**Clinical, neuropathological and genetic features of Lewy body dementias**

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**Abstract:**

Lewy body dementias are the second most common neurodegenerative dementias after Alzheimer’s disease, and include dementia with Lewy bodies and Parkinson’s disease dementia. They share similar clinical and neuropathological features but differ in the time of dementia and parkinsonism onset. Although Lewy bodies are their main pathological hallmark, several studies have shown the emerging importance of Alzheimer’s disease pathology. Clinical amyloid-β imaging using Pittsburgh Compound B (PiB) supports neuropathological studies which found that amyloid-β pathology is more common in dementia with Lewy bodies than in Parkinson’s disease dementia. Nevertheless, other co-occurring pathologies, such as cerebral amyloid angiopathy, TDP-43 pathology and synaptic pathology may also influence the development of neurodegeneration and dementia. Recent genetic studies demonstrated an important role of APOE genotype, and other genes such as GBA and SNCA which seem to be involved in the pathophysiology of Lewy body dementias. The aim of this article is to review the main clinical, neuropathological and genetic aspects of dementia with Lewy bodies and Parkinson’s disease dementia. This is particularly relevant as future management for these two conditions may differ.

**Keywords:** Lewy bodies, amyloid-β, cerebral amyloid angiopathy, APOE

**List of abbreviations:**

Aβ - amyloid-β
AD - Alzheimer’s disease
CAA - cerebral amyloid angiopathy
CSF – cerebrospinal fluid
DLB - dementia with Lewy bodies
DLB-MCI - DLB-mild cognitive impairment
DSM-IV – Diagnostic and Statistical Manual of Mental Disorders IV
GWAS - genome wide association studies

¹²³I-FP-CIT ¹²³I-N-fluoropropyl-2b-carbomethoxy-3b-(4-iodophenyl) nortropane
LBs - Lewy bodies
LRP - Lewy related pathology
MCI - mild cognitive impairment
MDS - Movement Disorders Society
MMSE - Mini Mental State Examination
MoCA – Montreal Cognitive Assessment
NFT - neurofibrillary tangle
PD - Parkinson’s disease
PDD - Parkinson’s disease dementia
PiB - Pittsburgh compound B
PIGD - postural instability and gait disturbance
RBD - REM sleep behaviour disorder
VH - visual hallucinations

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Introduction

Dementia with Lewy bodies (DLB) and Parkinson’s disease dementia (PDD), collectively known as Lewy body dementias, are clinically and neuropathologically similar disorders which differ in the time of onset of dementia and parkinsonism (1, 2). The term DLB is used if dementia occurs before or concurrently with parkinsonism or within 1 year of onset of motor symptoms. PDD describes dementia that starts 1 year or more after the diagnosis of well-established Parkinson’s disease (PD) (1).

Characteristic cognitive features of Lewy body dementias include hallucinations, fluctuations in cognitive function, with prominent executive dysfunction, visuospatial abnormalities and variable impairments in memory (2). Visual hallucinations (VH) are common, with prevalence of 60-80%. They are usually well-formed complex hallucinations of people, animals and objects (3). In DLB, VH present early in the course of the disease, and serve as a useful diagnostic clinical symptom (4).

Lewy bodies (LBs) are considered the main pathological hallmark of Lewy body dementias (1). However, DLB and PDD pathology is heterogeneous with neuronal loss, basal forebrain degeneration, Alzheimer-related and vascular pathology in addition to the presence of LBs (5). In PDD, the combination of Lewy body and Alzheimer’s disease (AD) pathology has the most robust correlation with severity of cognitive decline (6, 7). One study of pathologically confirmed PD and PDD cases found that cortical amyloid-β (Aβ) scores and Braak tau stages significantly correlated with the mini mental state examination (MMSE) scores (6). In DLB, Lewy body pathology mainly involves cortical and limbic structures, with studies suggesting high neocortical and limbic Lewy body burden is an independent predictor of dementia (8, 9). However, other studies found that AD pathology is more important in DLB (9, 10). Given these overlapping neuropathological findings, pathological diagnosis and differentiation between these two dementias, without sufficient clinical information, is difficult. There is a need to identify clear clinical and pathological differences that can differentiate PDD from DLB (9).

Methods

A literature search was performed using PubMed. Only papers relevant to the topic and written in English language were considered for review. Our search strategy included following terms: ‘Parkinson’s disease dementia’, ‘Dementia with Lewy bodies’, ‘Lewy body dementia(s)’ AND ‘risk factors’, ‘visual hallucinations’, ‘neuropathology’, ‘Lewy bodies’, ‘genetics’.

Clinical characteristics

Parkinson’s disease dementia

PDD is a frequent and late complication of PD (11). The prevalence of PDD varies, most likely reflecting the different study designs. The CampPalIGN study diagnosed dementia on the basis of MMSE scores (MMSE ≤ 24) and DSM- IV criteria and found that 46% of patients developed dementia.
10 years after diagnosis of PD (12). The Sydney Multicenter study demonstrated that 48% of patients developed dementia after 15 years (13) and 83% after 20 years of PD duration (14).

PDD occurs around 70 years of age (15) and identified risk factors are higher age, mild cognitive impairment (MCI) at baseline, and more severe parkinsonism (16, 17). Anang et al showed that REM sleep behaviour disorder (RBD) and orthostatic hypotension at baseline were strong predictors of PDD (18, 19). Other associated features with developing PDD are abnormalities in colour vision, higher baseline blood pressure, gait difficulties, falls and freezing (18). Schrag et al also found that early cognitive decline is a strong predictor of PDD as well as older age, reduced sense of smell and RBD. Reduced mean caudate uptake and asymmetry on DAT scan were also felt to be useful predictors of cognitive impairment in newly diagnosed PD patients at 2 year follow up. In addition, there was correlation between change in MoCA scores and low CSF Aβ₄₂ to t-tau ratio. Therefore, the combination of age, non-motor symptoms, DAT imaging and CSF biomarkers can help predict cognitive impairment in newly diagnosed PD patients (20).

PDD is more commonly observed in PD patients with predominant postural instability and gait disturbance (PIGD) phenotype (17). One study suggested that brainstem non-dopaminergic structures may be involved in motor impairment and also the development of PDD, and that axial motor impairment in PD may be the result of the disease and aging process affecting these brainstem regions (21). Other studies also demonstrated that PDD is more common in PD patients with akinetic rigid phenotype rather than tremor dominant or mixed types (22, 23).

One study of RBD as a risk factor for PDD found that 48% of PD patients with RBD had developed dementia four years after the initial evaluation (24).

Autonomic dysfunction (orthostatic hypotension, constipation and urinary incontinence) is common in Lewy body dementias. Early autonomic features have been associated with poorer prognosis and shorter survival in PD (25). Stubendorff et al found that persistent autonomic dysfunction is a possible predictor of shorter survival in PDD and DLB (26).

MCI preceding PDD can affect different cognitive domains, (27) and is characterised by insidious decline in cognitive abilities (28). MCI and cognitive dysfunction has been reported in 15% - 23% of PD patients at the time of diagnosis, which can precede development of motor symptoms (29, 30). MCI usually progresses to dementia later in the course of PD. Visuospatial and executive impairments are characteristic of MCI in PD, with relative sparing of memory compared with AD (29). The ‘dual syndrome hypothesis’ suggested that the cognitive deficits linked to temporal and posterior dysfunction (visuospatial impairment and recognition memory) are associated with subsequent dementia, whilst fronto-striatal dysfunction (executive and attentional dysfunction) is more stable (31).

In 2007 the Movement Disorders Society (MDS) Task Force developed clinical diagnostic criteria for PDD. Dementia is diagnosed by the presence of deficits in at least two of the four core cognitive domains (attention, memory, executive and visuo-spatial function) severe enough to interfere with activities of daily living (17, 32).

The typical cognitive profile of PDD is a dysexecutive syndrome with impairment of planning and abstract thinking. Prominent impairments of attention and visuospatial function, moderate
Impairment of episodic memory and relatively preserved core language functions characterize early stages of PDD (17, 27, 33). Attentional fluctuations are less frequent in PDD (29%) than in DLB (42%) (32), but clinically are indistinguishable (34), and one study of neuropathologically confirmed DLB cases were found to have attentional fluctuations in 82% (35).

Neuropsychiatric symptoms are frequent in PDD with depression, apathy, anxiety and hallucinations common (36). VH are usually complex, well-formed, and similar to those in DLB (17, 37). Patients complain of recurrent images of people, animals or objects, more prominent in the evening or night. Hallucinations are usually not frightening but may become more disturbing in patients with severe dementia or those who experience delusions (37).

Minor VH are typically associated with early PD, for example visual illusions, ‘passage’ and ‘sense of presence’ hallucinations, sometimes referred to as ‘extracampine hallucinations’. These hallucinations can reoccur with insight preserved (self-recognition that the experiences are hallucinations). However, as PD progresses insight becomes lost and patients may start to experience delusions (false beliefs) and hallucinations in other sensory modalities (38). Delusions in PDD are less common than hallucinations (17), found in around 17% of patients (39).

Minor passage, and presence hallucinations, can appear as early non-motor symptom that may predate the onset of parkinsonism. A prospective study of fifty drug naïve PD patients and 100 controls found these minor hallucinations, also associated with the presence of possible RBD (40).

The timing, profile and rate of cognitive decline in PD is variable. The average time to dementia from diagnosis of PD is approximately 10 years, but can be as long as 20 years (41).

**Dementia with Lewy bodies**

DLB describes dementia that occurs before or concurrently with parkinsonism, or within 1 year of motor symptom onset (1). It accounts for 4.2% of dementia patients diagnosed in the community, and 7.5% of those in the secondary care (42). Over the age of 75 years, DLB causes about 5% of all dementia cases (43). However, prevalence rates of DLB vary and range from 0 to 26% in clinical studies, and between 15-20% in neuropathological studies (44).

Risk factors for DLB combine aspects from both PD and AD. Advanced age, male gender, family history of PD, APOE ε4 allele, depression, anxiety and low caffeine intake are associated with increased risk of DLB (45). Development of DLB is also linked to idiopathic RBD, parkinsonism, primary autonomic dysfunction, MCI and VH (46). Non-motor features such as olfactory dysfunction, orthostatic dizziness, hypersalivation and constipation have increased prevalence in patients with mild DLB (47).

The main clinical requirement for the diagnosis of DLB is dementia, defined as a progressive cognitive decline which is severe enough to interfere with the usual activities of daily living. The fourth consensus DLB report describes recent diagnostic criteria and distinguishes between clinical symptoms and diagnostic biomarkers, and the diagnosis of possible or probable DLB (48).
Clinical features are of two categories: core and supportive. Core clinical features include RBD, fluctuating cognition, recurrent visual hallucinations and parkinsonism. Supportive clinical features are common and can present early in disease course. Hypersomnia and hyposmia, neuroleptic sensitivity, postural instability, repeated falls, syncope, severe autonomic dysfunction (e.g. constipation, orthostatic hypotension, urinary incontinence), hallucinations in other modalities (e.g. auditory hallucinations (49)), delusions, apathy, anxiety and depression are all described (48).

Diagnostic biomarkers are classified as indicative and supportive. Indicative biomarkers include reduced uptake on SPECT or PET imaging, reduced uptake on $^{123}$iodine-MIBG myocardial scintigraphy and confirmation of RBD on polysomnography. Supportive biomarkers include relative preservation of medial temporal lobe structures on CT/MRI, generalized low uptake on SPECT/PET perfusion/metabolism scan with reduced occipital activity +/- the cingulate island sign on FDG-PET and brain perfusion SPECT (50), and prominent posterior slow-wave EEG activity with periodic fluctuations in the pre-alpha theta range (48).

Fluctuations are the key clinical aspect of DLB and occur as spontaneous alterations in cognition, attention, and arousal. They present as episodes of behavioural inconsistency, incoherent speech, variable attention or altered consciousness including staring or zoning out (48, 51). The Clinician Assessment of Fluctuation scale, One Day Fluctuation Assessment scale (52) or The Mayo Fluctuations Composite Scale can be used for their formal detection and evaluation (53). Fluctuating cognition in DLB probably relates to thalamic involvement (54). Watson et al showed that attentional dysfunction and cognitive fluctuations relate to distinct patterns of thalamic atrophy and may predict faster disease decline in DLB (55).

Recurrent VH occur in up to 80% of DLB patients. They manifest early in the disease course and do not diminish at later stages (4). Well-formed hallucinations of people, children or animals, passage and presence hallucinations, and visual illusions are all described (48).

RBD may precede the onset of DLB by years (56). One study of autopsy-confirmed cases found that RBD occurred more frequently in DLB than non-DLB dementia patients, such as patients with AD, frontotemporal dementia and corticobasal syndrome (57).

DLB patients can develop parkinsonism of increasing severity over the years with prevalence between 60 and 92% (57), although 18% of neuropathologically confirmed DLB cases never developed (58). Rest tremor is less frequent in DLB than PDD (59-61) and in DLB is usually milder and more symmetrical (62). More severe parkinsonism is associated with PDD (61, 63); the PIGD phenotype is more likely to be found in PDD (88%) and DLB (69%) compared to PD (38%) (61).

Common screens for dementia such as MMSE and MoCA can be used to characterize global impairment in DLB whereas neuropsychological assessment should cover more specific cognitive domains (48).

Deficits in attention, executive function and visual processing with relative impairment of memory and naming are typical (48, 64, 65). The spatial and perceptual difficulties of DLB occur early whilst memory and object naming is less affected (48). Language skills such as confrontation naming are often preserved, while performance on measures of learning and memory is more variable (66).
Current efforts to characterise prodromal stages of DLB suggest three categories: a) DLB mild cognitive impairment (DLB-MCI) variant, b) delirium onset DLB and c) psychiatric onset DLB (67). DLB may be preceded by amnestic or non-amnestic cognitive impairment. Patients with non-memory domains are more likely to progress to DLB than those with single-domain amnestic MCI (68).

DLB has a poorer prognosis than AD. DLB patients have shorter survival, faster cognitive decline and higher admission rates to the residential care than AD patients, highlighting the need to identify clinical and pathological features related to poorer prognosis which may offer therapeutic targets (69).

**Summary of clinical differences between DLB and PDD**

Comparative studies have identified clinical differences between PDD and DLB in motor and, certain cognitive aspects. More severe parkinsonism has been associated with PDD rather than DLB (61, 70) with rest tremor being less frequent in DLB (61).

Visual recognition memory, semantic fluency and ideomotor praxis are more severely impaired in DLB patients (71), who also show significantly lower scores on the tests of attention, executive function and constructional tasks (60, 70, 72). Episodic verbal memory is also worse in DLB than PDD, (60, 72) and the rate of cognitive decline is faster in DLB than PDD and AD (73, 74). One study showed that the average annual decline in MMSE score in DLB is approximately two points in comparison with PDD (1.8) and AD (1.6) (74).

VH are usually complex and similar in both conditions (75) but more frequent in DLB. The content of hallucinations and delusions is indistinguishable (76). Delusions, especially paranoid are less common in both groups (77, 78).

**Neuroimaging and CSF biomarkers**

DLB is often misdiagnosed and there is need for reliable neuroimaging markers which can distinguish DLB from other types of dementia (79). DAT scans remain the best neuroimaging technique to differentiate DLB from AD (80). An abnormal 123I-FP-CIT SPECT strongly supports the diagnosis of DLB, although around 20% of DLB patients (mixed DLB+AD and pure DLB) can have a normal 123I-FP-CIT SPECT (81).

Amyloid imaging PET scans using Pittsburgh Compound B (PiB) in PD, PDD and DLB showed that 68% of DLB patients had positive scans, 34% of PDD and only 5% of PD-MCI were PiB positive. This findings support the results from pathological studies that amyloid pathology is more common in DLB than in PDD, and is rare in non-demented PD-patients (29, 82).

Structural imaging has found that patients with DLB have greater cortical atrophy compared to PDD (63, 83). MRI imaging studies indicated significant bilateral frontal atrophy in PDD whereas parietal and occipital atrophy was found in DLB cases. Similar grey matter reduction of the caudate nucleus was observed in both PDD and DLB (84).

Cerebrospinal fluid (CSF) AD profile is more common in DLB compared to PDD and PD and is associated with more severe cognitive impairment in DLB. A large multicentre CSF study found a
substantial proportion of DLB patients (25%) had abnormal CSF Aβ₄₂, t-tau and p-tau compared to only 9% of PDD and 3% of PD patients (85) (Table 1). Another study found levels of CSF tau, Aβ 1-42 and p-tau/tau ratio were useful in differentiation between DLB and PDD. Severity of dementia associated with CSF tau and p-tau levels in DLB and CSF tau and p-tau ratio in PDD. Also, rapid disease course was associated with the decrease of Aβ1-42 in DLB (86). Significantly lower levels of CSF Aβ 1-42 was found in neuropathologically confirmed DLB cases with Aβ plaques compared to DLB without Aβ plaques (87). A further study showed correlation between Braak stages of AD neuropathology and decreased Aβ 1-42 CSF levels in neuropathologically confirmed DLB. This study also found that DLB cases had normal or elevated tau and normal or decreased levels of Aβ 1-42 in the CSF(88). Other Aβ fragments were also investigated, including oxidized Aβ1-40 which had increased levels in DLB compared to PD (89). Low CSF levels of total α-synuclein were found in subjects with α-synucleinopathies compared to AD subjects and subjects with non-neurodegenerative disease controls (90) and high CSF levels of oligomeric α-synuclein were found in PDD and DLB compared to AD (91).

Neuropathology

Staging systems for Lewy body pathology

The first report indicating that Lewy body pathology progresses in a predictable manner was provided by Kosaka in 1984 (92, 93). His strategy was later implemented by others and currently two staging systems for Lewy body pathology are commonly adopted and recommended by the DLB Consortium (48, 51, 94, 95); Braak’s 6 stage system and McKeith’s three category system with the more recent addition of olfactory bulb and amygdala-predominant categories (93).

Neuropathological substrate of dementia

The term Lewy body disease was originally proposed by Kosaka who studied the neuropathological changes in patients with dementia (92, 96). In the 1980-90s the term dementia with Lewy bodies evolved and now includes the previous diagnostic terms such as Lewy body variant of Alzheimer’s disease, Lewy body dementia, cortical Lewy body disease, diffuse Lewy body disease and senile dementia of Lewy body type (94, 96).

The underlying pathology of Lewy body dementias is heterogeneous (Figure 1). Cortical LBs seem to be the most prevalent feature for PDD whereas Aβ plays a more prominent role in DLB (1, 5). Nevertheless, due to overlapping pathologies there are only minor neuropathological differences between PDD and DLB (97).

The strongest neuropathological substrate of emerging PDD is the spread of LBs (α-synuclein pathology) from the brainstem to limbic and neocortical areas. Almost 50% of patients with PDD also develop sufficient Aβ plaques and neurofibrillary tangles (tau pathology) for a secondary diagnosis of AD. These pathologies are likely to act synergistically with α-synuclein and lead to a worse prognosis (98, 99).
Cortical LBs and Lewy neurites are often widespread in PDD and DLB and correlate with the severity of the dementia. Currently there are no hallmark neuropathological features that distinguish PDD from DLB, probably because most patients die at the end stage of the disease and the brain is diffusely involved (5).

The DLB consortium defined consensus guidelines for clinical and neuropathological diagnosis of DLB including the likelihood that the specific neuropathological findings associate with the clinical syndrome. Nevertheless, the clinico-pathological correlations remain controversial (48, 100).

In PD and PDD, previous studies showed that the severity of cognitive impairment correlated with cortical LBs mainly in the frontal and cingulate gyrus, even if AD pathology was not present (101). Others also demonstrated that cortical LBs correlated with dementia most in PD (7, 102, 103). In addition, greater neurofibrillary tangle (NFT) pathology was also found in PDD cases (103) and more severe cerebral amyloid angiopathy was associated with PDD (7). In contrast, Compta et al found that the combination of Lewy body and AD pathology is a robust pathological correlate of PDD and a better predictor of dementia than the severity of any single pathology (6). Cortical Aβ burden was found to be linked with a faster progression to dementia (104). Others also found that the combination of Lewy body and AD pathology, especially in the prefrontal cortex and temporal cortex, in both PDD and DLB showed a significant relationship with the decline in the MMSE scores.

This supports the statement that the combination of pathologies is a better predictor of cognitive decline in Lewy body dementias (105). Another predictor of cognitive status in Lewy body dementias is the concentration of phosphorylated α-synuclein at Ser129 in brain tissue which is directly linked to the level of Aβ and NFT stages (106).

The population-based Vantaa 85+ study showed that clinical features of DLB were better associated with high NFT stage than with diffuse neocortical Lewy body pathology (100). Hippocampal Lewy body pathology and its contribution to memory impairment in DLB was investigated and the results showed the highest levels of Lewy body pathology in the hippocampal CA2 subregion and entorhinal cortex. However, correlation with memory performance was strongest with CA1 (107).

AD neuropathology is common in PDD and DLB and leads to a worse prognosis. One of the recent studies demonstrated that NFT burden, α-synuclein and Aβ pathology are the strongest predictors of a shorter time interval from onset of motor symptoms to dementia and overall survival (58). This study also found that an increasing number of patients with a clinical diagnosis of DLB had higher load of AD neuropathology when compared with PDD, which suggests that AD pathology and especially NFT burden are central to the pathogenesis of DLB (58).

Deposition of Aβ is more marked and more closely related to cognitive impairment in DLB than PDD and may contribute to the onset of dementia. The more pronounced executive impairment in DLB than PDD may be related to preferential loss of fronto-hippocampal projections. Medial temporal lobe structures are abnormal in both DLB and PDD, but hippocampal atrophy is less marked that that seen in AD. Both Lewy body disorders have significant but similar atrophy and pathology in the amygdala. Lewy body densities/scores are increased in temporal lobe in DLB and correlate with early occurrence of characteristic VH rather than dementia duration and severity. In contrast, increasing Lewy body densities in limbic and frontal cortices in PDD correlate with the severity of dementia (76).
Hepp et al showed that Aβ pathology was more often observed in the entorhinal cortex, amygdala and putamen in DLB versus PDD. Aβ phases and neuritic plaque scores were higher in DLB versus PDD, and in PDD versus PD, suggesting that the load and extent of Aβ pathology contributes to cognitive dysfunction in PDD and early stage severe dementia in DLB (108).

PDD and DLB (58) can also develop without significant AD pathology. One study demonstrated in PDD cases with and without AD type pathology that both groups had similar degrees of dementia and approximately half of PDD subjects had enough AD pathology for the neuropathological diagnosis of AD (109). One recent large multicentre study showed that 20% DLB and 80% of PDD cases had no AD pathology (58). 19% of pure neocortical Lewy body pathology in Lewy body disorders without other co-occurring neuropathologies was reported (110).

Other co-morbid pathologies may contribute to dementia in PDD and DLB. Approximately 12-20% of subjects have co-morbid cerebrovascular disease or limbic TDP-43 pathology, with no clear association with AD pathology or with time interval of motor symptoms to dementia (58).

Together, these findings indicate that the key neuropathological substrate of dementia in PDD and DLB is the cortical Lewy body burden. Faster progression to dementia correlates with both cortical LBs and Aβ plaques. High cortical Lewy body load was found in DLB and it has also been suggested that a shorter latency to dementia is linked to the APOE ε4 allele (8). More frequent APOE ε4 allele was found in Lewy body dementia cases with concomitant AD neuropathology and higher amount of AD pathology was associated with older age of motor symptoms onset, dementia and death (58).

**Neuropathology of parkinsonism**

Given the predominance of parkinsonism in PDD, neuronal loss in the substantia nigra is more severe in PDD than DLB. Quantitative assessment showed that PDD cases had lower neuronal density in the substantia nigra than DLB cases (24.2 ± 15.3/mm² in PDD; 34.4 ± 27.0/mm² in DLB) (111). A different study which used semi-quantitative assessment also showed less severe neuronal loss in DLB compared to PDD and PD (112). Interestingly, Buchman et al found that neuronal loss of other brainstem nuclei, such as locus coeruleus is also associated with the severity of parkinsonism in adults with age-related parkinsonism (113). Cases with incidental Lewy body disease (pre-motor phase of PD) showed even more severe neuronal loss in the locus coeruleus than in the pars compacta of the substantia nigra (114). Other studies showed more severe degeneration of locus coeruleus in PD/PDD/DLB than in AD (115, 116).

Ballard et al found a relationship between the duration of parkinsonism prior to dementia and the severity of plaques, cortical α-synuclein pathology, and severity of cortical cholinergic deficits. The individuals with longstanding parkinsonism prior to dementia differed in many ways from DLB, with a threefold reduction in frequency of abundant plaques and 20% less cortical α-synuclein pathology, but 30% greater loss of neocortical choline acetyltransferase (117).

**Neuropathology of visual hallucinations**
Previous studies showed that VH in Lewy body disorders are linked to LBs in limbic and temporal areas (118-122) (Table 2). Alzheimer-type pathology was also investigated in relation to VH in Lewy body dementias when Jacobson et al found that AD-related pathology in neocortex and limbic areas also contributes to VH in Lewy body disorders (123).

Other selected brain regions were examined in recent years in relation to VH. Sub-regions of the pulvinar were investigated in the post mortem brain tissue of DLB and AD cases with VH. LBs were present throughout the pulvinar in DLB but their presence was most severe in the medial pulvinar while the lateral pulvinar showed more severe neuronal loss in DLB in comparison with AD (124). Pathology of the lateral geniculate nucleus showed no significant differences between DLB with VH and AD. However, AD cases had significantly more Aβ, less parvocellular neurons and had magnocellular gliosis compared to controls and DLB (125). Results from the study of the superior colliculus showed reduced neuronal densities in DLB in the stratum griseum intermedium compared to AD and controls (126). Primary visual cortex in DLB was investigated pathologically and biochemically. Neither alpha-synuclein nor NFT pathology was found in the primary visual cortex of DLB cases and neuronal densities were unchanged. Nevertheless, microarray analysis showed altered GABAergic transmission which may contribute to VH in DLB (127).

Complex VH which can also occur later on in the course of AD suggest the presence of LBs and mixed neuropathology of AD+DLB (128). High level of AD-type pathology can mask the additional presence of characteristic Lewy body symptoms and the manifestation of Lewy body disease. Interestingly, it is not Aβ but tau pathology which obscures the presence of additional Lewy body symptoms such as VH and extrapyramidal symptoms (128, 129).

**Neuropathology of REM sleep behaviour disorder**

RBD is recognised as a prodromal stage of PD (130) and DLB (131). Greater density and greater range of α-synuclein pathology was found in PD patients with probable RBD (132). One study with different neurodegenerative disorders subjects (AD, PD, DLB, incidental Lewy body disease, PSP with and without Lewy body pathology) and healthy controls showed histological evidence that Lewy body pathology was more frequent (79.2%) in cases with probable RBD compared to those without probable RBD (39.5%) (133). Furthermore, PD patients with RBD have greater frequency of α-synuclein pathology in the enteric nervous system which suggests that RBD is associated with widespread α-synuclein neuropathology (134). A large clinicopathologic study showed that RBD can predict α-synuclein neuropathology with 98% accuracy in polysomnography confirmed RBD cases (135).

**Cerebral amyloid angiopathy**

Sporadic cerebral amyloid angiopathy (CAA) is due to Aβ deposition in the walls of small leptomeningeal and brain blood vessels, especially arteries, arterioles and capillaries. CAA is very often asymptomatic but can contribute to dementia, cerebral haemorrhage or cerebral ischaemia. It occurs in approximately 30% of the normal elderly and in 90-100% of AD cases (136).
While Lewy body and AD pathology have been studied in depth, there are only a few studies examining the association of CAA and cognitive decline in PD and DLB. Jellinger et al found an association of CAA with cognitive decline in both PD/PDD and DLB, particularly in cases with AD pathology. The same study also showed that both capillary CAA and generalized CAA were significantly more severe in both PDD and DLB than in PD without dementia (137). Similarly, Bertrand et al found a higher frequency of CAA and of parenchymal Aβ deposits in PDD than in PD cases (138). Wu et al also demonstrated more severe meningeal and parenchymal vessel CAA in DLB with AD pathology than without AD pathology (139).

Aβ burden is greater in patients with DLB than in PDD and increased load of Aβ is closely linked to a higher incidence of cerebral microbleeds (140). Gungor et al demonstrated different concentration and distribution of microbleeds in DLB and AD. In DLB, microbleeds were most densely concentrated in the occipital and frontal lobes followed by the parietal and temporal lobe. In AD, the highest concentration was found in the occipital lobe followed by parietal and temporal lobe. AD cases had lower densities of microbleeds in the frontal lobe compared to DLB (141). A different study comparing PDD and DLB cases showed that DLB had a greater burden of cerebral microbleeds and exhibited lobar predominance in comparison with PDD patients (140).

TDP-43 pathology

Transactive response DNA binding protein-43 (TDP-43) forms abnormal intraneuronal inclusions in some forms of frontotemporal lobe degeneration. TDP-43 inclusions may also be found in AD where five stages of pathology have been described showing progressive involvement of the amygdala, entorhinal cortex, dentate gyrus and occipitotemporal cortex, inferior temporal cortex and finally the mid-frontal cortex (142).

Similar TDP-43 neuropathological distribution to AD can be also seen in DLB. McAleese et al found significantly higher prevalence of TDP-43 pathology in AD and mixed AD/DLB cases in comparison with aged controls suggesting that AD pathology may trigger and worsen TDP-43 pathology. Furthermore, an association between age and TDP-43 pathology was shown in this study (143).

Synaptic pathology

A most recent study investigated synaptic proteins in the prefrontal cortex in three dementia groups: AD, DLB and PDD. Significant changes of 25 synaptic proteins were found in all three groups. Some of these 25 proteins could reliably differentiate between PDD and AD. In addition, loss of proteins including: SNAP47, SYBU, LRFN2, SV2C and GRIA3 significantly correlated with cognitive impairment and rate of cognitive decline (144).

A further study found synaptic changes and astrogliosis in the pulvinar in DLB cases compared to controls suggesting they contribute to the cognitive decline in DLB (145).

That DLB is a primary synaptopathy was supported by finding of small phosphorylated α-synuclein aggregates in presynaptic terminals, visualised by array tomography (146).
Molecular pathology, seeding and spreading of α-synuclein pathology

A key event in α-synucleinopathies is the conversion of soluble α-synuclein into insoluble protein. The insoluble α-synuclein may form self-sustaining seeds that can propagate from one cell to another in a prion-like manner via anatomical connections. This concept potentially underlies the Braak staging of Lewy body pathology (147). Furthermore, there is a concept that different α-synuclein strains can initiate the development of different clinical phenotypes. Specific α-synuclein strains may have different tropism for cell populations due to distinct membrane proteins expressed by neurons and astrocytes (147).

The olfactory bulb, with its close anatomical location to the limbic structures, is probably closely involved to the development of dementia in PD and DLB, with α-synuclein pathology spreading from the olfactory bulb to the amygdala and then neocortex (148). Nevertheless, in many DLB cases α-synuclein pathology was also found in the enteric nervous system and vagal nerve in the brainstem, making spread from the enteric nervous system by a ‘dual hit hypothesis’ a possibility (149).

Metabolic pathways including mitochondrial functions, energy and purine metabolism or protein synthesis were investigated in frontal cortex of DLB cases with typical and rapidly progressive forms. Changes in deregulated expression of some mRNAs and mitochondrial subunit proteins, reduced activity of mitochondrial respiratory chains complexes, or reduced expression of molecules involved in energy metabolism were found mainly in the rapidly progressive DLB (150).

Summary of pathologic differences between DLB and PDD

More severe neuronal loss in the substantia nigra is found in PD and PDD than in DLB (112). DLB cases have more abundant α-synuclein pathology in the neocortex and limbic system, especially in the CA2/3 areas of hippocampus (151). In comparison with PDD, DLB cases have higher Aβ load in the cortex and striatum, higher stages of Aβ plaques, neuritic plaque scores and increased load of tau in cortex and striatum (151). Cholinergic pedunculopontine cell loss was described in hallucinating PDD patients, but not in DLB (152). DLB cases showed higher 5-HT1A receptor binding in cerebral cortex than PDD (9). PDD and DLB have more profound cholinergic neuronal loss and reduced choline acetyltransferase activity in comparison with PD (153) (Table 1).

Genetics

In PD, it is unclear how genetics contributes to risk of dementia. Individuals at increased risk of PDD carry APOE ε2 and ε4 alleles, and are homozygous H1/H1 for MAPT (11). APOE might be associated with appearance of PD independently from cognitive impairment, although the literature is contradictory (11). The Rotterdam prospective population-based study showed that both APOE ε4 and APOE ε2 were associated with increased dementia risk, with a stronger effect for APOE ε2 (11, 154). The APOE ε4 allele is strongly associated with Alzheimer type pathology in Lewy body disorders (155) and in DLB, it is the strongest genetic risk factor for the disease (156).
Variations in the MAPT gene (encoding microtubule-associated protein tau) may also determine the genetic risk of dementia in PD with the H1/H1 haplotype being associated with a greater rate of cognitive decline and development of early dementia (157, 158).

A robust association between cognitive impairment in PD and duplication and, triplication of the α-synuclein gene (SNCA) was previously reported (27, 159, 160). SNCA duplications described in PD (161), may also lead to wider clinical phenotypes (162). SNCA variants have also been implicated in PD/PDD (163) and DLB (Table 3). In PD, there is an association with markers of the 3’ end of the gene, whereas in DLB the association is with the 5’ end. This different regional association in SNCA might influence the distinct distribution of LBs in the brains of PD and DLB patients (164). Bras et al showed that in DLB, the APOE locus is similar to the one that occurs in AD, but that SNCA and SCARB2 association regions are different to those implicated in PD or PDD (164).

Heterozygous mutations in GBA (encoding glucocerebrosidase) such as N370S, L444P or E326K (165, 166) are a risk factor for PD and DLB. There is also evidence linking GBA mutations with different neuropsychiatric phenotypes in PD and other disorders. Nevertheless, the underlying mechanism is not clear. One meta-analysis showed that GBA mutations are associated with a 2.4-fold increased risk of cognitive impairment and 1.8 and 2.2-fold increased risk of psychosis and depression (167). GBA mutations have been found 3.5% of one PD population and led to earlier and more progressive dementia compared to non-carriers (168).

Nalls et al found a significant association between GBA1 mutation carriers and DLB; DLB cases were 8 times more likely to carry GBA1 mutation in comparison to controls (165). The GBA1 variant E326K was also associated with DLB. However, there was no significant difference between Lewy body/neurite burden in mutation carriers and non-carriers (165). GBA1 mutations are therefore a significant risk factor for DLB and are associated with earlier disease onset and age of death compared to DLB non-carriers. In addition, parkinsonism was more severe and VH more common in DLB cases with GBA1 mutations (165).

The frequency of GBA variants in DLB patients varies between populations, ranging from 3.5% in neuropathologically confirmed DLB cases from the USA to 33% in a DLB cohort of Ashkenazi Jews, a population where GBA variants are overrepresented (169).

Other studies suggested that variants in genes associated with PD (SNCA, LRRK2 and GBA) or AD (PSEN1, PSEN2, APP, APOE) and MAPT are associated with DLB, potentially explaining genetic overlap between DLB, PD and AD (169). A Belgian study examined AD and PD associated genes including APOE and GBA and known and novel pathogenic mutations associated with DLB and PDD were identified, including those in PSEN1, PSEN2, GRN, MAPT, PINK1 and PARK2 (Table 3) (162). These mutations were identified in gene based mutation analysis studies using algorithm key for the classification of mutations’ pathogenicity (170) and computational programmes predicting the damaging effect of the mutation – PolyPhen2 (171), PMut (172), SNPS & GO (173).

C9orf72 was also investigated in a recent large international cohort study in neuropathologically or clinically confirmed DLB case but no repeat expansion was causally associated with DLB (174).

The first large-scale genome-wide association study (GWAS) in DLB confirmed previously reported associations of APOE, SNCA, GBA and provided some evidence for a novel candidate locus CNTN1
encoding protein contactin 1 (156). SCARB2 and the p.N370S variant in GBA were also shown to be associated with DLB and suggest the role of lysosomal dysfunction in this disease (164).

A GWAS based on neuropathologically confirmed elderly cases with neocortical Lewy-related pathology (LRP) identified suggestive novel risk factors for neocortical LRP; SPTBN1 which encodes beta-spectrin, an α-synuclein binding protein and a component of LBs (175).

Global transcriptional changes in the frontal cortex were investigated in PD, DLB and incidental Lewy body disease. Different co-expressed gene sets were identified, showing the evidence of molecular changes in the cortex and involvement of different metabolic pathways and genes (i.e. genes linked to heat-shock/chaperones proteins involved in refolding and clearance of α-synuclein aggregates) which may be linked to cognitive problems or dementia (176).

**Conclusion**

DLB and PDD are two dementias with overlapping clinical and neuropathological phenotypes. The conundrum whether these two disorders represent two different entities or the same disease remains unresolved. Clinical diagnostic criteria and the so called ‘1-year rule’ are used in the clinical and research settings and can help us to distinguish between these two disorders mainly according to the time of onset of dementia and parkinsonism. Clinico-pathological comparative studies have identified important clinical and pathological differences between DLB and PDD. From the clinical standpoint, it is clear that DLB patients have less severe parkinsonism and more profound cognitive deficit with higher frequency of visual hallucinations than PDD patients. Pathologically, DLB cases have higher load of Aβ and Lewy body pathology and less severe neuronal loss in the substantia nigra in comparison with PDD. Interestingly, recent genetic studies have highlighted unique genetic risk profile of DLB in comparison with PD and PDD (156, 162, 164).

Nevertheless, the current neuropathological guidelines have difficulty differentiating between PDD and DLB without ancillary clinical information (9, 177). Preliminary neuropathological criteria for DLB and PDD have been proposed but their validation in the future clinico-pathological studies will be necessary (9).

The use of the term Lewy body dementias would seem to be appropriate until clear distinction between PDD and DLB at clinical, neuropathological and biochemical level can be achieved. Better understanding of the composition of Lewy bodies, including the characteristics of α-synuclein such as variations in post-translational modification and protein conformation, which may give rise to different protein strains in PD, PDD and DLB will be exciting areas of research that could enhance our understanding of Lewy body dementias.

**New information and future directions:**

- DLB has unique genetic profile, the most recent GWAS revealed novel candidates - CNTN1, SCARB2
• Prion hypothesis as a possible pathophysiological mechanism underlying Lewy body dementias
• Need for PDD and DLB biomarkers

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DH wrote the manuscript and designed tables. HL revised the manuscript and helped to create the histology figure. TL revised the manuscript. JH revised and contributed to the final manuscript and chose histology images for the histology figure. TW revised the manuscript.

Conflict of interest
Authors have no conflicts of interest to disclose.

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