Dementia with Lewy Bodies and Parkinson’s Disease-Dementia: Current Perspectives

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Abstract

Dementia with Lewy bodies (DLB) and Parkinson’s disease-dementia (PDD) are two closely related major neurocognitive disorders with Lewy bodies of unknown etiology, showing notable overlap in their clinical presentation, pathological features, biochemistry, and genetic risk factors. According to international consensus, their diagnosis is based on an arbitrary distinction between the time of onset of motor and cognitive symptoms: dementia preceding parkinsonism in DLB, while it develops after onset of parkinsonism in PDD (the one-year rule). Clinically, both syndromes show cognitive impairment with severe deficits in executive function, visuo-spatial processing, fluctuating attention and parkinsonism, with higher prevalence of Alzheimer-type lesions in DLB that may account for earlier onset and severity of cognitive deficits. These are also associated with multiple neurotransmitter deficits indicating that cognitive impairment in Lewy body diseases is multifactorial. Recent intravital neuroimaging, clinico-pathological studies and animal models suggest that DLB and PDD represent closely related but different, heterogenic subtypes of an α-synuclein-associated disease spectrum (Lewy body diseases) or parts of a continuum reflecting a regional cerebrovascular paresis. The multifold overlap between DLB and PDD has led to debating whether they should be classified as the same disease (see [1,2]).

Keywords

Dementia with Lewy bodies, Parkinson’s disease-dementia, Synucleinopathies, Clinical features, Diagnostic criteria, Neuropathology, Pathogenesis, Management

Background

Dementia with Lewy bodies (DLB) and Parkinson’s disease-dementia (PDD) are major neurocognitive disorders with α-synuclein (αSyn) deposits/Lewy bodies (LB), the nosological relations of which are under discussion (see [1,2]). Both entities are closely related with notable overlap in their clinical presentation, pathological features, biochemistry, and genetic risk factors. Even though the diagnostic criteria for these α-synucleinopathies are well established, their precise clinical diagnosis is often difficult, because DLB, Parkinson’s disease (PD), PDD and Alzheimer’s disease (AD) share clinical, morphological and biochemical characteristics, suggesting «overlap» syndromes between synucleinopathies (PD) and tauopathies (AD) [3]. Based on international consensus, DLB is diagnosed when dementia precedes parkinsonian signs for at least 1 year [4], whereas in PDD cognitive impairment develops in the setting of well-established PD [5]. The clinical features of both entities are similar and include parkinsonism with severe deficits in executive function, visuo-spatial processing, cognitive fluctuations, visual hallucinations, REM sleep behavior disorder (RBD), and memory disorders, the latter being more severe in PDD [6,7]. Despite different temporal sequences of motor and cognitive deficits (the 1 year rule), both syndromes show similar, albeit locally and quantitatively divergent morphological lesions, with variable mixtures of αSyn/LB and AD-related lesions, but increased cortical Aβ and tau load in DLB [8,9]. The multifold overlap between DLB and PDD has led to debating whether they should be classified as the same disease [10] or parts of a continuum reflecting a regional cerebral pathology [1] or distinct «diseases» with different predisposing genetic factors but sharing those with PD.
and AD [11]. However, recent studies indicate a regional overlap of multiple pathologies between synucleinopathies (PD) and tauopathies (AD) [3,12].

Clinical Manifestations and Diagnostic Criteria

Clinically, DLB is marked by four core symptoms: fluctuating cognition, parkinsonism, visual hallucinations, RBD, and cognitive impairment across multiple domains with moderate memory impairment [13]. DLB is a heterogenous disease. Cluster analysis yielded 3 different groups: cognitive-predominant (showing longer duration), neuropsychotict-dominant (older at onset), and parkinson-predominant (showing a shorter time from onset to presence of parkinsonism and dementia [14]). DLB patients with mild cognitive impairment (MCI) perform worse on visuospatial function and letter fluency tests and better on episodic memory tests than AD-MCI [15]. Cognitive impairment in PD patients being more common in the akinetic/rigid phenotype than in tremor-dominant and mixed phenotypes [16] is similar in quality to what is observed in DLB [6], but the rate of cognitive decline is faster in DLB than in PDD and AD [17,18], and shows more severely impaired frontal and temporal area-associated cognitive profiles [19]. The clinical overlaps and dissimilarities between DLB and PDD have been summarized recently (Table 1).

DLB accounts for up to 5% of all dementia cases, while PDD affects between 75 and 95% of PD patients, with incidence rates of 2.5 to 3.5/100,000 person/years, the incidence of both syndromes being around 6% [20]. The average age at diagnosis is 70 to 76 years [21]. Individuals with DLB and PDD have increased mortality compared to the general population [22], the average survival time for DLB from the beginning of symptoms is 5-8 years, while PDD antedates death by about 4 years [23].

Genetics

Both DLB and PDD are primarily sporadic diseases, yet some different genetic factors may be involved, none of which, however, being diagnostic [24]. Glucocerebrosidase mutations and SNCA (αSyn gene) have been associated with both DLB and PDD [25-27]. In the clinical continuum between DLB and PDD, carriers of severe glucocerebrosidase mutations have a clinical phenotype that is closer to DLB [28]. APOE4 allele frequency is higher in DLB compared to PDD and may influence the risk for DLB [29]. Genome-wide association studies (GWAS) have found associations of variants of APOE, SNCA and other loci with DLB but not PDD, suggesting that DLB may share genetic loci with PD and AD [11], although the ways of involvement may be different, underpinning the concept of different pathomechanisms for PDD and DLB. However, the genetic differences between both entities have, so far, not been studied in detail [30].

Diagnostic Biomarkers

Multimodal imaging methods have improved ante mortem diagnosis of both DLB and PDD [31,32]. Striatal dopamine imaging shows reduced dopamine transporter (DAT) binding in putamen in both entities [33] indicating nigrostriatal loss being more severe in PDD consistent with the severity of parkinsonism, while others found no differences between DLB and PDD [34]. FDG-PET and 123I-FP-CIT SPECT are used to distinguish DLB from AD but have limited sensitivity since DAT imaging is also abnormal in other atypical parkinsonian syndromes [35]. Recent studies showed lower 123I-FP-CIT bindings to the striatal DAT, but not to the extrastriatal serotonin transporter (SET) in PD compared to DLB [36]. The sensitivity of FP-CIT imaging in probable MCI-DLB was 61% [37]. Semiquantitative ratings of FP-CIT SPECT scans were more accurate than visual ratings [38].

Cardiac neuroimaging using 123 I-metaiodobenzylguanidine (MIBG) as marker of postganglionic sympathetic innervation, shows reduced MIBG uptake in both DLB and PDD and allows no differentiation between the two disorders [39]. Its diagnostic usefulness in early stages of DLB was suggested [40].
So far, the contribution of MRI to the diagnosis of DLB and PDD is limited. Magnetic resonance volumetry (VM), shows cortical thinning in different cortical areas but similar relative preservation of the medial temporal lobe (MTL) in both disorders. There is similar atrophy of striopallidum but more extensive atrophy of thalamus in DLB. The latter may be a marker of disease severity indicating rapid decline [41], while evaluation of white matter hypointensities and MTL atrophy may indicate progression of AD-related pathology in DLB and perhaps can distinguish DLB from PDD [42,43].

Functional MRI showed a different disruption of cortical functional connectivity in PDD (predominant frontal disruption) compared to DLB (predominant parietal and occipital) [44]. Molecular changes in the pulvinar may result in decreased cortical synchrony in DLB [45]. Brain PET revealed occipital hypoperfusion in both DLB and PDD with no or only subtle metabolic differences [46,47]. FDG PET is one alternative biomarker that can differentiate AD and DLB but lacks the evidence base of both DAT and MIBG scans [48]. Mapping of brain acetylcholinesterase (ACHE) showed alterations in cortical and subcortical levels in both PDD and DLB [49,50]. Recent PET studies of the vesicular ACh transporter (VACHt) showed more extensive reductions affecting neocortical, limbic and thalamic regions in DLB than in AD [51]. 11C PIB-PET imaging showed more frequent and severe Aβ brain deposition in DLB than in PDD [52,53], predictive of faster degeneration in cortex and striatum [54]. Tau pathology visualized by PET imaging along with temporal atrophy, indicative of coexisting AD pathology, is more common in DLB compared to PDD [33], amyloid playing an important role for tau accumulation [55]. A recent review of neuroimaging in DLB emphasized the importance of a multimodel approach [56].

Quantitative EEG features may specifically differentiate DLB, PDD and AD [57], and transcranial sonographic hyperechogenicity of substantia nigra is more common in DLB than in PDD [58].

Many cerebrospinal fluid (CSF) and some plasma biomarkers have been identified in DLB and PDD, but very few studies examined samples from both disorders simultaneously, and only a minority have been confirmed by postmortem studies [59,60]. Large scale studies showed lower levels of Aβ42 and higher tau in DLB than in PDD. A CSF AD profile with elevated Aβ40 but decreased Aβ42 and higher tau levels is more common in DLB than in PDD [51], which may be related to increased AD pathology. Levels of αSyn oligomers are increased in PDD but not in DLB [59,62,63]. However, the current use of CSF biomarkers in the diagnosis of DLB and PDD is not yet recommended by the American Academy of Neurology [64].

Neuropathological Features

Both DLB and PDD show similar morphological features, with a variable mixture of αSyn/LB and AD-related lesions and a multi-organ distribution of αSyn pathology [2,65]. A common pathophysiological factor is synaptic dysfunction due to initial aggregation of αSyn in presynapses causing functional disconnection [66,67] due to interference with axonal transport and neurotransmitter deprivation [68]. Studies of large cohorts have shown a strong correlation between both corticial Lewy and AD-related pathologies, suggesting that phosphorylated αSyn promotes the phosphorylation of tau [69,70], while tau oligomers mediate αSyn toxicity [71]. The relationship between phosphorylated αSyn and tau accumulation to Aβ deposition in cerebral cortex supports an overlap in the pathology of DLB, PDD and AD and that Aβ promotes the accumulation of both αSyn and tau [3,12,72]. A recent study showed that cerebral tau, Aβ and αSyn pathologies are strong predictors of a shorter interval between onset of motor and cognitive symptoms and shorter survival in LB dementias [73]. Thus, cognitive impairment in both DLB and PDD is not only induced by αSyn caused neurodegeneration but by multiple regional pathological scores. Despite many similarities, several morphological differences have been demonstrated, e.g. higher amyloid load in striatum [74,75] and amygdala, higher Aβ phases and neuritic plaque scores in cortex [76], as well as more frequent tau pathology in striatum in DLB [77]. Minor differences are more severe αSyn load in hippocampal subareas C2/3 in DLB and differences in the severity and distribution pattern of substantia nigra lesions (predominant neuronal loss in ventrolateral vs. dorsolateral cell groups in PDD vs. DLB) [78,79]. Recent morphological studies revealed differential vulnerability of the anterior insular cortex to αSyn pathology in PDD and DLB due to a decreasing gradient of αSyn immunoreactivity from the anterior allocortical to the posterior isocortical granular insula in iLBD, PD, PDD, and DLB [80](Table 2 [2]). The heterogeneous neurochemistry of both entities also supports the overlap between synucleinopathies and tauopathies [3].

At present, neuropathological diagnosis of PDD and DLB without sufficient clinical data would be difficult due to the heterogeneity of synucleinopathies, but preliminary criteria have been proposed (Table 3). For their validation, further clinicopathological studies will be necessary in order to further promote our understanding of the molecular and pathogenic backgrounds of both DLB and PDD.

Pathophysiology of Cognitive Impairment

The neurobiological basis for cognitive impairment in DLB and PDD is multifocal, related to a synergistic effect of both αSyn/LB and AD pathologies and dysfunction of dopaminergic, noradrenalinergergic, serotoninergic, and cholinergic systems [70,81,82]. The emergence of PDD and DLB occurs on the background of severe dopamine deficits and correlates with a marked loss of lim-
**Table 2: Morphological overlap and dissimilarities between DLB and PDD [2].**

<table>
<thead>
<tr>
<th>Morphological overlap</th>
<th>Morphological dissimilarities</th>
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</thead>
<tbody>
<tr>
<td>Mixture of cortical and subcortical LB/αSyn and AD-related pathologies</td>
<td>Higher Aβ load in cortex and striatum in DLB</td>
</tr>
<tr>
<td>Similar Braak LB stages (4-6) and Braak neuritic stages (5 or 6)</td>
<td>Aβ phases and neuritic plaque scores higher in DLB</td>
</tr>
<tr>
<td>Relation between αSyn and tau aggregation to Aβ deposition in cortex</td>
<td>Higher cortical LB load in temporal &amp; parietal cortex in DLB</td>
</tr>
<tr>
<td>Initial αSyn aggregation in pre-synapses inducing neurodegeneration via interference with axonal transport</td>
<td>Increased tau loads in cortex and striatum in DLB</td>
</tr>
<tr>
<td>Postsynaptic protein downregulation</td>
<td>More frequent and severe αSyn load in hippocampal subareas CA2 in DLB</td>
</tr>
<tr>
<td></td>
<td>Differential vulnerability to αSyn pathology in anterior insular cortex (PD &gt; PDD &gt; DLB)</td>
</tr>
<tr>
<td></td>
<td>Minor deviations in severity and lesion pattern in SNc</td>
</tr>
<tr>
<td></td>
<td>Pedunculopontine cholinergic cell loss in hallucinating PDD, but not in DLB</td>
</tr>
<tr>
<td></td>
<td>Higher 5-HT1A receptor binding in cerebral cortex in DLB</td>
</tr>
</tbody>
</table>

**Table 3: Preliminary neuropathological criteria for dementia with Lewy bodies (DLB) and Parkinson disease with dementia (PDD) [2].**

<table>
<thead>
<tr>
<th>Type of lesion</th>
<th>DLB</th>
<th>PDD</th>
</tr>
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<tbody>
<tr>
<td>LB/αSyn pathology</td>
<td>Both show a combination of progressed LB (LB Braak stage 5-6) and AD pathology of variable severity and extent (Braak neuritic stage 5-6)</td>
<td></td>
</tr>
<tr>
<td>Aβ load</td>
<td>More severe and extended in cortex and striatum</td>
<td>Less severe and less extended</td>
</tr>
<tr>
<td>Tau load</td>
<td>Higher tau load (in medial temporal cortex!)</td>
<td>Low tau load in cortex and striatum</td>
</tr>
<tr>
<td>Cortical LB load</td>
<td>Higher in temporal &amp; parietal cortex, hippocampus</td>
<td>Diffuse or focal</td>
</tr>
<tr>
<td>αSyn load (hippocampus)</td>
<td>CA2 more severely involved</td>
<td>CA 2/3 more frequently involved</td>
</tr>
<tr>
<td>SN neuronal cell loss</td>
<td>Preferentially in dorsolateral SNc</td>
<td>More severe, preferentially in medioventral SNc</td>
</tr>
<tr>
<td>Pedunculopontine cholinergic cell loss</td>
<td>Negative</td>
<td>In hallucinating PDD positive</td>
</tr>
<tr>
<td>5-HT1A receptor binding density in cortex</td>
<td>Higher</td>
<td>Lower</td>
</tr>
</tbody>
</table>

**Table 4: Summary of clinical, morphological, and functional changes in PDD and DLB.**

- αSyn causing additional symptoms that accelerate the disease course [96]. On the other hand, galanin upregulation within the basal forebrain cholinergic system in DLB, similar to that in AD but not in PDD, may represent an intrinsic adaptive response to neurodegeneration of these areas [97]. Indices of reduced cortical cholinergic innervation in DLB are similar to PDD and lower than in AD [98]. Cortical cholinergic activity was lower in hallucinating compared to nonhallucinating DLB cases, while SET activity was relatively preserved [99].

- Severe pathology also involves the noradrenergic locus ceruleus (LC) [100] and the serotoninergic dorsal raphe nucleus [101] as well as the ventral tegmental area not always associated with coincidental AD lesions [102]. LC neuronal loss and the accompanying norepinephrinergic deficiency are an important cause and pharmacological target for the (symptomatic) treatment of PD/PDD/DLB [103,104]. The prominent role of serotoninergic degeneration also involving the anterior caudate nucleus, the orbitofrontal and cingulate cortex for neuropsychiatric symptoms in PD [105], emphasizes its important role in both PDD and DLB, and stimulates new insight into novel treatments by modulating 5-HT receptors [106].

Whereas dopamine dysfunction has been highlighted because of its obvious role in PD/PDD/DLB, the role of the other neurotransmitter systems in the pathogenesis of cognitive impairment in these LB disorders has not yet been sufficiently explored, but its close relation-
ship with combined LB and AD-pathologies suggests synergism of variable pathogenic mechanisms in the clinical manifestation of these disorders [82].

Pathogenesis

The clinicopathological features of DLB, PDD and other synucleinopathies are highly variable and heterogeneous [107], documented by 4 current staging systems in use for LB disorders, one for PD [108,109], another one for DLB [110], revised guidelines [13,111,112], and a recent one [68]. Based on semiquantitative assessment of LBs, a staging of the chronological spread of pathology was proposed to designate its predictable caudorostral spreading [113], which, however, is not identical with the spreading of αSyn pathology [114]. The McKeith criteria distinguish between three types: (1) Brainstem-predominant LB pathology corresponding to classical PD with low probability of developing clinical dementia; (2) Limbic or transitional type (DLB), in which clinical dementia may be associated with severe AD-related pathologies, and (3) Diffuse neocortical LB pathology (Braak LB stages 5 and 6), strongly associated with clinical dementia. These criteria differ from Braak LB stages insofar as they do not strictly postulate a stepwise progression of αSyn pathology from the olfactory bulb and medulla to midbrain, limbic areas and neocortex correlating with clinical dementia [115], since cases may show severe neocortical αSyn pathology with only minimal involvement of brainstem regions [116]. Moreover, this differs from the changes in DLB, where Parkinsonism develops an average of 2 years after the onset of cognitive symptoms with a reported prevalence of parkinsonism between 66% and 92% [117].

Transcellular propagation of protein aggregate «seeds» has been proposed to mediate the progression of neurodegeneration in tauopathies and synucleinopathies [118,119]. This «prion-like» transmission of αSyn and other pathological proteins, appears also essential for the pathogenesis of both PDD and DLB [115,119-121]. It has been suggested that distinct species of αSyn are responsible for propagation and differences of regional distribution of lesions in various synucleinopathies [122], and that different strains of pathological αSyn are involved in the heterogeneity of synucleinopathies [123]. This has been confirmed by recent studies demonstrating that distinct αSyn strains are determined by both misfolded seeds and intracellular environments [124] and that different types of αSyn assemblies have a unique and causative role in distinct synucleinopathies [125-127].

Management

Currently, no disease-modifying therapies of LB dementias are available. Clinical management of both disorders include cholinesterase inhibitors (ChEIs) to treat cognitive and psychiatric symptoms [128,129]. Although the effects of ChEIs were relatively small [130], they gave a better response of cognitive impairment in DLB and PDD than in AD [131]. The use of antipsychotics should be avoided given the risk of serious reactions in DLB [13], while atypical antipsychotic agents like quetiapine and clozapine less likely may exacerbate parkinsonism. Levodopa was generally well tolerated, but produced less motor response in DLB than in PDD [132] and may increase the risk of psychosis [128]. Bilateral deep brain stimulation of the nucleus basalis of Meynert for PDD showed no improvement in primary cognitive outcomes [133]. A recent review of nonpharmacological interventions did not offer any definite recommendations [134]. Future therapeutic strategies might include disease-modifying methods, based on vaccination trials against αSyn, Aβ and tau proteins [135,136], inhibition of αSyn aggregation or promoting degeneration, prevention of cell-to-cell transmission of pathological αSyn, deep brain stimulation of the cholinergic nucleus basalis of Meynert or transcranial current stimulation [137,138]. Preliminary results of anti-αSyn-immunotherapy in a combined model of synucleinopathy [139] may open the way to potential new treatments.

Conclusion and Future Outlook

DLB and PDD are multi-faced neurocognitive disorders with LB and AD-related pathologies, sharing many clinical, genetic, morphological, histochemical, neuroimaging, and pathogenetical features. Up to now, a clear and definite distinction between the two entities other than the arbitrary timing of the appearance of motor and cognitive impairments (1-year rule) has not been achieved [4,13], and the recent Movement Disorder Society (MDS) Panel has rather confused than clarified the distinction between the two disorders [140]. In view of the clinical and neuropathological heterogeneity of both disorders that share a similar if not identical pathogenesis and pathophysiology, the question whether the 1-year rule may be a biologically valid distinction or whether they are subtypes of a continuum of LB disorders awaits further elucidation. Despite validated criteria for DLB and PDD [5,13,141], in almost 50% of the cases, the clinical diagnosis is incorrect [142,143], whereas the specificity was below 60% [144]. The sex ratio in DLB is balanced between AD and PDD and, thus, also suggests that DLB is a distinct disease with characteristics intermediate between AD and PD [145], while recent MRI findings indicate that DLB is more similar to AD than to PDD [146].

The available clinical and morphological data clearly indicate that in DLB, the topographical spreading pattern of αSyn/LB pathology differs from that of PDD indicating pathogenic differences between them [147]. Despite considerable overlap between both conditions, recent studies have demonstrated differences in the quantity and distribution pattern of both αSyn and AD-related pathologies, with higher Aβ and tau load in cortical and subcortical areas in DLB, indicating an overlap between
effort is necessary to differentiate them more clearly and to clarify the underlying pathogenic mechanisms to enable effective treatment, while, currently, no disease-modifying therapies are available.

Conflict-of-Interest Statement

The author has no conflict of interest to declare.

Acknowledgement

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References


Core tip

Dementia with Lewy bodies (DLB) and Parkinson’s disease-dementia (PDD) are two closely related neurocognitive disorders with overlap in their clinical, morphological and pathogenic features. Their diagnosis is based on an arbitrary distinction between the time of onset of motor and cognitive symptoms (“one-year rule”) related to a variable mixture of Lewy body and Alzheimer-related pathologies, and multiple neurotransmitter deficits. DLB and PDD are suggested to represent subtypes of an α-synuclein-associated disease spectrum (Lewy body diseases) or parts of a continuum showing strong pathogenic correlations with Alzheimer’s disease. The nosology of both disorders is a matter of discussion, their differential diagnosis can be challenging and much

Figure 1: Spectrum of Lewy body diseases with relations between Braak LB and Braak neuritic (NFT) stages ranging from iLBD to DLB/AD. Modified from [2].

LB: Lewy Body; NFT: Neurofibrillary Tangle; iLBD: Incidental Lewy Body Disease; PD/ND: Parkinson Disease - Not Demented; PDD: Parkinson’s Disease-Dementia; DLB: Dementia with Lewy Bodies; DLB/AD: DLB with Alzheimer Disease; AD Alzheimer’s Disease.


