Dementia with Lewy bodies — from scientific knowledge to clinical insights

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Abstract | Dementia with Lewy bodies (DLB) is the underlying aetiology of 10–15% of all cases of dementia and as such is a clinically important diagnosis. In the past few years, substantial advances have been made in understanding the genetics and pathology of this condition. For example, research has expanded our knowledge of the proteinaceous inclusions that characterize the disease, has provided an appreciation of the role of disease-associated processes such as inflammation and has revealed an association between DLB and genes such as *GBA*. These insights might have broader relevance to other neurodegenerative conditions and are beginning to be translated into clinical trials. In this Review, we provide clinical insights for the basic scientist and a basic science foundation for the clinician. We discuss the history of the condition; the definition of DLB; the relationship between DLB and other neurodegenerative conditions; current understanding of the pathology, genetics, clinical presentation and diagnosis of DLB; options for treatment; and potential future directions for research.

In 1912, the German neurologist Fritz Heinrich Lewy provided the first description of intracellular inclusions of protein within the neurons of the cerebral cortex of patients with Parkinson disease (PD) while working in Alois Alzheimer's laboratory[1,2]. Seven years later, Konstantin Nikolaevich Tretiakoff identified the presence of similar proteinaceous inclusions in the substantia nigra of patients with PD and coined the term 'Lewy bodies' for these inclusions[3]. In 1976, Kenji Kosaka and colleagues described the first post-mortem case of presenile dementia with 'Lewy-like-bodies' pathology and, in 1984, Kosaka introduced the term 'diffuse Lewy body disease'[4,5]. The clinical features of three patients with diffuse cortical Lewy body disease were described 3 years later by Gibb and colleagues and, in 1992, the first operational criteria of senile dementia of Lewy body type were defined[6,7].

Despite these early descriptions, the first International Consensus Diagnostic Criteria on Dementia with Lewy Bodies were not published until 1996 (REF.[8]). In these criteria, the term dementia with Lewy bodies (DLB) was introduced as an attempt to clarify what had previously been a disparate nomenclature that included the similar but overlapping terms Lewy body variant of Alzheimer disease (AD), dementia associated with cortical Lewy bodies and senile dementia of Lewy body type[9–12]. In the same year, the first in vivo ^{123}I-ioflupane single-photon emission CT (^{123}I-FP-CIT SPECT) in patients with DLB demonstrated the loss of dopamine-secreting neurons in these individuals[13].

In 1997, α-synuclein protein was identified as the key component of Lewy bodies, and mutations in this gene were found to be associated with PD[14,15]. The following year, the description of the clinical syndrome was improved, including recognition of the presence of rapid eye movement (REM) sleep behaviour disorder (RBD)[16,17]. In 2001, ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy was suggested to have potential use as a diagnostic tool for DLB, and imaging findings on this modality were identified as a potential disease biomarker[18,19]. In 2006, ^{123}I-FP-CIT SPECT was licensed in the European Union for use in differentiating between DLB and AD[20]. Key events in the study of DLB are summarized in FIG. 1.

The nomenclature of these conditions can be confusing, not least because Lewy body dementia and DLB are sometimes incorrectly used as synonyms. Lewy body dementia is now generally used as a broad term that includes a range of dementias in which Lewy bodies are present, which includes dementia in PD as well as DLB[21]. In this Review, we focus on DLB, as defined by the consensus criteria outlined below[22]. The substantial progress made in DLB research the past few years, and in particular the translation of findings to large-scale clinical trials, makes a review of this condition timely. Here, we summarize the growing DLB literature to provide an easily accessible overview for clinicians and basic scientists, including disease definition, pathology, genetics, prognosis, clinical features, investigations and current and potential future treatments.

Definition of DLB

Dementia is a clinical syndrome characterized by progressive decline in performance in one or more cognitive domains with subsequent impairment of activities

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Key points

- Dementia with Lewy bodies (DLB) is a common cause of dementia.
- Although DLB is hard to diagnose clinically, accurate diagnosis is important as it influences management.
- Awareness of the disorder and investigative techniques such as ^{123}I-ioflupane single-photon emission CT can enhance diagnostic accuracy.
- Our understanding of the genetics and pathology of the condition is growing.
- This increased understanding is feeding through to new therapeutic strategies and clinical trials.

of daily living in the absence of other physical or psychiatric conditions that could account for the presentation[23]. Approximately 10 million new cases of dementia are diagnosed worldwide every year — an average of 1 every 3 seconds[24]. The largest risk factor for development of dementia is age and, as the world population ages, the number of individuals with the condition is predicted to increase. Dementia is the largest single health challenge of our time, not least because of the high care needs and social and economic costs associated with the condition.

AD, the most common cause of dementia, accounts for more than half of cases. In western populations, DLB accounts for approximately 4% and 7% of dementia clinically diagnosed in primary and secondary care, respectively[25]. Note that this value represents only around half of the total number of cases that would be predicted from post-mortem studies that examine histopathology, which suggests that many cases are not clinically diagnosed. Accurate diagnosis is important because it directly influences management; for example, patients with DLB can exhibit extreme sensitivity to neuroleptic drugs, which should, therefore, be avoided in this group.

Clinical diagnosis is a considerable challenge, with as many as half of all patients with DLB misdiagnosed with another type of dementia[26,27]. The reasons for this misdiagnosis are not entirely clear. Contributory factors might include the overlap of key clinical features with delirium and the poor discrimination of basic neuropsychological testing between subtypes of dementia[28]. A further issue is the potential overlap of characteristic AD and DLB pathology, which results in a mixed clinical presentation[22,29–31].

In 2017, the DLB Consortium updated their recommendations for the clinical, pathological and research criteria of DLB for the fourth time[22]. The revised criteria describe essential, core clinical and supportive features as well as indicative and supportive biomarkers.

The essential criteria are similar to the umbrella definition of dementia. They are defined as "a progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational functions, or with usual daily activities. Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. Deficits on tests of attention, executive function, and visuoperceptual ability may be especially prominent and occur early"[22]. The first three core clinical features of DLB are fluctuation in cognition and attention, recurrent visual hallucinations and RBD, all of which should be present from early in the disease course. The fourth core clinical feature is spontaneous parkinsonian motor signs, which often occurs later in the disease than the first three features. Supportive clinical features of DLB include sensitivity to antipsychotic agents, postural instability, repeated falls, syncope or other transient episodes of unresponsiveness, severe autonomic dysfunction, hypersomnia, hyposmia, hallucinations in other modalities, systematized delusions, apathy, anxiety and depression.

Biomarkers that can indicate the presence of DLB include low dopamine transporter uptake in basal ganglia, abnormally low uptake on ^{123}I-MIBG myocardial scintigraphy and REM sleep without atonia, confirmed by polysomnography. All of these features and their relative contribution to a diagnosis of DLB are described in FIG. 2. It is important to recognize that dementia is common in PD and that parkinsonian motor symptoms can occur in DLB. Indeed, these clinical presentations might represent two ends of a disease continuum. The primacy of the symptoms is important for clinical diagnosis. If motor symptoms are predominant and antecede cognitive decline by a year or more, then the diagnosis should be one of PD dementia.

Pathology

Intracellular inclusions of protein that are predominantly composed of α-synuclein comprise the characteristic microscopic hallmark of DLB. α-Synuclein, encoded by *SNCA*, is a 14 kDa presynaptic soluble protein abundantly found in the brain. The protein consists of 140 amino acids and is composed of 3 domains: the amino-terminal domain (containing 11 amino acids), the central hydrophobic domain (also known as the non-amyloid-β component owing to its initial characterization in AD) and the acidic carboxy-terminal domain[32–34]. In physiologically normal conditions, the protein exists as an unfolded membrane-bound monomer[35,36].

α-Synuclein is not the only component of Lewy bodies. These inclusions also contain ubiquitin, neurofilaments and α-crystallin B, but the relevance of these components in disease is currently uncertain[37,38]. Although some evidence suggests that proteinaceous inclusions can be protective in some neurodegenerative diseases, inclusions in DLB are thought to have a role in the progressive loss of structure and functions of the neuron, leading to neural cell death[15,39–41]. The 3D structure of α-synuclein and the formation of Lewy bodies[42] is shown in FIG. 3. A growing body of evidence suggests that it is not just intracellular inclusions of α-synuclein that are deleterious but that extracellular release of the protein might also contribute to pathology[43]. As an α-synucleinopathy, DLB is one of a family of diseases that also includes PD, multisystem atrophy, neurodegeneration with brain iron accumulation type I and pure autonomic failure[44,45].

Other proteins identified in other neurodegenerative conditions also have been implicated in DLB. For example, TAR DNA-binding protein 43 (TDP43) pathology is found in DLB, although this protein does not localize with Lewy bodies themselves, which suggests that the presence of TDP43 pathology in DLB is not due to the association of TDP43 protein with Lewy bodies[46]. By contrast, other proteins associated with

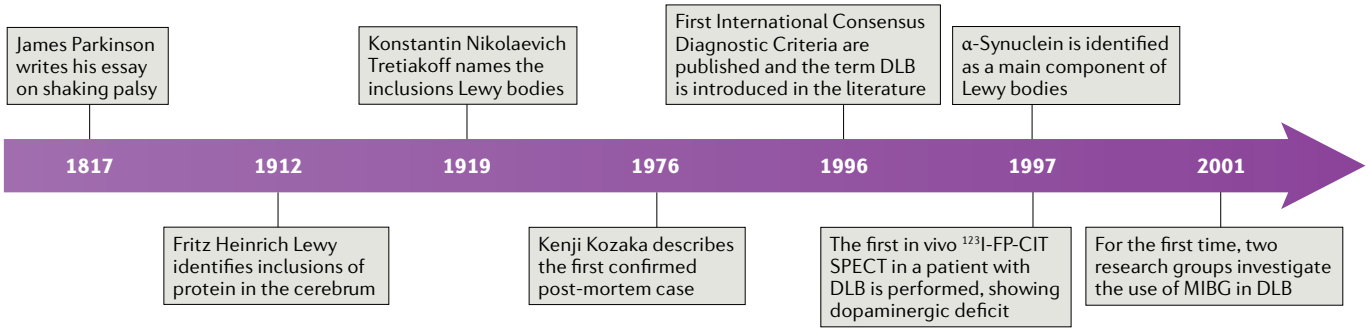

Fig. 1 | **Key events in the study of DLB.** Eight of the most important contributions to the understanding of dementia with Lewy bodies (DLB) are presented here, starting with the first clinical description of a parkinsonian syndrome in 1817. Other sequential milestones include the identification and naming of the characteristic proteinaceous inclusions, early description of clinical cases linked to the histopathological changes, drawing up of diagnostic criteria, development of diagnostic single-photon emission CT (SPECT) scanning, identification of α-synuclein as the major contributing protein to Lewy bodies and metaiodobenzylguanidine (MIBG) as a potential diagnostic tool. ^{123}I-FP-CIT, ^{123}I-ioflupane.

neurodegenerative diseases such as valosin-containing protein do seem to form a part of Lewy body inclusions[47]. These apparent pathological similarities between different neurodegenerative diseases raises the interesting possibility of shared pathological processes that in turn might be amenable to common therapeutic interventions.

In the past few years, a number of studies have raised the possibility that inflammation plays a part in pathology in neurodegenerative disease. Microglia might play a part in the distribution and phosphorylation of tau[48,49]. Secondary peripheral inflammatory responses are detected in the prodromal stages of DLB and AD, and inflammatory markers such as IL-1β, IL-2, IL-4 and IL-10 are elevated early in the disease[50].

The histopathology of Lewy bodies differs according to anatomical location and, therefore, also according to clinical diagnosis. Neurohistopathological studies have shown that the structure of Lewy bodies found at the cortex differs from those located in the brainstem, with the latter having an eosinophilic core, concentric lamellar bands and a pale halo. By contrast, cortical Lewy bodies typically lack a halo[4,51]. The distribution of Lewy body, amyloid-β and tau pathologies in the CNS also differs between types of synucleinopathies. In PD, neuronal loss is primarily located in the substantia nigra, resulting in a predominant motor clinical representation whereas, in DLB, Lewy bodies are found largely in the cortex[8,22,30,52–57]. Thus, Braak and Braak staging of sporadic PD does not entirely fit DLB.

The genetics of DLB

As with the histopathology and clinical features, the genetic basis of DLB overlaps with PD and other dementias. However, although families with more than one affected member have been described, a clear association with autosomal dominant mutations, as seen in other forms of dementia, has been difficult to find in DLB[58]. Homozygosity for the ε4 allele of apolipoprotein E, which is well known to be a risk factor for AD, can also confer an increased risk of DLB[59,60].

The potential relevance of common mutations that are important in other neurodegenerative diseases was tested in DLB by whole-exome sequencing of 91 post-mortem confirmed cases of DLB to look for mutations in genes known to lead to familial PD, AD or frontotemporal dementia. Probable pathogenic variants were found in 4.4% of cases, including mutations in *PSEN2*, *CHMP2B*, *PRKN* and *SQSTM1*. In addition, *APOE* genotype was found to increase not only the risk of disease but also disease severity as measured by time to death[61]. Nevertheless, the majority of the progress in understanding the genetics of DLB has been in genes that confer modestly increased risk rather than being pathologically deterministic.

Mutations in the lysosomal enzyme glucocerebrosidase (GBA) have been identified as a risk factor for development of DLB. Recessive mutations in this gene cause Gaucher disease, which can manifest with neurological dysfunction and an increased risk of PD. One study found *GBA* mutations in 7.6% of patients with pure DLB compared with 0.8% of controls. A higher than average frequency of this mutation is found in specific groups; for example, 31% of Ashkenazi Jews with DLB have *GBA* mutations[62,63]. The odds ratio for DLB in individuals carrying a *GBA* mutation compared with control individuals in one multicentre international study was 8.28 (REF.[64]). These mutations might also influence the nature of the disease and increase the risk of severe motor and cognitive deficits[64].

A large genome-wide association study of DLB has been published that reassuringly confirmed associations with genes previously described, including *APOE*, *GBA* and *SNCA*. The study also estimated the heritability of DBA to be 36%[65]. These insights into the genetic basis of DLB are essential to understand the mechanism of disease, which in turn can inform future biomarkers and therapeutic strategies.

Prognosis

Although the exact clinical path is variable, DLB typically progresses through increasing disability and ultimately to death. One study that looked at a large clinical data set found a median time from first presentation with cognitive symptoms to death of 3.3 years for men and 4.4 years for women compared with 6.7 and 7 years, respectively, in AD[66].

Diagnosis		Essential	Core criteria	Indicative biomarkers	Supportive clinical features	Supportive biomarkers

		Dementia
		Defined as "progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational functions, or with usual daily activities. Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. Deficits on tests of attention, executive function, and visuoperceptual ability may be especially prominent and occur early."
			Features that typically occur early in disease
			• Fluctuating cognition with pronounced variations in
			  • Attention
			  • Alertness
			  • Concentration
			• Recurrent visual hallucinations
			• REM sleep behaviour disorder
			
			Can occur late in the disease
			• Parkinsonism, for example,
			  • Bradykinesia
			  • Resting tremor
			  • Rigidity
				• Reduced dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET
				• Abnormal (low uptake) ^{123}I-MIBG myocardial scintigraphy
				• Polysomnographic confirmation of REM sleep without atonia
					• Severe sensitivity to antipsychotic agents
					• Postural instability
					• Repeated falls
					• Syncope or other transient episodes of unresponsiveness
					• Severe autonomic dysfunction, such as
					  • Constipation
					  • Orthostatic hypotension
					  • Urinary incontinence
					• Hypersomnia
					• Hyposmia
					• Hallucinations in other modalities
					• Systematized delusions
					• Other psychiatric features
					  • Apathy
					  • Anxiety
					  • Depression
						• Relative preservation of medial temporal lobe structures on MRI or CT scan
						• Generalized low uptake on SPECT or PET perfusion–metabolism scan with reduced occipital activity with or without cingulate island sign on FDG–PET imaging
						• Prominent posterior slow-wave activity on EEG with periodic fluctuations in the pre-alpha and/or theta range

Probable	Option A	✓	≥2 features			
	Option B	✓	1 feature	≥1 indicative biomarker		
Possible	Option A	✓	1 feature			
	Option B	✓	0 features	≥1 indicative biomarker		

Fig. 2 | **Consensus criteria for diagnosis of DLB.** This figure illustrates the essential, core and suggestive features of dementia with Lewy bodies (DLB) as described in the consensus criteria, as well as related biomarkers. A probable diagnosis requires two core clinical criteria or one core criterion and an indicative biomarker. Possible DLB requires at least one core criterion or one indicative biomarker. All diagnoses require the essential criteria for dementia to be met. MIBG, metaiodobenzylguanidine; REM, rapid eye movement; SPECT, single-photon emission CT.

Clinical presentation

The core clinical features of DLB have been described previously in this article with regards to the definition of DLB. Here, we describe some of the subtle early features of the condition and the difference between these features, normal ageing and other forms of dementia. We also discuss associated clinical features, including variants of core features and other associated symptoms. These features can be forgotten when the focus is on the core features to make a diagnosis, but they are common, important to patients and treatable, and as such they deserve some attention.

Early cognitive changes

Although many cognitive functions decline with age, dementia is not synonymous with normal ageing or accelerated ageing[67,68]. A state in which cognition is impaired to a greater extent than would be predicted by age but in which no functional impairment is present is often referred to as mild cognitive impairment (MCI). MCI has conventionally been divided into amnestic versus non-amnestic subtypes or states that involve one or more than one cognitive domain[69]. This phase of illness has attracted intense attention as it might provide the earliest opportunity for intervention. Not all patients with MCI will progress to full-blown dementia, and identification of those individuals who will (and thus might benefit from treatment) is a major goal of current dementia research. These inquiries have included attempts to identify a characteristic form of MCI that is likely to develop into DLB.

Although many cognitive domains decline with age, usually no particular area is disproportionately affected. When this imbalance does occur, it can be an indicator of underlying pathology. Impaired performance on specific areas of neuropsychological testing have been described in very early DLB. These areas include increased decline in verbal fluency and visuospatial tasks on extended bedside testing and impaired digit vigilance, cube copying and angle task test in more formal neuropsychological assessment[70–72]. By contrast, registration and episodic recall tend to be preserved relative to these areas[73]. As a result, a putative distinct prodromal phase of DLB (termed MCI-LB) has been suggested as a distinct clinical entity from that associated with AD (MCI-AD)[74,75].

Perhaps unsurprisingly, core features of DLB seem to be more common in MCI-LB than in MCI-AD. One study found that more than half of patients with MCI-LB experienced fluctuations in cognition over the course of a day and 49% described RBD[76]. Almost one-third of these individuals experienced visual hallucinations, possibly owing to dysfunction of the temporal lobe and the GABAergic system in the primary visual cortex[77–79].

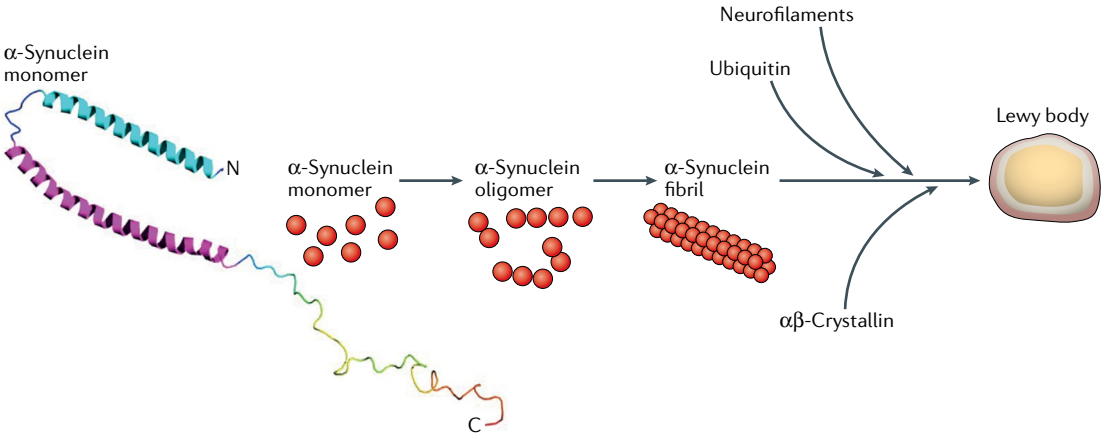

Fig. 3 | **3D structure of α-synuclein and formation of Lewy bodies.** The 3D structure of α-synuclein and the progression of monomers to oligomers that combine together with other proteinaceous components to comprise the Lewy body, the pathogenic hallmark of dementia with Lewy bodies. α-Synuclein monomer was rendered as a cartoon in PyMOL Molecular Graphics System, Version 1.8 Schrödinger, LLC (REF.[142]). C, carboxyl terminus; N, amino terminus.

Additional symptoms

Symptom presentation might not be uniform between patients with DLB, even for core features. For example, patients with DLB can present with a complex mixed tremor type, with characteristics of resting and postural tremor — although most patients with DLB do not exhibit a tremor at all[80]. Individuals with DLB also commonly show other motor symptoms associated with parkinsonism; for example, hypomimia, difficulty with motor initiation and a characteristic shuffling gait. Hyposmia is common, as is constipation. The latter might arise from direct effects of α-synuclein on the enteric nerve cells or from autonomic dysfunction as seen in PD[81,82]. Patients with DLB experience autonomic failure, probably due to the presence of Lewy body depositions in the midbrain, which results in orthostatic hypotension. This feature, in conjunction with motor symptoms, contributes to the high risk of falls[83,84]. Another prodromal sign that arises from autonomic dysfunction is urinary incontinence due to lower urinary tract dysregulation, which can be associated with an increased risk of infection[85,86]. Increased drooling or rhinorrhoea also occurs in prodromal DLB, but the underlying pathophysiology is not well understood. Drooling might result from decreased salivary clearance, which would not only give rise to a potentially distressing symptom but also might increase the risk of aspiration, which could present a particular risk in individuals with pharyngeal dysphagia (a feature present in some individuals with DLB).

Neuropsychiatric disturbance seems to be more common in MCI-LB than in MCI-AD, with more anxiety, apathy, depression and sleep disturbance described[75,87]. In a retrospective study, 13.8% of a series of 167 consecutive patients with depression aged over 50 years who were admitted to a psychiatric ward were ultimately diagnosed with DLB[88]. Apathy and pervasive anhedonia also seem to be higher in individuals with DLB than in those with AD[89]. This excess of psychiatric morbidity occurs throughout the disease course of DLB and has an important effect on quality of life both for patients and for caregivers. Symptoms such as psychosis and agitation are distressing for patients and caregivers and are associated with increased carer stress, difficulty with care delivery and patient institutionalization. These difficulties, in combination with clinical features that result in increased risk of falls and delirium, might go some way to account for the high mortality described in DLB.

Imaging and physiological studies

The challenging nature of clinical diagnosis of DLB heightens the importance of having reliable and objective diagnostic tools and biomarkers. The most robust feature of DLB on structural imaging is the preservation of the medial temporal lobe in the context of dementia, which guidelines now include as a supportive biomarker[90,91]. Compared with AD, the CA1 regions of the hippocampus are preserved in patients with DLB, indicating less atrophy in this region in DLB than in AD[92]. Some structural abnormalities on imaging have been suggested in research settings that enable positive discrimination of DLB from AD, including insula grey matter loss in patients with prodromal DLB and atrophy in the right substantia innominate and putamen compared with patients with early AD, who experience greater volume loss in the parietal cortical and parahippocampal grey matter than patients with DLB[93–95]. Late in the disease course, patients with DLB tend to experience grey matter volume loss in the frontotemporal lobes, the putamen, the pons and the insula in contrast to the medial temporal atrophy seen in AD[90,96]. Quantitative MRI techniques have indicated a dysfunction of the microstructure of posterior networks of the brain in DLB[97]. However, none of these research findings are robust enough to translate into routine clinical use, and overall straightforward structural imaging, such as CT or MRI, is not associated with a pathognomonic pattern of atrophy in DLB.

Similarly, functional MRI studies demonstrate abnormalities in patients with DLB but do not provide findings that are robust enough to be used clinically. These abnormalities include altered connectivity between the precuneus, the dorsal attention network and visual

cortices; loss of visual system inhibition; and altered response to stimuli in higher visual areas[98–100].

SPECT and PET studies in patients with DLB have demonstrated occipital dysfunction that affects primary and association visual cortices. The cingulate island sign — a distinctive area of normal metabolism in the posterior cingulate cortex compared with the dysfunctional metabolism observed in patients with AD — has been described in FDG–PET studies of patients with DLB[101]. This sign has been proposed as a marker of progression and a predictor of cognitive decline[102]. Abnormalities on perfusion SPECT and metabolic PET are both associated with temporal atrophy and memory deficits, but again these abnormalities are not specific enough to have clinical application[102–104].

Currently, the best-established imaging method for the diagnosis of DLB in clinical use is dopaminergic ^{123}I-FP-CIT SPECT scanning. This radioactive molecule has a high affinity for the dopamine transporter and as such can act as a proxy measure of the number of dopaminergic neurons. The compound is commercially available under the trade name DaTSCAN. Studies performed with ^{123}I-FP-CIT have shown a reduction in the levels of dopamine transporter in striatal neuronal pathways, in the bilateral caudate nucleus and in the putamen both in individuals with PD and in those with DLB[22,105–107]. Studies suggest that this technique has more than 85% accuracy in the differentiation of DLB from AD[20] and might be more accurate than clinical examination when excluding AD as a diagnosis[108]. Representative images that show characteristic changes on MRI and ^{123}I-FP-CIT in AD and DLB are shown in FIG. 4.

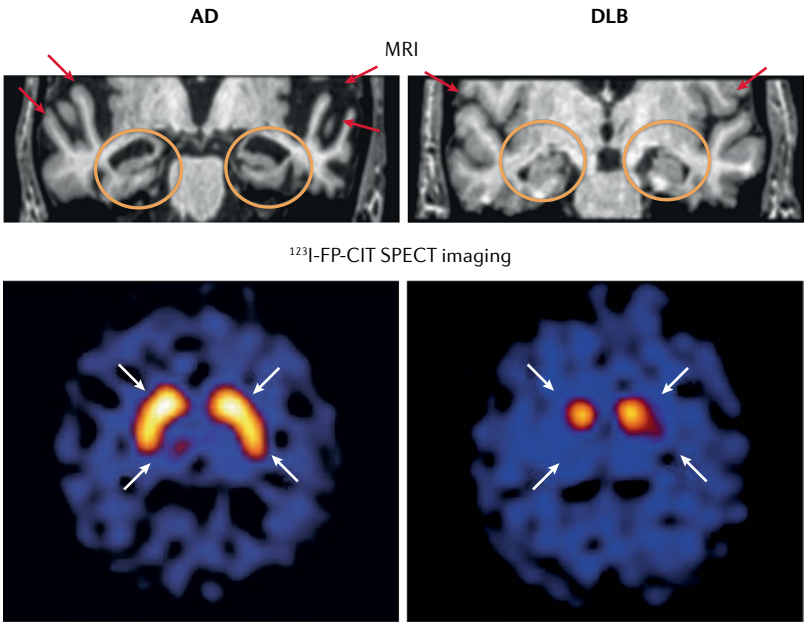

Fig. 4 | **Characteristic imaging findings in AD and DLB.** The upper panel shows cross-sectional brain MRI images of a patient with Alzheimer disease (AD) on the left and dementia with Lewy bodies (DLB) on the right. The lower panel shows characteristic results for ^{123}I-ioflupane (^{123}I-FP-CIT) single-photon emission CT (SPECT) imaging. Note the relative preservation of the hippocampus (orange circles) and temporal lobe (red arrows) in DLB compared with AD on MRI and the loss of dopaminergic neurons on SPECT in DLB but comparative preservation in AD (white arrows). Adapted from REF.[107], CC-BY-4.0 (https://creativecommons.org/licenses/by/4.0/).

^{123}I-MIBG scintigraphy is a cardiac sympathetic technique that has been investigated as a diagnostic tool in PD. The radiotracer ^{123}I-MIBG has affinity for adrenergic tissue and has substantially reduced uptake in the presence of Lewy bodies in DLB or PD. As such, ^{123}I-MIBG scintigraphy has been suggested as a possible diagnostic tool, and combination of ^{123}I-MIBG and ^{123}I-FP-CIT scanning might further increase diagnostic accuracy in unclear clinical presentations[19,109,110].

In polysomnographic studies, more than 50% of patients diagnosed with DLB demonstrate RBD that is unrelated to motor or breathing symptoms. Although REM sleep without atonia can be present in prodromal phases of DLB, it is not entirely clear whether this phenomenon is an early feature of DLB[111–113]. Quantitative analysis of EEGs presents a potentially promising new approach, with some evidence that it could operate as tool to predict conversion from MCI to DLB[114,115].

Attempts have been made to combine some of the techniques mentioned here to improve diagnostic accuracy. For example, computational combination of MRI and EEG data to discriminate DLB from AD has shown some promising early results[116,117].

Current treatment of DLB

No disease-modifying treatments are currently available for DLB. Consequently, current management is focused on symptomatic relief.

Pharmacological interventions

Antipsychotic avoidance. DLB is often misdiagnosed as other types of dementia or psychiatric conditions, both in primary and in secondary care[118,119]. The presence of psychotic phenomena in DLB increases the risk of prescription of antipsychotic agents. Treatment with antipsychotic drugs is associated with increased mortality in patients with dementia[120]. In addition, individuals with DLB have high neuroleptic sensitivity and, consequently, have an increased risk of neuroleptic malignant syndrome, akinetic crisis and extrapyramidal adverse effects[121,122]. Second-generation antipsychotics should be considered only in individuals with DLB when other therapeutic options have been taken into account, and prescription should be undertaken only by doctors with specific expertise in this area. The diagnosis of DLB should be clearly documented in patient notes with a comment on the importance of the avoidance of neuroleptics, if possible.

Cognitive symptoms. Reduced choline acetyltransferase activity is a feature of DLB, and in vivo N-[^{11}C] methylpiperidin-4-yl acetate PET imaging shows that this loss occurs at an earlier stage of disease in DLB than in AD[41,123,124]. Cholinesterase inhibitors, specifically rivastigmine and donepezil, have a wide range of benefits in DLB, including improvement of attention, processing speed, apathy, anxiety, visual hallucinations and delusions, and do not cause any substantial deterioration in motor function[125–127]. The evidence around the benefits of the NMDA receptor antagonist memantine in DLB is less clear than for cholinesterase inhibitors; however, some studies have suggested a benefit and

Table 1 | **Comparison of DLB, AD and PDD**

	Neuropsychiatric testing deficits	Early symptoms	Conventional CT or MRI	^{123}I-FP-CIT SPECT	MIBG	FDG–PET	SGA sensitivity
DLB	Amnestic features, and defects in visuoconstruction, attention and executive function[8,23,70,71,75,143]	Apathy, sleep disturbances, falls, hyposmia, visual hallucinations, constipation, parkinsonism and micrography[22,75,81]	Preservation of medial temporal lobe compared with AD and PDD[90–92]	Reduced uptake in caudate nucleus and putamen[105]	Reduced myocardial uptake[144–146]	Cingulate island sign and normal metabolism of the posterior cingulate cortex[101,102]	Sensitive
AD	Amnestic features including learning, recent episodic memory, semantic memory and verbal fluency[92,147–149]	Difficulties in remembering events, names and disorientation episodes[147]	Enlarged ventricles and atrophy of tempo-parietal lobe and hippocampus[147]	Normal uptake	Normal cardiac uptake	Hypometabolism in parietal and temporal lobes and in the posterior cingulate cortex[103]	Less sensitive than DLB and PDD
PDD	Executive function and visuospatial and attention deficits[24]	Similar to DLB and multitasking, organizing and language changes, but motor symptoms are predominant within a year of cognitive symptoms[150]	Preservation of temporal, occipital and parietal lobes compared with DLB	Reduced uptake in caudate nucleus and putamen	Reduced myocardial uptake	Similar to DLB	Sensitive

AD, Alzheimer disease; DLB, dementia with Lewy bodies; ^{123}I-FP-CIT SPECT, ^{123}I-ioflupane single-photon emission CT; MIBG, metaiodobenzylguanidine; PDD, Parkinson disease dementia; SGA, second-generation antipsychotics.

memantine is now recommended by the UK National Institute for Health and Care Excellence for DLB when cholinesterase inhibitors are not tolerated[128–132].

Parkinsonism. Dopaminergic agents are associated with an increased risk of psychotic symptoms, although clinical experience suggests this risk can be ameliorated by concomitant use of acetylcholinesterase inhibitors. The risk of psychotic symptoms tends to limit the use of dopaminergic agents in individuals in whom psychiatric symptoms predominate over motor symptoms. One phase II study supported the idea that the combination of levodopa with zonisamide (a sulfonamide anticonvulsant) could ameliorate motor symptoms of DLB without exacerbating psychiatric symptoms[133].

Depression. Although depression is a common symptom of DLB — possibly twice as common as in AD — no high-quality clinical trials of depression treatment have been conducted in individuals with DLB to date. Consequently, antidepressant selection should be made on the basis of concurrent symptoms (such as sleep disturbance or anxiety), patient preference and adverse effect profile. In treatment-resistant depression, electroconvulsive therapy (ECT) or transcranial magnetic stimulation (TMS) can be considered[88].

Visual hallucinations. Before considering treatments for visual hallucinations in DLB, delirium and adverse drug reactions should be excluded and visual acuity maximized by the use of appropriate illumination, corrected visual acuity and treatment of coexisting conditions such as cataracts. As with most treatment in DLB, there is a paucity of high-quality trial evidence, although some evidence suggests that cholinesterase inhibitors can help to alleviate visual hallucination — a benefit that is associated with improved glucose metabolism in the occipital cortex[134]. There is little evidence to support the use of antipsychotics to improve visual hallucinations, including low-dose quetiapine, which is often used for this purpose despite the lack of a compelling evidence base[135].

Other behavioural and psychological symptoms of dementia. Apart from depression and hallucinations, behavioural and psychological symptoms of dementia include psychosis, anxiety, agitation, aberrant motor behaviour, elation, irritability, apathy, disinhibition, delusions, poor sleep and appetite changes. Cholinesterase inhibitors can help to alleviate some of these symptoms and antipsychotics should generally be avoided, as previously discussed. At least one large study has described improvements on the neuropsychiatric inventory after treatment with memantine in DLB. However, as in AD, the efficacy of memantine for neuropsychiatric symptoms is not clear[87,131]. For RBD in patients with DLB, low doses of clonazepam are often used but can increase the risk of drowsiness and falls[136].

Non-pharmacological interventions

Non-pharmacological interventions in DLB are important in improving the quality of life for patients and carers[137]. Such interventions include techniques to minimize fluid aspiration, low-intensity exercises, physiotherapy and gait interventions, music therapy, social care and psychological support. Although research findings are limited, ECT, TMS and psychological support were beneficial in small-sample studies in depressed patients. By contrast, deep brain stimulation has not been shown to be beneficial to patients with DLB. TABLE 1 summarizes the differences between DLB, AD and PD dementia in terms of presentation and investigations.

Potential future treatment for DLB

In this Review, we have covered the exciting and fairly rapid advances that have occurred in the past 20 years in the genetics, pathology and diagnosis of DLB. The focus of current research in DLB is likely to result in further progress in these areas. Understanding the basis of the condition is essential to the production of new treatments. The current absence of any disease-modifying treatment and lack of major advances in symptomatic treatment are disappointing. We have described a number of areas of basic science where overlap exists between

the pathology of DLB and other forms of dementia, both in general terms such as the shared phenomena of proteinaceous inclusions and more specifically with regards to genes that are associated with DLB and other dementias. Work on common pathways from related conditions raises the prospect of therapeutic strategies that might translate across disease boundaries, for example, the enhancement of clearance of abnormal proteins, management of prolonged unfolded protein response or treatment of pathology caused by inflammation[138–140].

The first large-scale commercial trial conducted in DLB explored the use of rivastigmine in DLB. In this study, 45% of participants with DLB showed overall improvement in clinical symptoms[125]. Since this initial trial, a similar drug study of a novel compound, intepirdine, a 5-hydroxytryptamine receptor 6 antagonist designed to boost cholinergic transmission[141], has concluded and reported results at the beginning of 2018. The trial was negative in terms of its primary end points but is encouraging for a number of reasons. The conclusion of this study demonstrates that high-quality, large-scale international trials in DLB are possible, that results can be achieved quickly (2 years from trial commencement to results being reported) and that large pharmaceutical companies remain interested in this condition. The combination of exciting progress in basic science, leading to plausible therapeutic drug strategies, and the demonstration of the feasibility of clinical trials provides strong reason to be optimistic for the availability of new treatments in the near future. Trial activity would be considerably enhanced by the development of reliable diagnostic tools, particularly those sensitive to early disease. New technologies, including machine learning and tools to synthesize complex data sets, provide opportunities to enhance current diagnostic tools in addition to attempts to find more accurate and novel biomarkers.

Conclusions

DLB is a common cause of dementia. Clinical diagnosis of this disease can be challenging, but accuracy has been enhanced by improved clinical understanding and new diagnostic tools. Accurate diagnosis is important as it informs management, some of which is different from other forms of dementia. In addition, we have developed an increasingly sophisticated understanding of the genetic, pathological and clinical symptomatology of DLB. This improved understanding has led to only modest translation into effective treatments thus far. Conversion of basic science into treatment provides the immediate future challenge in this disease. This goal will require a broad approach to future research that builds on basic science, develops new treatments, identifies new diagnostic tools and translates potential treatments and other health-enhancing interventions via high-quality clinical trials. As described in this Review, substantial progress has been made in all of these areas in the past 20 years; therefore, there is reason to be optimistic that benefits for patients with DLB will be achieved.

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