Clinical, neuropathological and genetic features of Lewy body dementias

Hansen D[1], Ling H[1,2], Lashley T[2], Holton JL[2], Warner TT[1,2]

[1]Reta Lila Weston Institute, UCL Queen Square Institute of Neurology, London

[2]Queen Square Brain Bank for Neurological Disorders, UCL Queen Square Institute of Neurology, London

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

^{123}I-FP-CIT ^{123}I-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

Corresponding author:

Professor TT Warner, Reta Lila Weston Institute for Neurological Studies, UCL Queen Square Institute of Neurology, 1 Wakefield Street, London WC1N 1PJ

Tel: +44 207 6794246

Email: t.warner@ucl.ac.uk

Number of figures and tables: 1 figure in colour, 3 tables

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 CampPaIGN 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 $A\beta_{42}$ 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 a 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 ^{123}I-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 ^{123}I-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 $A\beta_{42}$, 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 PDD (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-occuring 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 el 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

Acknowledgements

This work has been supported by the Reta Lila Weston Trust for medical research. We would like to thank Queen Square Brain Bank for Neurological Disorders for providing histology images and DH would like to thank all co-authors for their guidance and support.

Authors' contributions

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.

References

1. Walker Z, Possin KL, Boeve BF, Aarsland D. Lewy body dementias. Lancet. 2015;386(10004):1683-97.
2. Gomperts SN. Lewy Body Dementias: Dementia With Lewy Bodies and Parkinson Disease Dementia. Continuum (Minneap Minn). 2016;22(2 Dementia):435-63.
3. Mosimann UP, Rowan EN, Partington CE, Collerton D, Littlewood E, O'Brien JT, et al. Characteristics of visual hallucinations in Parkinson disease dementia and dementia with lewy bodies. Am J Geriatr Psychiatry. 2006;14(2):153-60.
4. Weisman D, McKeith I. Dementia with Lewy bodies. Semin Neurol. 2007;27(1):42-7.
5. Lippa CF, Duda JE, Grossman M, Hurtig HI, Aarsland D, Boeve BF, et al. DLB and PDD boundary issues: diagnosis, treatment, molecular pathology, and biomarkers. Neurology. 2007;68(11):812-9.
6. Compta Y, Parkkinen L, O'Sullivan SS, Vandrovcova J, Holton JL, Collins C, et al. Lewy- and Alzheimer-type pathologies in Parkinson's disease dementia: which is more important? Brain. 2011;134(Pt 5):1493-505.
7. Irwin DJ, White MT, Toledo JB, Xie SX, Robinson JL, Van Deerlin V, et al. Neuropathologic substrates of Parkinson disease dementia. Ann Neurol. 2012;72(4):587-98.
8. Ruffmann C, Calboli FC, Bravi I, Gveric D, Curry LK, de Smith A, et al. Cortical Lewy bodies and Abeta burden are associated with prevalence and timing of dementia in Lewy body diseases. Neuropathol Appl Neurobiol. 2016;42(5):436-50.
9. Jellinger KA. Dementia with Lewy bodies and Parkinson's disease-dementia: current concepts and controversies. J Neural Transm (Vienna). 2017.

10. Deramecourt V, Bombois S, Maurage CA, Ghestem A, Drobecq H, Vanmechelen E, et al. Biochemical staging of synucleinopathy and amyloid deposition in dementia with Lewy bodies. J Neuropathol Exp Neurol. 2006;65(3):278-88.
11. Garcia-Ptacek S, Kramberger MG. Parkinson Disease and Dementia. J Geriatr Psychiatry Neurol. 2016;29(5):261-70.
12. Williams-Gray CH, Mason SL, Evans JR, Foltynie T, Brayne C, Robbins TW, et al. The CamPaIGN study of Parkinson's disease: 10-year outlook in an incident population-based cohort. J Neurol Neurosurg Psychiatry. 2013;84(11):1258-64.
13. Hely MA, Morris JG, Reid WG, Trafficante R. Sydney Multicenter Study of Parkinson's disease: non-L-dopa-responsive problems dominate at 15 years. Mov Disord. 2005;20(2):190-9.
14. Hely MA, Reid WG, Adena MA, Halliday GM, Morris JG. The Sydney multicenter study of Parkinson's disease: the inevitability of dementia at 20 years. Mov Disord. 2008;23(6):837-44.
15. Reid WG, Hely MA, Morris JG, Loy C, Halliday GM. Dementia in Parkinson's disease: a 20-year neuropsychological study (Sydney Multicentre Study). J Neurol Neurosurg Psychiatry. 2011;82(9):1033-7.
16. Aarsland D, Kurz MW. The epidemiology of dementia associated with Parkinson's disease. Brain Pathol. 2010;20(3):633-9.
17. Emre M, Aarsland D, Brown R, Burn DJ, Duyckaerts C, Mizuno Y, et al. Clinical diagnostic criteria for dementia associated with Parkinson's disease. Mov Disord. 2007;22(12):1689-707; quiz 837.
18. Anang JB, Gagnon JF, Bertrand JA, Romenets SR, Latreille V, Panisset M, et al. Predictors of dementia in Parkinson disease: a prospective cohort study. Neurology. 2014;83(14):1253-60.
19. Anang JB, Nomura T, Romenets SR, Nakashima K, Gagnon JF, Postuma RB. Dementia Predictors in Parkinson Disease: A Validation Study. J Parkinsons Dis. 2017;7(1):159-62.
20. Schrag A, Siddiqui UF, Anastasiou Z, Weintraub D, Schott JM. Clinical variables and biomarkers in prediction of cognitive impairment in patients with newly diagnosed Parkinson's disease: a cohort study. Lancet Neurol. 2017;16(1):66-75.
21. Levy G, Tang MX, Cote LJ, Louis ED, Alfaro B, Mejia H, et al. Motor impairment in PD: relationship to incident dementia and age. Neurology. 2000;55(4):539-44.
22. Selikhova M, Williams DR, Kempster PA, Holton JL, Revesz T, Lees AJ. A clinico-pathological study of subtypes in Parkinson's disease. Brain. 2009;132(Pt 11):2947-57.
23. Svenningsson P, Westman E, Ballard C, Aarsland D. Cognitive impairment in patients with Parkinson's disease: diagnosis, biomarkers, and treatment. Lancet Neurol. 2012;11(8):697-707.
24. Postuma RB, Bertrand JA, Montplaisir J, Desjardins C, Vendette M, Rios Romenets S, et al. Rapid eye movement sleep behavior disorder and risk of dementia in Parkinson's disease: a prospective study. Mov Disord. 2012;27(6):720-6.
25. De Pablo-Fernandez E, Tur C, Revesz T, Lees AJ, Holton JL, Warner TT. Association of Autonomic Dysfunction With Disease Progression and Survival in Parkinson Disease. JAMA Neurol. 2017;74(8):970-6.
26. Stubendorff K, Aarsland D, Minthon L, Londos E. The impact of autonomic dysfunction on survival in patients with dementia with Lewy bodies and Parkinson's disease with dementia. PLoS One. 2012;7(10):e45451.
27. Hanagasi HA, Tufekcioglu Z, Emre M. Dementia in Parkinson's disease. J Neurol Sci. 2017;374:26-31.
28. Litvan I, Goldman JG, Troster AI, Schmand BA, Weintraub D, Petersen RC, et al. Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. Mov Disord. 2012;27(3):349-56.
29. Aarsland D. Cognitive impairment in Parkinson's disease and dementia with Lewy bodies. Parkinsonism Relat Disord. 2016;22 Suppl 1:S144-8.
30. Muslimovic D, Post B, Speelman JD, Schmand B. Cognitive profile of patients with newly diagnosed Parkinson disease. Neurology. 2005;65(8):1239-45.

31. Williams-Gray CH, Foltynie T, Brayne CE, Robbins TW, Barker RA. Evolution of cognitive dysfunction in an incident Parkinson's disease cohort. Brain. 2007;130(Pt 7):1787-98.
32. Goetz CG, Emre M, Dubois B. Parkinson's disease dementia: definitions, guidelines, and research perspectives in diagnosis. Ann Neurol. 2008;64 Suppl 2:S81-92.
33. Petrova M, Raycheva M, Traykov L. Cognitive profile of the earliest stage of dementia in Parkinson's disease. Am J Alzheimers Dis Other Demen. 2012;27(8):614-9.
34. Varanese S, Perfetti B, Monaco D, Thomas A, Bonanni L, Tiraboschi P, et al. Fluctuating cognition and different cognitive and behavioural profiles in Parkinson's disease with dementia: comparison of dementia with Lewy bodies and Alzheimer's disease. J Neurol. 2010;257(6):1004-11.
35. Byrne EJ, Lennox G, Lowe J, Godwin-Austen RB. Diffuse Lewy body disease: clinical features in 15 cases. J Neurol Neurosurg Psychiatry. 1989;52(6):709-17.
36. Aarsland D, Bronnick K, Ehrt U, De Deyn PP, Tekin S, Emre M, et al. Neuropsychiatric symptoms in patients with Parkinson's disease and dementia: frequency, profile and associated care giver stress. J Neurol Neurosurg Psychiatry. 2007;78(1):36-42.
37. Ballard C, Aarsland D, Francis P, Corbett A. Neuropsychiatric symptoms in patients with dementias associated with cortical Lewy bodies: pathophysiology, clinical features, and pharmacological management. Drugs Aging. 2013;30(8):603-11.
38. Ffytche DH, Creese B, Politis M, Chaudhuri KR, Weintraub D, Ballard C, et al. The psychosis spectrum in Parkinson disease. Nat Rev Neurol. 2017;13(2):81-95.
39. Pagonabarraga J, Llebaria G, Garcia-Sanchez C, Pascual-Sedano B, Gironell A, Kulisevsky J. A prospective study of delusional misidentification syndromes in Parkinson's disease with dementia. Mov Disord. 2008;23(3):443-8.
40. Pagonabarraga J, Martinez-Horta S, Fernandez de Bobadilla R, Perez J, Ribosa-Nogue R, Marin J, et al. Minor hallucinations occur in drug-naive Parkinson's disease patients, even from the premotor phase. Mov Disord. 2016;31(1):45-52.
41. Aarsland D, Creese B, Politis M, Chaudhuri KR, Ffytche DH, Weintraub D, et al. Cognitive decline in Parkinson disease. Nat Rev Neurol. 2017;13(4):217-31.
42. Vann Jones SA, O'Brien JT. The prevalence and incidence of dementia with Lewy bodies: a systematic review of population and clinical studies. Psychol Med. 2014;44(4):673-83.
43. Hogan DB, Fiest KM, Roberts JI, Maxwell CJ, Dykeman J, Pringsheim T, et al. The Prevalence and Incidence of Dementia with Lewy Bodies: a Systematic Review. Can J Neurol Sci. 2016;43 Suppl 1:S83-95.
44. Kane JPM, Surendranathan A, Bentley A, Barker SAH, Taylor JP, Thomas AJ, et al. Clinical prevalence of Lewy body dementia. Alzheimers Res Ther. 2018;10(1):19.
45. Boot BP, Orr CF, Ahlskog JE, Ferman TJ, Roberts R, Pankratz VS, et al. Risk factors for dementia with Lewy bodies: a case-control study. Neurology. 2013;81(9):833-40.
46. Auning E, Rongve A, Fladby T, Booij J, Hortobagyi T, Siepel FJ, et al. Early and presenting symptoms of dementia with lewy bodies. Dement Geriatr Cogn Disord. 2011;32(3):202-8.
47. Chiba Y, Fujishiro H, Iseki E, Ota K, Kasanuki K, Hirayasu Y, et al. Retrospective survey of prodromal symptoms in dementia with Lewy bodies: comparison with Alzheimer's disease. Dement Geriatr Cogn Disord. 2012;33(4):273-81.
48. McKeith IG, Boeve BF, Dickson DW, Halliday G, Taylor JP, Weintraub D, et al. Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. Neurology. 2017;89(1):88-100.
49. McKeith IG, Perry RH, Fairbairn AF, Jabeen S, Perry EK. Operational criteria for senile dementia of Lewy body type (SDLT). Psychol Med. 1992;22(4):911-22.
50. Imabayashi E, Soma T, Sone D, Tsukamoto T, Kimura Y, Sato N, et al. Validation of the cingulate island sign with optimized ratios for discriminating dementia with Lewy bodies from Alzheimer's disease using brain perfusion SPECT. Ann Nucl Med. 2017;31(7):536-43.

51. McKeith IG, Dickson DW, Lowe J, Emre M, O'Brien JT, Feldman H, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. Neurology. 2005;65(12):1863-72.
52. Walker MP, Ayre GA, Cummings JL, Wesnes K, McKeith IG, O'Brien JT, et al. The Clinician Assessment of Fluctuation and the One Day Fluctuation Assessment Scale. Two methods to assess fluctuating confusion in dementia. Br J Psychiatry. 2000;177:252-6.
53. Ferman TJ, Smith GE, Boeve BF, Ivnik RJ, Petersen RC, Knopman D, et al. DLB fluctuations: specific features that reliably differentiate DLB from AD and normal aging. Neurology. 2004;62(2):181-7.
54. Delli Pizzi S, Franciotti R, Taylor JP, Thomas A, Tartaro A, Onofrj M, et al. Thalamic Involvement in Fluctuating Cognition in Dementia with Lewy Bodies: Magnetic Resonance Evidences. Cereb Cortex. 2015;25(10):3682-9.
55. Watson R, Colloby SJ, Blamire AM, Wesnes KA, Wood J, O'Brien JT. Does attentional dysfunction and thalamic atrophy predict decline in dementia with Lewy bodies? Parkinsonism Relat Disord. 2017;45:69-74.
56. Molano J, Boeve B, Ferman T, Smith G, Parisi J, Dickson D, et al. Mild cognitive impairment associated with limbic and neocortical Lewy body disease: a clinicopathological study. Brain. 2010;133(Pt 2):540-56.
57. Ferman TJ, Boeve BF, Smith GE, Lin SC, Silber MH, Pedraza O, et al. Inclusion of RBD improves the diagnostic classification of dementia with Lewy bodies. Neurology. 2011;77(9):875-82.
58. Irwin DJ, Grossman M, Weintraub D, Hurtig HI, Duda JE, Xie SX, et al. Neuropathological and genetic correlates of survival and dementia onset in synucleinopathies: a retrospective analysis. Lancet Neurol. 2017;16(1):55-65.
59. Fritz NE, Kegelmeyer DA, Kloos AD, Linder S, Park A, Kataki M, et al. Motor performance differentiates individuals with Lewy body dementia, Parkinson's and Alzheimer's disease. Gait Posture. 2016;50:1-7.
60. Takemoto M, Sato K, Hatanaka N, Yamashita T, Ohta Y, Hishikawa N, et al. Different Clinical and Neuroimaging Characteristics in Early Stage Parkinson's Disease with Dementia and Dementia with Lewy Bodies. J Alzheimers Dis. 2016;52(1):205-11.
61. Burn DJ, Rowan EN, Minett T, Sanders J, Myint P, Richardson J, et al. Extrapyramidal features in Parkinson's disease with and without dementia and dementia with Lewy bodies: A cross-sectional comparative study. Mov Disord. 2003;18(8):884-9.
62. Del Ser T, McKeith I, Anand R, Cicin-Sain A, Ferrara R, Spiegel R. Dementia with Lewy bodies: Findings from an international multicentre study. Int J Geriatr Psych. 2000;15(11):1034-45.
63. Peraza LR, Colloby SJ, Firbank MJ, Greasy GS, McKeith IG, Kaiser M, et al. Resting state in Parkinson's disease dementia and dementia with Lewy bodies: commonalities and differences. Int J Geriatr Psychiatry. 2015;30(11):1135-46.
64. Kao AW, Racine CA, Quitania LC, Kramer JH, Christine CW, Miller BL. Cognitive and neuropsychiatric profile of the synucleinopathies: Parkinson disease, dementia with Lewy bodies, and multiple system atrophy. Alzheimer Dis Assoc Disord. 2009;23(4):365-70.
65. Yoshizawa H, Vonsattel JP, Honig LS. Early neuropsychological discriminants for Lewy body disease: an autopsy series. J Neurol Neurosurg Psychiatry. 2013;84(12):1326-30.
66. Ferman TJ, Smith GE, Boeve BF, Graff-Radford NR, Lucas JA, Knopman DS, et al. Neuropsychological differentiation of dementia with Lewy bodies from normal aging and Alzheimer's disease. Clin Neuropsychol. 2006;20(4):623-36.
67. McKeith I, Taylor JP, Thomas A, Donaghy P, Kane J. Revisiting DLB Diagnosis: A Consideration of Prodromal DLB and of the Diagnostic Overlap With Alzheimer Disease. J Geriatr Psychiatry Neurol. 2016;29(5):249-53.
68. Ferman TJ, Smith GE, Kantarci K, Boeve BF, Pankratz VS, Dickson DW, et al. Nonamnestic mild cognitive impairment progresses to dementia with Lewy bodies. Neurology. 2013;81(23):2032-8.

69. Mueller C, Ballard C, Corbett A, Aarsland D. The prognosis of dementia with Lewy bodies. Lancet Neurol. 2017;16(5):390-8.
70. Petrova M, Mehrabian-Spasova S, Aarsland D, Raycheva M, Traykov L. Clinical and Neuropsychological Differences between Mild Parkinson's Disease Dementia and Dementia with Lewy Bodies. Dement Geriatr Cogn Dis Extra. 2015;5(2):212-20.
71. Lee JE, Park HJ, Park B, Song SK, Sohn YH, Lee JD, et al. A comparative analysis of cognitive profiles and white-matter alterations using voxel-based diffusion tensor imaging between patients with Parkinson's disease dementia and dementia with Lewy bodies. J Neurol Neurosurg Psychiatry. 2010;81(3):320-6.
72. Park KW, Kim HS, Cheon SM, Cha JK, Kim SH, Kim JW. Dementia with Lewy Bodies versus Alzheimer's Disease and Parkinson's Disease Dementia: A Comparison of Cognitive Profiles. J Clin Neurol. 2011;7(1):19-24.
73. Blanc F, Mahmoudi R, Jonveaux T, Galmiche J, Chopard G, Cretin B, et al. Long-term cognitive outcome of Alzheimer's disease and dementia with Lewy bodies: dual disease is worse. Alzheimers Res Ther. 2017;9(1):47.
74. Kramberger MG, Auestad B, Garcia-Ptacek S, Abdelnour C, Olmo JG, Walker Z, et al. Long-Term Cognitive Decline in Dementia with Lewy Bodies in a Large Multicenter, International Cohort. J Alzheimers Dis. 2017;57(3):787-95.
75. Frei K, Truong DD. Hallucinations and the spectrum of psychosis in Parkinson's disease. J Neurol Sci. 2017;374:56-62.
76. Aarsland D, Ballard CG, Halliday G. Are Parkinson's disease with dementia and dementia with Lewy bodies the same entity? J Geriatr Psychiatry Neurol. 2004;17(3):137-45.
77. Goldman JG, Williams-Gray C, Barker RA, Duda JE, Galvin JE. The spectrum of cognitive impairment in Lewy body diseases. Mov Disord. 2014;29(5):608-21.
78. Peavy GM, Edland SD, Toole BM, Hansen LA, Galasko DR, Mayo AM. Phenotypic differences based on staging of Alzheimer's neuropathology in autopsy-confirmed dementia with Lewy bodies. Parkinsonism Relat Disord. 2016;31:72-8.
79. Mak E, Su L, Williams GB, O'Brien JT. Neuroimaging characteristics of dementia with Lewy bodies. Alzheimers Res Ther. 2014;6(2):18.
80. Surendranathan A, O'Brien JT. Clinical imaging in dementia with Lewy bodies. Evid Based Ment Health. 2018;21(2):61-5.
81. Thomas AJ, Attems J, Colloby SJ, O'Brien JT, McKeith I, Walker R, et al. Autopsy validation of 123I-FP-CIT dopaminergic neuroimaging for the diagnosis of DLB. Neurology. 2017;88(3):276-83.
82. Petrou M, Dwamena BA, Foerster BR, MacEachern MP, Bohnen NI, Muller ML, et al. Amyloid deposition in Parkinson's disease and cognitive impairment: a systematic review. Mov Disord. 2015;30(7):928-35.
83. Beyer MK, Larsen JP, Aarsland D. Gray matter atrophy in Parkinson disease with dementia and dementia with Lewy bodies. Neurology. 2007;69(8):747-54.
84. Borroni B, Premi E, Formenti A, Turrone R, Alberici A, Cottini E, et al. Structural and functional imaging study in dementia with Lewy bodies and Parkinson's disease dementia. Parkinsonism Relat Disord. 2015;21(9):1049-55.
85. van Steenoven I, Aarsland D, Weintraub D, Londos E, Blanc F, van der Flier WM, et al. Cerebrospinal Fluid Alzheimer's Disease Biomarkers Across the Spectrum of Lewy Body Diseases: Results from a Large Multicenter Cohort. J Alzheimers Dis. 2016;54(1):287-95.
86. Gmitterova K, Gawinecka J, Llorens F, Varges D, Valkovic P, Zerr I. Cerebrospinal fluid markers analysis in the differential diagnosis of dementia with Lewy bodies and Parkinson's disease dementia. Eur Arch Psychiatry Clin Neurosci. 2018.
87. Slaets S, Le Bastard N, Theuns J, Sleegers K, Verstraeten A, De Leenheir E, et al. Amyloid pathology influences abeta1-42 cerebrospinal fluid levels in dementia with lewy bodies. J Alzheimers Dis. 2013;35(1):137-46.

88. Brunnstrom H, Hansson O, Zetterberg H, Londos E, Englund E. Correlations of CSF tau and amyloid levels with Alzheimer pathology in neuropathologically verified dementia with Lewy bodies. Int J Geriatr Psychiatry. 2013;28(7):738-44.
89. Bibl M, Mollenhauer B, Esselmann H, Lewczuk P, Klafki HW, Sparbier K, et al. CSF amyloid-beta-peptides in Alzheimer's disease, dementia with Lewy bodies and Parkinson's disease dementia. Brain. 2006;129(Pt 5):1177-87.
90. Mollenhauer B, Cullen V, Kahn I, Krastins B, Outeiro TF, Pepivani I, et al. Direct quantification of CSF alpha-synuclein by ELISA and first cross-sectional study in patients with neurodegeneration. Exp Neurol. 2008;213(2):315-25.
91. Hansson O, Hall S, Ohrfelt A, Zetterberg H, Blennow K, Minthon L, et al. Levels of cerebrospinal fluid alpha-synuclein oligomers are increased in Parkinson's disease with dementia and dementia with Lewy bodies compared to Alzheimer's disease. Alzheimers Res Ther. 2014;6(3):25.
92. Kosaka K, Yoshimura M, Ikeda K, Budka H. Diffuse type of Lewy body disease: progressive dementia with abundant cortical Lewy bodies and senile changes of varying degree--a new disease? Clin Neuropathol. 1984;3(5):185-92.
93. Alafuzoff I, Hartikainen P. Alpha-synucleinopathies. Handb Clin Neurol. 2017;145:339-53.
94. McKeith IG, Galasko D, Kosaka K, Perry EK, Dickson DW, Hansen LA, et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. Neurology. 1996;47(5):1113-24.
95. Braak H, Del Tredici K, Rub U, de Vos RA, Jansen Steur EN, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging. 2003;24(2):197-211.
96. McKeith I. Dementia with Lewy bodies and Parkinson's disease with dementia: where two worlds collide. Pract Neurol. 2007;7(6):374-82.
97. Kovari E, Horvath J, Bouras C. Neuropathology of Lewy body disorders. Brain Res Bull. 2009;80(4-5):203-10.
98. Irwin DJ, Lee VM, Trojanowski JQ. Parkinson's disease dementia: convergence of alpha-synuclein, tau and amyloid-beta pathologies. Nat Rev Neurosci. 2013;14(9):626-36.
99. Lashley T, Holton JL, Gray E, Kirkham K, O'Sullivan SS, Hilbig A, et al. Cortical alpha-synuclein load is associated with amyloid-beta plaque burden in a subset of Parkinson's disease patients. Acta Neuropathol. 2008;115(4):417-25.
100. Oinas M, Polvikoski T, Sulkava R, Myllykangas L, Juva K, Notkola IL, et al. Neuropathologic findings of dementia with lewy bodies (DLB) in a population-based Vantaa 85+ study. J Alzheimers Dis. 2009;18(3):677-89.
101. Mattila PM, Rinne JO, Helenius H, Dickson DW, Roytta M. Alpha-synuclein-immunoreactive cortical Lewy bodies are associated with cognitive impairment in Parkinson's disease. Acta Neuropathol. 2000;100(3):285-90.
102. Hurtig HI, Trojanowski JQ, Galvin J, Ewbank D, Schmidt ML, Lee VM, et al. Alpha-synuclein cortical Lewy bodies correlate with dementia in Parkinson's disease. Neurology. 2000;54(10):1916-21.
103. Kempster PA, O'Sullivan SS, Holton JL, Revesz T, Lees AJ. Relationships between age and late progression of Parkinson's disease: a clinico-pathological study. Brain. 2010;133(Pt 6):1755-62.
104. Compta Y, Parkkinen L, Kempster P, Selikhova M, Lashley T, Holton JL, et al. The significance of alpha-synuclein, amyloid-beta and tau pathologies in Parkinson's disease progression and related dementia. Neurodegener Dis. 2014;13(2-3):154-6.
105. Howlett DR, Whitfield D, Johnson M, Attems J, O'Brien JT, Aarsland D, et al. Regional Multiple Pathology Scores Are Associated with Cognitive Decline in Lewy Body Dementias. Brain Pathol. 2015;25(4):401-8.
106. Swirski M, Miners JS, de Silva R, Lashley T, Ling H, Holton J, et al. Evaluating the relationship between amyloid-beta and alpha-synuclein phosphorylated at Ser129 in dementia with Lewy bodies and Parkinson's disease. Alzheimers Res Ther. 2014;6(5-8):77.

107. Adamowicz DH, Roy S, Salmon DP, Galasko DR, Hansen LA, Masliah E, et al. Hippocampal alpha-Synuclein in Dementia with Lewy Bodies Contributes to Memory Impairment and Is Consistent with Spread of Pathology. J Neurosci. 2017;37(7):1675-84.
108. Hepp DH, Vergoossen DL, Huisman E, Lemstra AW, Netherlands Brain B, Berendse HW, et al. Distribution and Load of Amyloid-beta Pathology in Parkinson Disease and Dementia with Lewy Bodies. J Neuropathol Exp Neurol. 2016;75(10):936-45.
109. Sabbagh MN, Adler CH, Lahti TJ, Connor DJ, Vedders L, Peterson LK, et al. Parkinson disease with dementia: comparing patients with and without Alzheimer pathology. Alzheimer Dis Assoc Disord. 2009;23(3):295-7.
110. Robinson JL, Lee EB, Xie SX, Rennert L, Suh E, Bredenberg C, et al. Neurodegenerative disease concomitant proteinopathies are prevalent, age-related and APOE4-associated. Brain. 2018;141(7):2181-93.
111. Colloby SJ, McParland S, O'Brien JT, Attems J. Neuropathological correlates of dopaminergic imaging in Alzheimer's disease and Lewy body dementias. Brain. 2012;135(Pt 9):2798-808.
112. Tsuboi Y, Dickson DW. Dementia with Lewy bodies and Parkinson's disease with dementia: are they different? Parkinsonism Relat Disord. 2005;11 Suppl 1:S47-51.
113. Buchman AS, Nag S, Shulman JM, Lim AS, VanderHorst VG, Leurgans SE, et al. Locus coeruleus neuron density and parkinsonism in older adults without Parkinson's disease. Mov Disord. 2012;27(13):1625-31.
114. Dickson DW, Fujishiro H, DelleDonne A, Menke J, Ahmed Z, Klos KJ, et al. Evidence that incidental Lewy body disease is pre-symptomatic Parkinson's disease. Acta Neuropathol. 2008;115(4):437-44.
115. Brunnstrom H, Friberg N, Lindberg E, Englund E. Differential degeneration of the locus coeruleus in dementia subtypes. Clin Neuropathol. 2011;30(3):104-10.
116. German DC, Manaye KF, White CL, 3rd, Woodward DJ, McIntire DD, Smith WK, et al. Disease-specific patterns of locus coeruleus cell loss. Ann Neurol. 1992;32(5):667-76.
117. Ballard C, Ziabreva I, Perry R, Larsen JP, O'Brien J, McKeith I, et al. Differences in neuropathologic characteristics across the Lewy body dementia spectrum. Neurology. 2006;67(11):1931-4.
118. Gallagher DA, Parkkinen L, O'Sullivan SS, Spratt A, Shah A, Davey CC, et al. Testing an aetiological model of visual hallucinations in Parkinson's disease. Brain. 2011;134(Pt 11):3299-309.
119. Harding AJ, Broe GA, Halliday GM. Visual hallucinations in Lewy body disease relate to Lewy bodies in the temporal lobe. Brain. 2002;125(Pt 2):391-403.
120. Kalaitzakis ME, Christian LM, Moran LB, Graeber MB, Pearce RK, Gentleman SM. Dementia and visual hallucinations associated with limbic pathology in Parkinson's disease. Parkinsonism Relat Disord. 2009;15(3):196-204.
121. Papapetropoulos S, McCorquodale DS, Gonzalez J, Jean-Gilles L, Mash DC. Cortical and amygdalar Lewy body burden in Parkinson's disease patients with visual hallucinations. Parkinsonism Relat Disord. 2006;12(4):253-6.
122. Ferman TJ, Arvanitakis Z, Fujishiro H, Duara R, Parfitt F, Purdy M, et al. Pathology and temporal onset of visual hallucinations, misperceptions and family misidentification distinguishes dementia with Lewy bodies from Alzheimer's disease. Parkinsonism Relat Disord. 2013;19(2):227-31.
123. Jacobson SA, Morshed T, Dugger BN, Beach TG, Hentz JG, Adler CH, et al. Plaques and tangles as well as Lewy-type alpha synucleinopathy are associated with formed visual hallucinations. Parkinsonism Relat Disord. 2014;20(9):1009-14.
124. Erskine D, Thomas AJ, Attems J, Taylor JP, McKeith IG, Morris CM, et al. Specific patterns of neuronal loss in the pulvinar nucleus in dementia with lewy bodies. Mov Disord. 2017;32(3):414-22.
125. Erskine D, Taylor JP, Firbank MJ, Patterson L, Onofrj M, O'Brien JT, et al. Changes to the lateral geniculate nucleus in Alzheimer's disease but not dementia with Lewy bodies. Neuropathol Appl Neurobiol. 2016;42(4):366-76.

126. Erskine D, Thomas AJ, Taylor JP, Savage MA, Attems J, McKeith IG, et al. Neuronal Loss and Alpha-Synuclein Pathology in the Superior Colliculus and Its Relationship to Visual Hallucinations in Dementia with Lewy Bodies. Am J Geriatr Psychiatry. 2017;25(6):595-604.
127. Khundakar AA, Hanson PS, Erskine D, Lax NZ, Roscamp J, Karyka E, et al. Analysis of primary visual cortex in dementia with Lewy bodies indicates GABAergic involvement associated with recurrent complex visual hallucinations. Acta Neuropathol Commun. 2016;4(1):66.
128. Thomas AJ, Mahin-Babaei F, Saidi M, Lett D, Taylor JP, Walker L, et al. Improving the identification of dementia with Lewy bodies in the context of an Alzheimer's-type dementia. Alzheimers Res Ther. 2018;10(1):27.
129. Merdes AR, Hansen LA, Jeste DV, Galasko D, Hofstetter CR, Ho GJ, et al. Influence of Alzheimer pathology on clinical diagnostic accuracy in dementia with Lewy bodies. Neurology. 2003;60(10):1586-90.
130. Barone DA, Henchcliffe C. Rapid eye movement sleep behavior disorder and the link to alpha-synucleinopathies. Clin Neurophysiol. 2018;129(8):1551-64.
131. Marchand DG, Postuma RB, Escudier F, De Roy J, Pelletier A, Montplaisir J, et al. How does dementia with Lewy bodies start? prodromal cognitive changes in REM sleep behavior disorder. Annals of Neurology. 2018;83(5):1016-26.
132. Postuma RB, Adler CH, Dugger BN, Hentz JG, Shill HA, Driver-Dunckley E, et al. REM sleep behavior disorder and neuropathology in Parkinson's disease. Mov Disord. 2015;30(10):1413-7.
133. Shprecher DR, Adler CH, Zhang N, Hentz JG, Serrano GE, Dugger BN, et al. Predicting alpha-synuclein pathology by REM sleep behavior disorder diagnosis. Parkinsonism Relat Disord. 2018.
134. Leclair-Visonneau L, Clairembault T, Coron E, Le Dily S, Vavasseur F, Dalichampt M, et al. REM sleep behavior disorder is related to enteric neuropathology in Parkinson disease. Neurology. 2017;89(15):1612-8.
135. Boeve BF, Silber MH, Ferman TJ, Lin SC, Benarroch EE, Schmeichel AM, et al. Clinicopathologic correlations in 172 cases of rapid eye movement sleep behavior disorder with or without a coexisting neurologic disorder. Sleep Med. 2013;14(8):754-62.
136. Love S, Chalmers K, Ince P, Esiri M, Attems J, Jellinger K, et al. Development, appraisal, validation and implementation of a consensus protocol for the assessment of cerebral amyloid angiopathy in post-mortem brain tissue. Am J Neurodegener Dis. 2014;3(1):19-32.
137. Jellinger KA, Attems J. Cerebral amyloid angiopathy in Lewy body disease. J Neural Transm (Vienna). 2008;115(3):473-82.
138. Bertrand E, Lewandowska E, Stepien T, Szpak GM, Pasennik E, Modzelewska J. Amyloid angiopathy in idiopathic Parkinson's disease. Immunohistochemical and ultrastructural study. Folia Neuropathol. 2008;46(4):255-70.
139. Wu E, Lipton RB, Dickson DW. Amyloid angiopathy in diffuse Lewy body disease. Neurology. 1992;42(11):2131-5.
140. Kim SW, Chung SJ, Oh YS, Yoon JH, Sunwoo MK, Hong JY, et al. Cerebral Microbleeds in Patients with Dementia with Lewy Bodies and Parkinson Disease Dementia. AJNR Am J Neuroradiol. 2015;36(9):1642-7.
141. Gungor I, Sarro L, Graff-Radford J, Zuk SM, Tosakulwong N, Przybelski SA, et al. Frequency and topography of cerebral microbleeds in dementia with Lewy bodies compared to Alzheimer's disease. Parkinsonism Relat Disord. 2015;21(9):1101-4.
142. Josephs KA, Murray ME, Whitwell JL, Parisi JE, Petrucelli L, Jack CR, et al. Staging TDP-43 pathology in Alzheimer's disease. Acta Neuropathol. 2014;127(3):441-50.
143. McAleese KE, Walker L, Erskine D, Thomas AJ, McKeith IG, Attems J. TDP-43 pathology in Alzheimer's disease, dementia with Lewy bodies and ageing. Brain Pathol. 2017;27(4):472-9.
144. Bereczki E, Branca RM, Francis PT, Pereira JB, Baek JH, Hortobagyi T, et al. Synaptic markers of cognitive decline in neurodegenerative diseases: a proteomic approach. Brain. 2018;141(2):582-95.

145. Erskine D, Ding J, Thomas AJ, Kaganovich A, Khundakar AA, Hanson PS, et al. Molecular changes in the absence of severe pathology in the pulvinar in dementia with Lewy bodies. Mov Disord. 2018.
146. Colom-Cadena M, Pegueroles J, Herrmann AG, Henstridge CM, Munoz L, Querol-Vilaseca M, et al. Synaptic phosphorylated alpha-synuclein in dementia with Lewy bodies. Brain. 2017;140(12):3204-14.
147. Peelaerts W, Bousset L, Baekelandt V, Melki R. E-Synuclein strains and seeding in Parkinson's disease, incidental Lewy body disease, dementia with Lewy bodies and multiple system atrophy: similarities and differences. Cell Tissue Res. 2018;373(1):195-212.
148. Cersosimo MG. Propagation of alpha-synuclein pathology from the olfactory bulb: possible role in the pathogenesis of dementia with Lewy bodies. Cell Tissue Res. 2018;373(1):233-43.
149. Beach TG, Adler CH, Sue LI, Vedders L, Lue L, White Iii CL, et al. Multi-organ distribution of phosphorylated alpha-synuclein histopathology in subjects with Lewy body disorders. Acta Neuropathol. 2010;119(6):689-702.
150. Garcia-Esparcia P, Lopez-Gonzalez I, Grau-Rivera O, Garcia-Garrido MF, Konetti A, Llorens F, et al. Dementia with Lewy Bodies: Molecular Pathology in the Frontal Cortex in Typical and Rapidly Progressive Forms. Front Neurol. 2017;8:89.
151. Jellinger KA. Significance of brain lesions in Parkinson disease dementia and Lewy body dementia. Front Neurol Neurosci. 2009;24:114-25.
152. Hepp DH, Ruiter AM, Galis Y, Voorn P, Rozemuller AJ, Berendse HW, et al. Pedunculopontine cholinergic cell loss in hallucinating Parkinson disease patients but not in dementia with Lewy bodies patients. J Neuropathol Exp Neurol. 2013;72(12):1162-70.
153. Francis PT, Perry EK. Cholinergic and other neurotransmitter mechanisms in Parkinson's disease, Parkinson's disease dementia, and dementia with Lewy bodies. Mov Disord. 2007;22 Suppl 17:S351-7.
154. de Lau LM, Schipper CM, Hofman A, Koudstaal PJ, Breteler MM. Prognosis of Parkinson disease: risk of dementia and mortality: the Rotterdam Study. Arch Neurol. 2005;62(8):1265-9.
155. Wider C, Ross OA, Nishioka K, Heckman MG, Vilarino-Guell C, Jasinska-Myga B, et al. An evaluation of the impact of MAPT, SNCA and APOE on the burden of Alzheimer's and Lewy body pathology. J Neurol Neurosurg Psychiatry. 2012;83(4):424-9.
156. Guerreiro R, Ross OA, Kun-Rodrigues C, Hernandez DG, Orme T, Eicher JD, et al. Investigating the genetic architecture of dementia with Lewy bodies: a two-stage genome-wide association study. Lancet Neurol. 2018;17(1):64-74.
157. Goris A, Williams-Gray CH, Clark GR, Foltynie T, Lewis SJ, Brown J, et al. Tau and alpha-synuclein in susceptibility to, and dementia in, Parkinson's disease. Ann Neurol. 2007;62(2):145-53.
158. Healy DG, Abou-Sleiman PM, Lees AJ, Casas JP, Quinn N, Bhatia K, et al. Tau gene and Parkinson's disease: a case-control study and meta-analysis. J Neurol Neurosurg Psychiatry. 2004;75(7):962-5.
159. Farrer M, Kachergus J, Forno L, Lincoln S, Wang DS, Hulihan M, et al. Comparison of kindreds with parkinsonism and alpha-synuclein genomic multiplications. Ann Neurol. 2004;55(2):174-9.
160. Sironi F, Trotta L, Antonini A, Zini M, Ciccone R, Della Mina E, et al. alpha-Synuclein multiplication analysis in Italian familial Parkinson disease. Parkinsonism Relat Disord. 2010;16(3):228-31.
161. Fuchs J, Nilsson C, Kachergus J, Munz M, Larsson EM, Schule B, et al. Phenotypic variation in a large Swedish pedigree due to SNCA duplication and triplication. Neurology. 2007;68(12):916-22.
162. Meeus B, Verstraeten A, Crosiers D, Engelborghs S, Van den Broeck M, Mattheijssens M, et al. DLB and PDD: a role for mutations in dementia and Parkinson disease genes? Neurobiol Aging. 2012;33(3):629 e5- e18.
163. Kruger R, Kuhn W, Leenders KL, Sprengelmeyer R, Muller T, Woitalla D, et al. Familial parkinsonism with synuclein pathology: clinical and PET studies of A30P mutation carriers. Neurology. 2001;56(10):1355-62.

164. Bras J, Guerreiro R, Darwent L, Parkkinen L, Ansorge O, Escott-Price V, et al. Genetic analysis implicates APOE, SNCA and suggests lysosomal dysfunction in the etiology of dementia with Lewy bodies. Hum Mol Genet. 2014;23(23):6139-46.
165. Nalls MA, Duran R, Lopez G, Kurzawa-Akanbi M, McKeith IG, Chinnery PF, et al. A multicenter study of glucocerebrosidase mutations in dementia with Lewy bodies. JAMA Neurol. 2013;70(6):727-35.
166. Mata IF, Samii A, Schneer SH, Roberts JW, Griffith A, Leis BC, et al. Glucocerebrosidase gene mutations: a risk factor for Lewy body disorders. Arch Neurol. 2008;65(3):379-82.
167. Creese B, Bell E, Johar I, Francis P, Ballard C, Aarsland D. Glucocerebrosidase mutations and neuropsychiatric phenotypes in Parkinson's disease and Lewy body dementias: Review and meta-analyses. Am J Med Genet B Neuropsychiatr Genet. 2017.
168. Winder-Rhodes SE, Evans JR, Ban M, Mason SL, Williams-Gray CH, Foltynie T, et al. Glucocerebrosidase mutations influence the natural history of Parkinson's disease in a community-based incident cohort. Brain. 2013;136(Pt 2):392-9.
169. Vergouw LJM, van Steenoven I, van de Berg WDJ, Teunissen CE, van Swieten JC, Bonifati V, et al. An update on the genetics of dementia with Lewy bodies. Parkinsonism Relat Disord. 2017;43:1-8.
170. Guerreiro RJ, Baquero M, Blesa R, Boada M, Bras JM, Bullido MJ, et al. Genetic screening of Alzheimer's disease genes in Iberian and African samples yields novel mutations in presenilins and APP. Neurobiol Aging. 2010;31(5):725-31.
171. Ramensky V, Bork P, Sunyaev S. Human non-synonymous SNPs: server and survey. Nucleic Acids Res. 2002;30(17):3894-900.
172. Ferrer-Costa C, Gelpi JL, Zamakola L, Parraga I, de la Cruz X, Orozco M. PMUT: a web-based tool for the annotation of pathological mutations on proteins. Bioinformatics. 2005;21(14):3176-8.
173. Calabrese R, Capriotti E, Fariselli P, Martelli PL, Casadio R. Functional annotations improve the predictive score of human disease-related mutations in proteins. Hum Mutat. 2009;30(8):1237-44.
174. Kun-Rodrigues C, Ross OA, Orme T, Shepherd C, Parkkinen L, Darwent L, et al. Analysis of C9orf72 repeat expansions in a large international cohort of dementia with Lewy bodies. Neurobiol Aging. 2017;49:214 e13- e15.
175. Peuralinna T, Myllykangas L, Oinas M, Nalls MA, Keage HA, Isoviita VM, et al. Genome-wide association study of neocortical Lewy-related pathology. Ann Clin Transl Neurol. 2015;2(9):920-31.
176. Santpere G, Garcia-Esparcia P, Andres-Benito P, Lorente-Galdos B, Navarro A, Ferrer I. Transcriptional network analysis in frontal cortex in Lewy body diseases with focus on dementia with Lewy bodies. Brain Pathol. 2018;28(3):315-33.
177. Halliday GM, Holton JL, Revesz T, Dickson DW. Neuropathology underlying clinical variability in patients with synucleinopathies. Acta Neuropathol. 2011;122(2):187-204.