive to response to treatment intervention.[109] Other key domains of executive functioning, visual perception, and memory systems must also be measured. The most important neuropsychiatric target symptoms include visual hallucinations, delusions, delusional misidentification, apathy, anxiety, and depression. The desired behavioural outcomes might be a reduction in both the intensity and frequency of these key behavioural symptoms with an effect

Search strategy and selection criteria
This review was based on articles identified by a MEDLINE search with the terms "Lewy body", "dementia", and "Parkinson's disease" as the main keywords or identified from the reference lists of relevant articles, review papers, and book chapters. Articles for citation were chosen for their historical value, importance, ease of access, and timeliness based on the expert knowledge of the delegates.

on non-patient-centred outcomes including improvement in time, workload, and stress for carers. Functional and global assessments will be influenced by the presence of parkinsonism. Scales measuring extrapyramidal motor function can be modified to account for the confounding effects of cognitive impairment on motor performance.[110]

Global awareness of DLB and educational and treatment needs

Most dementia research has been done in North America, Australia, and Europe, but even in these regions, awareness of DLB is only now becoming widespread within specialist care. In countries with less developed dementia services and with greater reliance on primary care, there are substantial difficulties in translating current methods of case detection and diagnosis—eg, administration of cognitive tests to patients who are illiterate or have little education. In most cultures, dementia has been regarded as a normal part of ageing, and patients are brought for help only when behaviour becomes troublesome. Such patients could include those with DLB, and accurate diagnosis is imperative to avoid increased morbidity and mortality from the inappropriate use of neuroleptic agents and to ensure that they are not denied access to cholinesterase inhibitors and other interventions that might be beneficial. The first goal must be to raise awareness. Possible strategies to address these problems in the parts of the world that have the most rapidly expanding elderly populations include combining efforts with international and regional organisations for Parkinson's disease and Alzheimer's disease to include DLB in their educational campaigns, to develop appropriate educational materials, and to disseminate these through accessible internet sites that are linked with existing Lewy-body disease resources.

Conclusions

DLB is one of a group of neurodegenerative disorders that has been characterised as the α-synucleinopathies. The group includes Parkinson's disease with and without dementia and primary autonomic failure. Clinical criteria and assessment scales for the accurate diagnosis of DLB have been developed in the past decade, and these are useful in the differentiation of DLB from other dementia subtypes, particularly Alzheimer's disease and vascular cognitive impairment. But diagnostic accuracy of DLB still needs to be improved. Progress may be difficult given the inevitable pathological heterogeneity that occurs in the ageing brain. Many patients with DLB have substantial additional pathology that modifies the core clinical features and makes those cases difficult to recognise by existing clinical methods. Some modifications to the application of existing diagnostic criteria could help to increase case detection. For example, clinicians assessing elderly patients with cognitive dysfunction should be routinely asking about features that support a DLB diagnosis, such as REM sleep behaviour disorder, repeated falls, or neuroleptic sensitivity. Existing clinical methods and criteria need to be more widely disseminated with the message that patients with DLB can respond well to cholinergic treatment and extremely badly to neuroleptic drugs. A biological diagnostic marker is urgently required. Functional neuroimaging of the dopaminergic system could soon provide such a marker by aiding the distinction between DLB and dementias that lack nigrostriatal dopaminergic degeneration.

A different approach is required to address the distinction between DLB and PDD. These syndromes could be so similar at a biological level that a categorical distinction is inappropriate and the use of a generic term such as Lewy-body disease or α-synucleinopathy for all cases might be preferable. But such terms imply prior knowledge of the underlying pathology and, in the absence of this, diagnosticians might additionally need to use diagnostic terms (DLB, PDD) that describe the individual patient's clinical presentation taking into consideration both the temporal sequence of symptom onset and their relative severity.

No rigorously tested treatment algorithms for DLB have been published, and some basic information is still lacking, for example the responsiveness of parkinsonian features to levodopa. Avoidance of neuroleptic agents is important. Long-term use of cholinesterase inhibitors seems to be helpful for neuropsychiatric and cognitive symptoms, but further clinical trials are needed to clarify how these agents should be used and to identify their side-effect profile in this population. When disease-modifying agents are developed for Parkinson's disease or Alzheimer's disease, they should be tried in DLB and PDD also. Virtually unrecognised 20 years ago, DLB could within this decade be one of the most treatable neurodegenerative disorders of late life.

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Author contributions

All the authors shared responsibility for producing draft reviews of the topic areas chaired by them at the expert meeting. IMcK completed the literature searches and produced a combined draft for final review by all authors. JM proposed the meeting and obtained financial support. All listed participants reviewed materials and presented them at the meeting.

Conflict of interest

IGMcK has received travel sponsorship, honoraria, and research support from Pfizer/Eisai, Novartis, Janssen-Cilag, and Amersham Health. JM has acted as consultant for Eli Lilly, Abbott, AstraZeneca, and Bristol-Myers Squibb and received grants/research support from Eisai America, Inc, Janssen Research Foundation, Novartis, and Pfizer. DA has received travel sponsorship, honoraria, and research support from Pfizer, Novartis, and Janssen-Cilag. JD has received travel support and/or honoraria from Pharmacia, Novartis, and Janssen Pharmaceuticals and research support from Pfizer Pharmaceuticals. HF has received honoraria and research support and has been a paid consultant for Lilly Pharma, Eisai Pfizer, Novartis, and Janssen. SG has acted as consultant to Pfizer, Novartis, and Janssen-Cilag, who are developing drugs useful in DLB. BL has received travel sponsorship, honoraria from Janssen Cilag, Lilly, Pfizer, Astra Zeneca, Wyeth, Organon, Bristol Myers Squibb, and Glaxo Wellcome, and research support from Wyeth. CL is on the speakers' bureau for Pfizer, Novartis, Eisai, OrthoMcNeil, and Janssen (honoraria recipient). JO'B has acted as consultant and/or accepted hospitality and honoraria from Janssen-Cilag, Novartis, Pfizer/Eisai, and Amersham Health. DB, HC, JC-M, DD, BD, GH, OL, JM, JP, and WR have no conflicts of interest to declare.

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