

Review

Dementia with Lewy bodies – a clinicopathological update

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Abstract

Dementia is one of the major burdens of our aging society. According to certain predictions, the number of patients will double every 20 years. Although Alzheimer's disease (AD), as the most frequent neurodegenerative dementia, has been extensively analysed, less is known about dementia with Lewy bodies (DLB). Neuropathological hallmarks of DLB are the deposition of intracellular Lewy bodies (LB) and Lewy neurites (LN). DLB belongs to the α -synucleinopathies, as the major component of these inclusions is pathologically aggregated α -synuclein. Depending on the localization of LBs and LNs in the central nervous system cognitive and motor symptoms can occur. In our work, we will systematically review the possible etiology and epidemiology, pathological (both macroscopic and microscopic) features, structural and functional imaging findings, with a special emphasis on the clinico-pathological correlations. Finally, we summarize the latest clinical symptoms-based diagnostic criteria and the novel therapeutic approaches. Since DLB is frequently accompanied with AD pathology, highlighting possible differential diagnostic approaches is an integral part of our paper. Although our present knowledge is insufficient, the rapid development of diagnostic and research methods provide hope for better diagnosis and more efficient treatment, contributing to a better quality of life.

Keywords: α -synuclein, Biomarkers, Diagnostic criteria, Clinico-pathological correlation, Dementia with Lewy bodies

Abbreviations

AA, Alzheimer's Association; **AD**, Alzheimer's disease; **A β** , Amyloid-beta; **APOE**, Apolipoprotein E gene; **BNE**, BrainNet Europe Consortium; **BOLD**, Blood oxygen level dependent; **ChAT**, Choline-acetyltransferase; **ChAT-I**, Acetyl-cholinesterase inhibitors; **CR**, Creatinine; **CSF**, Cerebrospinal fluid; **DLB**, Dementia with Lewy bodies; **DMN**, Default mode network; **DSM**, Diagnostic Statistical Manual; **fMRI**, Functional MRI; **FP-CIT**, [123I] 2 β -carbomethoxy-3 β -(4-iodophenyl)-N-(3-fluoropropyl) nortropane; **GBA**, Glucosylceramidase-beta gene; **iLBD**, Incidental Lewy body disease; **LB**, Lewy-body; **LBDA**, Lewy Body Dementia Association; **LN**, Lewy neurite; **MAPT**, Microtubule associated protein tau gene; **MDS**, Movement Disorders Society; **MRI**, Magnetic resonance imaging; **NAA**, N-acetyl aspartate; **NCD**, Neurocognitive disorder; **NF**, Neurofilament; **NIA**, National Institute on Aging; **NMDAR**, N-methyl-D-aspartate receptor; **PD**, Parkinson's disease; **PDD**, Parkinson's disease dementia; **PET**, Positron emission tomography; **PSD95**, Density protein 95; **REM**, Rapid-eye-movement; **SCARB2**, Scavenger Receptor Class B Member 2; **SNARE**, SNAP (Soluble NSF Attachment Protein) Receptor; **SNCA**, α -synuclein gene; **SPECT**, Single-photon emission computed tomography; **SSRI**, Selective serotonin reuptake inhibitors; **UPR**, Unfolded protein response; **WML**, White matter lesions; **ZnT3**, Zinc transporter 3

Epidemiology and etiology

Dementia with Lewy bodies (DLB) is the second most common primary neurodegenerative dementia. The etiology is mainly unknown, however, in certain cases there is strong evidence of genetic background. A few papers have reported families with accumulating occurrence of cognitive impairment throughout generations¹. The vast majority of the familial cases are traced to α -synuclein (*SNCA*) gene alterations, particularly to E46K mutation². Five candidate genes, including *APOE*, *GBA*, *MAPT*, *SNCA* and *SCARB2*, are considered as a significant risk factor for DLB, nevertheless, further genetic studies are needed³. Although it mostly appears in older age, dementia is not strictly associated with aging. Rarely it may occur under the age of 65 and even in young adulthood. Surprisingly in the case report of a teenager, the clinical symptoms and *post-mortem* pathological findings were consistent with those of in DLB⁴. The prevalence of the disease is not clearly established. According to a comprehensive analysis of epidemiological data, the prevalence is 4.2% in community based and 7.5% in clinical studies, while the incidence is 3.8% and grows linearly with aging⁵, while the prevalence of DLB among patients with dementia is probably around 15%⁶.

Pathologic background

1. Macroscopic observation

Many of the general pathologic features resemble those in Parkinson's disease (PD). The brain weight is often within the normal limits, mild cortical atrophy of the frontal lobe, neuromelanin pigment loss in the substantia nigra and locus coeruleus are noted. In the case of severe concomitant AD pathology, atrophy of the temporal and parietal regions is more evident. In contrast to AD, the general brain atrophy is less prominent in DLB along with the relatively preserved temporal lobe and hippocampus⁷.

2. Microscopic features

Lewy bodies (LBs), the key pathological findings in DLB, were initially described by Friedrich Lewy in 1912⁸. However, LBs are characteristic of other neurodegenerative diseases including PD. Their typical appearance, stained with conventional hematoxylin-eosin, is a central spherical eosinophilic core surrounded by a peripheral halo situated intracellularly, causing dislocation of sub-cellular organs. These features are regularly found in brainstem predominant LB formation. The rest of the brain expresses rather irregular LBs without the typical peripheral halo (Figure 1).

Histopathologically, the dominant component of the central core is α -synuclein, while the peripheral halo consists of several ubiquitinated proteins⁹. Lewy neurites (LNs), as an additional hallmark of α -synucleinopathies, are abnormal thickened neurites containing filaments corresponding to those in LBs¹⁰. Interestingly, in experimental mouse models mutant *SNCA* inoculation of wild type mouse causes LB/LN-like pathology, supporting the pathognomonic role of the protein¹¹. The background of LB genesis is still undiscovered, although numerous hypotheses have been proposed trying to explain the proper mechanism. According to the aggresome hypothesis, LB formation is originally a neuroprotective process, facilitating the cells to remove harmful proteins¹². However, failure of the aggresome formation may occur, leading to excessive LB development¹³. Other authors presume that autophagy dysfunction is responsible for the neuronal loss¹⁴. A recent study suggests that the increased unfolded protein response (UPR) activation has an important role in the LB pathology¹⁵. Nevertheless, according to Tompkins *et al.* neurons burdened with LBs are less apoptotic¹⁶. Moreover, the downregulation of tyrosine hydroxylase enzymes protects against toxic products of dopamine oxidation¹⁷. These findings confirm the theory that α -synuclein is physiologically involved in the maintenance of cell homeostasis

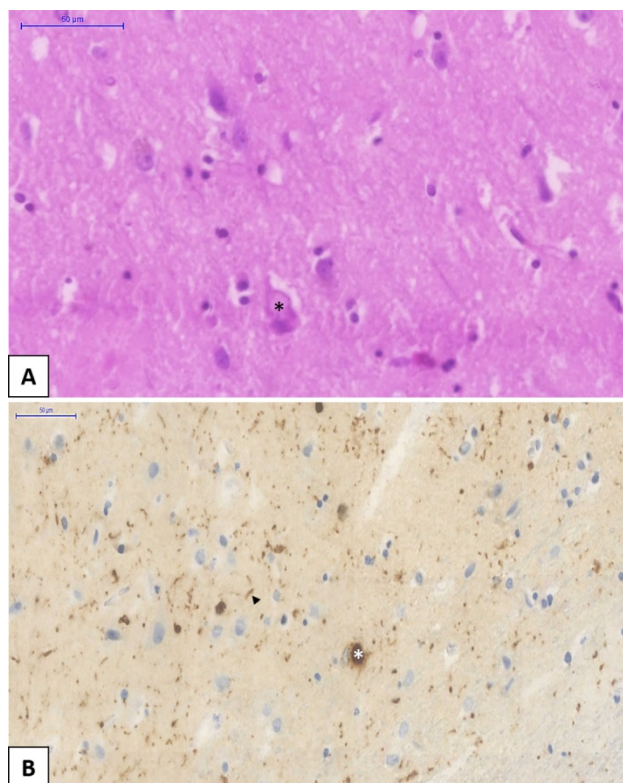


Figure 1. Dementia with Lewy bodies (DLB) specific pathological changes are shown with hematoxylin and eosin (HE) staining (Panel A) and α -synuclein immunohistochemistry (ICH) (Panel B). Cortical-type Lewy bodies (LBs) are eosinophilic intracellular neuronal inclusions which dislocate the nucleus (Panel A, black star). α -synuclein ICH highlights LBs (white star, Panel B) and LNs (arrowhead, Panel B).

The first standardized criterion assessing the connections between pathological findings and DLB was made by Kosaka *et al.* in 1984. Based on the anatomical distribution of pathology they determined three different subtypes: i) brainstem predominant LBs (commonly in PD) ii) limbic (transitional) LBs and iii) diffuse cortical LBs¹⁸. Later the Consortium on DLB International Workshop has improved the original assignment and published a more detailed instruction emphasizing the importance of the diagnostic procedure. The widely used immunohistochemical markers, α -synuclein (the most specific) and p62 serve the accurate pathological diagnosis¹⁹. The latest McKeith diagnostic consensus criteria recommends a semiquantitative grading of 10 different brain regions (dorsal motor nucleus of Vagus, locus coeruleus, substantia nigra, nucleus basalis of Meynert, amygdala, transentorhinal and cingulate gyri, temporal, frontal- and parietal lobes) based on the lesion density instead of the previously used LB counting method. Moreover, it suggests two additional categories, the amygdala-predominant and the olfactory bulb only DLB. According to the distribution of LB pathology on α -synuclein immunostained slides, the scoring system

distinguishes four stages: 1 – mild (sparse LBs or LNs); 2 – moderate ($1 < \text{LBs}$ in a low power field and sparse LNs); 3 – severe ($4 \leq \text{LBs}$ and scattered LNs in a low power field); 4 – very severe (numerous LBs and numerous LNs). Finally, as a synthesis of score and localization it ranks the seen pathology into one out of the three previously mentioned subtypes²⁰. Besides the McKeith staging and subtyping, the other widely used evaluating technique is the Braak staging²¹. The authors proposed to assess the severity of Lewy-type pathology labelled by α -synuclein immunostaining in 13 different brain areas (dorsal motor nucleus of Vagus, locus coeruleus, raphe, substantia nigra, CA2 region of hippocampus, nucleus basalis of Meynert, transentorhinal-, cingulate- and insular gyri, temporo-occipital-, temporal-, frontal- and parietal lobes). Considering that neither McKeith nor Braak protocol could reach more than 80% inter-observer agreement; the original methods have been modified by Leverenz *et al.*²² and Müller *et al.*²³, respectively. However, their results did not lead to a significant improvement in the scoring systems. Thus, in 2009 the BrainNet Europe Consortium (BNE) revised their former assignments and suggested modifications, to reach a better inter-observer agreement. Using the original McKeith and Braak staging, but eliminating their major pitfalls and obstacles as well as introducing the amygdala predominant category, BNE's novel strategy resulted in above 80% agreement in both typing and staging of α -synuclein pathology²⁴. Beach *et al.* also published their unified staging system with the aim of dividing every subject with Lewy-type α -synuclein pathology into a well-defined neuropathological group²⁵. In 2009 they used McKeith²⁶ and Braak²¹ staging systems and failed to categorize individuals with olfactory bulb or limbic-predominant LB pathology. Investigating 10 standard brain regions they could classify all patients with PD, DLB, incidental Lewy body disease (iLBD) and AD with concomitant LB pathology into one of the following stages: I Olfactory Bulb Only; IIa Brainstem-predominant; IIb Limbic-predominant; III Brainstem and Limbic; IV Neocortical. Moreover, they found strong correlation between the progression through these stages and the severity of nigrostriatal degeneration, cognitive impairment and motor dysfunction. It should be noted that olfactory bulb only and amygdala-predominant subtypes are also included in the current McKeith criteria²⁰. As mentioned above, AD pathology is frequently encountered in DLB. Approximately 80% of patients have diffuse amyloid-beta ($A\beta$) plaques and 60% have neurofibrillary tangles with varying severity in the entorhinal cortex and rarely in the neocortex. Some of these cases meet the pathological criteria of AD²⁷. In contrast, "pure" neuropathological form of DLB is less common. Autopsy series suggest that the frequency of this entity is approximately 25% of all DLB cases^{28,29}.

LB pathology	Alzheimer pathology NIA-AA/ Braak stage			
	None, low / Braak 0-II	Intermediate / Braak III-IV.	High / Braak V-VI.	
<i>Brainstem-predominant</i>	High	High	Intermediate	Likelihood of DLB clinical syndrome
<i>Limbic (transitional)</i>	High	Intermediate	Low	
<i>Diffuse neocortical</i>	Low	Low	Low	
<i>Amygdala-predominant</i>	Low	Low	Low	
<i>Olfactory bulb only</i>	Low	Low	Low	

Table 1. Likelihood of Dementia with Lewy bodies (DLB) clinical syndrome resulting from the assessment of Alzheimer’s-type and Lewy body pathology (LB= Lewy body; DLB=Dementia with Lewy bodies; NIA-AA = National Institute on Aging – Alzheimer’s Association) [Modified from McKeith *et al.*²⁰]

Theoretically, the likelihood to manifest DLB clinical syndrome is directly proportional to the severity of LB pathology and inversely proportional to the severity of AD pathology. The McKeith classification integrates the assessment of concomitant AD pathology by National Institute on Aging and Alzheimer’s Association (NIA-AA)³⁰, the Braak criteria and the type of LB pathology²⁰. Table 1 shows the probability of pathological findings in relation to DLB clinical syndrome. It is likely that not only the α -synuclein pathology is responsible for the cognitive decline, but plaques and phosphorylated tau proteins also contribute to the overall deficit³¹.

Cognitive impairment is also a common hallmark of DLB and Parkinson’s disease dementia (PDD). These two neurocognitive disorders share several clinical and neuropathological features, i.e. they are both characterized by cortical and subcortical α -synuclein/LB, β -amyloid and tau pathologies³².

According to Jellinger *et al.*, a common pathophysiology in DLB and PDD is synaptic dysfunction due to aggregation of α -synuclein in the presynapses. This results in disruption of axonal transport and neurotransmitter deprivation leading to neurodegeneration³². Interestingly, there are some morphologic differences as well. DLB seems to show higher load of β -amyloid and tau in several brain regions primarily in striatum, cortex, claustrum, amygdala and putamen compared to PDD³². Jellinger *et al.* also describes that α -synuclein distribution is different in DLB and PDD where α -synuclein load

was highest in hippocampal subarea CA2 and in amygdala in DLB, whereas in PD it is highest in the cingulate cortex. Moreover, nigral neuronal loss is more marked in PDD which ultimately results in dopaminergic upregulation³². A simple interpretation of above findings could support the current diagnostic criteria where DLB is associated with early cognitive impairment including memory problems, which differs from PDD with mainly motor impairment in the early phase.

In reality, it is not easy to define DLB based upon only the histological findings, thus in uncertain cases, anamnestic clinical data has invaluable support for the diagnostics. It is important to highlight that the listed strategies are not absolute or perfect diagnostic criteria, but rather useful schemes to predict the clinical syndrome of DLB based on the observed pathological findings. As mentioned above, a major weakness of current guidelines is the low inter-observer agreement; therefore further research is needed to assess the accuracy of the current clinical diagnostic criteria versus neuropathology similar to studies assessing the 2005 criteria in this respect³³.

3. Synaptic alterations

In connection with the dopaminergic neuronal loss of substantia nigra, dopamine transporter level is decreased in the striatum in DLB, although not to the same extent observed in PD³⁴. The choline-acetyltransferase

(ChAT) levels are lower than in patients with AD, who suffer from similarly severe dementia^{35,36}. Interestingly, Dynamin-1, which takes part in the regulation of synaptic transmission, shows significantly decreased levels in the prefrontal cortex in parallel with the severity of cognitive decline³⁷. In addition, the amount of zinc transporter 3 (ZnT3) and postsynaptic density protein 95 (PSD95), are significantly reduced in DLB compared to aged-controls and patients with AD^{38,39}. It should be noted that at the beginning of the disease, an upregulation of soluble NSF attachment protein receptors (SNARE) complex is observed, probably as a compensatory response to the synaptic loss. However, during the progression of DLB synaptotagmin, synapsin and synaptophysin, proteins involved in the SNARE complex steadily disintegrate, contributing further to synaptic dysfunction^{40,41}. Recent studies have revealed that more than 90% of α -synuclein aggregates are located at the presynapses leading to neurotransmitter deficits^{42,43}. These findings suggest that degeneration of postsynaptic neurons may result from the loss of their inputs. This theory serves as a potential explanation for the DLB-specific clinical symptoms as well as raises the possibility of future curative treatments by pharmaceutical modification of neurotransmission.

4. Incidental Lewy-body disease (iLBD)

In iLBD, patients have histologically detectable α -synuclein deposits in their brain, without presenting any clinical symptoms. Researchers accept that iLBD, which appears in approximately 8-17% of the clinically normal 60+ years old patients, is the early stage of PD or DLB^{44,45}. Confirming this hypothesis, it is frequently observed in patients who represent the prodromes of PD, including olfactory dysfunction or bowel frequency^{46,47}. The presence of neuronal loss is usually minimal in these cases contrary to PD or DLB⁴⁸. Distribution of α -synuclein pathology in iLBD is particularly predictive, i.e. the brainstem predominant subtype frequently results in PD, while the cortical predominant subtype often leads to DLB⁴⁴.

Clinical symptoms

The new Diagnostic Statistical Manual (DSM-5) (published in 2013) created a new neurocognitive disorder (NCD) group, replacing the former 'dementia, delirium, amnesic and other cognitive disorders' category, that were used in the previous DSM-IV handbook. The definition emphasizes that NCD is a progressive, acquired decline; which implies that disorders occurring at birth or at the early stage of cognitive development are

excluded from this category. As an advantage, the new handbook removed the stigmatizing debilitating term, dementia. Within the NCD there are two subcategories: major and mild neurocognitive disorders based upon the severity of decline. For the diagnosis, six main fields are examined by DSM-5: complex attention, executive function, learning and memory, language, perceptual motor or social cognition⁴⁹.

In the case of DLB, patients show both cortical and subcortical progressive dementia symptoms. Characteristic features comprise of attention and spatial perception disorder, dysexecutive syndrome, fluctuating cognitive performance lasting from minutes to days. Among the psychiatric alteration the most frequent is the visual hallucination, although anxiety, apathy or organised delusions could also be detected.^{50,51} Interestingly, advanced cerebral amyloid angiopathy and small vessel disease are associated with psychosis in AD and not in DLB⁵². Depression is more common in patients with DLB than in patients with AD. It may accompany with mild dementia, although more frequent in cases of advanced DLB^{53,54}. The vast majority of the patients, from the beginning or during the progression, show extrapyramidal signs, such as action tremor, gait disturbances, rigidity or changes in facial expressions⁵⁵. Rapid-eye-movement (REM) parasomnia is frequently diagnosed in DLB, characterised by vivid, often frightening dreams and complex purposeful motor activity. Since it often appears in different neurodegenerative disorders, REM parasomnia might be an early herald of these diseases⁵⁶. In DLB the autonomic nervous system dysfunction is more severe than in AD. Patients usually complain of dizziness, falls or loss of consciousness. Orthostatic hypotension, cardioinhibitory carotid sinus hypersensitivity and urinary incontinency often accompany with DLB⁵⁷. Pathognomonic feature is the neuroleptic hypersensitivity, triggered by even a small dose of drug, leading to severe parkinsonism²⁰. A 5-year prospective cohort study published by Rongve *et al.* has reported that the progression of cognitive decline from mild to severe stage is more rapid in patients with DLB than in patients with AD⁵⁸.

Many clinical symptoms of DLB cannot be explained only by the intracerebral localization of LBs and LNs³³. Neurotransmitter depletion, synaptic alterations, concomitant AD-type pathology and metabolic changes highly influence the clinical presentation of DLB, and correlate with the severity of cognitive decline^{6,42,59,60}. Moreover, a recent paper has reported association of serum potassium levels with cognitive decline in DLB, specifically in patients not using any medications that affect serum K⁺ levels⁶¹. Reduced perfusion and dysconnectivity of the occipital lobe may contribute to visual hallucinations and disturbance of visuospatial orientation^{62,63}. REM sleep behavior disorder (RBD) is also asso-

ciated with striatal dopamine depletion⁶⁴. Vegetative dysfunctions (i.e. orthostatic hypotension) may result from the deposition of LBs in the autonomic ganglia⁶⁵. Decreased ZnT3 levels were also identified in patients with depression, providing a novel therapeutic target^{38,66}. Interestingly, several clinical symptoms of DLB are transient in nature, however LBs and LNs permanently occur in the brain. Probably, metabolic disturbances⁶⁷, hormonal alterations⁶⁸, circadian rhythm⁶⁹ and comorbidities such as high blood pressure⁷⁰ can affect the clinical appearance of DLB.

Radiologic features

Besides the clinical symptoms, the most significant diagnostic tool in the identification of DLB is the rapidly developing imaging techniques. The numerous reachable modalities allow both structural and functional examination.

Magnetic resonance imaging (MRI) examination

Regarding the structural changes, the literature is not consistent: some studies have noted significant atrophy of the insular, frontal, inferior parietal, temporal or occipital cortex⁷¹, whereas others have found only a minimal volumetric decrease in the frontal and parietal lobe, or in the territory of hypothalamus, basal forebrain and midbrain⁷². However, these alterations are not specific to DLB and might appear in AD. Although differentiation from AD is usually based on the absence of medial temporal atrophy, its presence cannot rule out the diagnosis of DLB⁷³. Sabattoli *et al.* have found atrophic changes in the anterior CA1, CA2/3 hippocampus, subiculum and presubiculum in DLB. This pattern differs significantly from those in AD⁷⁴. According to an MRI study, the annual progression rate of cortical atrophy is approximately 2x higher in patients with AD⁷². The role of white matter lesions (WML) in DLB, including loss of myelin, axonal damage and gliosis is not consistent. Presumably, WMLs are implicated in vascular dementia rather than being specific feature of neurodegenerative disorders⁷⁵. MRI spectroscopy provides a chance to indirectly assess the neuronal and glial function by measuring the key metabolites. N-acetyl aspartate (NAA) and creatinine (CR) are two widely used markers in the characterization of central nervous system metabolism. Watson *et al.* have found that the NAA/CR ratio is relatively preserved in DLB in comparison to AD⁷⁶.

Functional imaging

Although, task-related functional MRI (fMRI) has been performed in very few cases of DLB, a paper has

reported reduced activity in response to movement activity compared with aged controls and patients with AD⁷⁷. Alternatively, researchers have examined the functional activity during rest. The resting-state network shows increased activity during rest and decreased activity during cognitive tasks. The most investigated resting-state network to date is the default mode network (DMN), including prefrontal cortex, posterior cingulate gyrus, medial temporal lobe and precuneus. In these areas the task-related deactivation during the colour and motion tasks were decreased in DLB, but it was not significantly different from AD⁷⁸. A technique for evaluation of functional resting state connectivity is based on the functional alterations in blood oxygen level dependent (BOLD) activity. Galvin *et al.* have noted increased resting state connectivity between precuneus seeding regions, inferior parietal cortex and putamen, with decreased connectivity between medial prefrontal, frontoparietal operculum and visual cortex⁷⁹. Taking into account that the results in DLB significantly differed from those of in AD, the method can be considered in the *in vivo* differential diagnosis.

The real value of perfusion imaging techniques in the identification of DLB is not fully consistent. The vast majority of the authors described occipital hypoperfusion as a hallmark of the disease on single-photon emission computed tomography (SPECT) images, whereas the specificity of the method is variable depending on the study⁸⁰. [123I] 2β-carbomethoxy-3b-(4-iodophenyl)-N-(3-fluoropropyl) nortropane (FP-CIT) could be useful to discover DLB in early stages before the full spectrum of clinical symptoms evolve, moreover it reliably identifies neurobiological changes in the dopaminergic system⁸¹. In DLB there is markedly reduced tracer uptake in the regions of caudate and putamen reflecting the severely affected dopaminergic system. Strong connection has been found between striatal FP-CIT uptake and certain clinical symptoms, such as depression, anxiety, apathy and daytime somnolence⁸².

Positron emission tomography (PET) is probably a more sensitive functional imaging technique than SPECT in different dementias. Ishii *et al.* have compared the two methods and found that PET is more reliable in the detection of occipital and parietal lobe hypometabolism⁸³. Besides the dopaminergic system, cholinergic transmission also has a crucial role in the pathomechanism of DLB, for instance in the alteration of memory, attention or arousal. Significant cholinergic neuronal loss and reduced ChAT activity are noted extensively in the cortical and subcortical regions, including both nicotinic and muscarinic systems, compared to AD³⁶. Shimada *et al.* have shown reduced ChAT enzymatic activity in the medial occipital cortex with relatively preserved temporal activity in DLB, in contrast to AD⁸⁴.

The fact that EEG is involved in the McKeith criteria further justifies its diagnostic relevance. Compared to AD the detectable slower background activity and more diffuse slow-wave activity probably reflect the severe cholinergic deficit in DLB⁸⁵.

Biomarkers

It is difficult to find specific biomarkers of DLB that would allow us to discriminate neuropathologically 'pure' forms of the disease from cases with concomitant AD pathology⁸⁶, as that majority of DLB cases show a combination of α -synuclein, tau and β -amyloid pathologies^{87,88}. However, novel biomarkers such as reduced electroencephalography activity⁸⁹ and the detection of RBD⁹⁰ also have some value.

Recent DLB biomarker research has focused on targets that are primarily related to AD. As in AD, CSF levels of A β 1-42 are decreased in DLB⁹¹, although tau seems to show an opposite relationship from AD⁹². That said tau has been shown to be higher in DLB when compared to PD and PDD^{87,93,94}.

DLB is considered α -synucleinopathy alongside with PD and PDD. When α -synuclein was discovered as a major component of LB this initiated a string of studies investigating α -synuclein as a biomarker in CSF^{95,96}. In general, some groups have reported reduced α -synuclein^{97,98} while others have shown contradictory results^{99,100}. These discrepancies may arise from the nature of α -synuclein expression. α -synuclein appears in four isoforms, (α -syn98, α -syn112, α -syn126 and α -syn140), based on alternative splicing of exon 3 and 5, and the largest isoform, α -syn140, is the most abundant isoform in the brain^{101,102}. Nonetheless, to overcome this issue several groups have tried using a combination of antibodies to quantify 'total' α -synuclein¹⁰³. In addition to this, many are convinced that oligomeric α -synuclein is potentially a more pathogenic form¹⁰⁴ and efforts have been made to measure this in both CSF and in plasma¹⁰⁵⁻¹⁰⁷.

In addition to α -synuclein and AD biomarkers, other potential biomarkers such as neurofilaments (NF) have been investigated¹⁰⁸. NFs are components within a cell that assists in maintaining the structural integrity. It has been shown that NFs are associated with AD and other degenerative disorders¹⁰⁹⁻¹¹¹, however that is not the case with DLB. NFs seem to provide only a general hint of neuronal and axonal dysfunction without providing any differential value to separate DLB from other disorders. On the other hand, other isoforms of NFs¹¹² do exist and would have to be further investigated in DLB.

Since there is greater involvement of the dopaminergic and serotonergic neurotransmitters in DLB compared to AD, several groups have investigated metabolites from these pathways. In combination with CSF A β 1-42, reduced levels of 5-hydroxyindolacetic acid and 3-methoxy-4-hydroxyphenylethylenglycol have been found in DLB compared with AD^{104,113}.

In summary, current studies suggest that DLB is intermediate to AD and PD, such that biomarkers from AD and PD have been tested in DLB with moderate success¹¹⁴. Likewise, new diagnostic proteins may be discovered in the future with further proteomic studies which could provide a better differentiation of DLB from other closely related neurodegenerative disorders¹¹⁵⁻¹¹⁷.

Diagnostic criteria

Considering the heterogeneous phenotype and the frequently associated AD pathology, the clinical symptom-based diagnosis of DLB is rather difficult. To date, there is no consensus on the guidelines for assessing clinical symptoms of DLB. A recent paper⁵⁸ recommends the following rating strategies: for evaluating cognitive decline – Clinical Dementia Rating scale¹¹⁸; for estimating fluctuating cognition – Clinician Assessment of Cognitive Fluctuations¹¹⁹ or Mayo Fluctuation Questionnaire¹²⁰; for investigating REM parasomnia – Mayo Sleep Questionnaire¹²¹; for rating parkinsonism – Unified Parkinson's Rating Scale¹²²; for testing disability – Rapid Disability Rating Scale-2¹²³; for diagnosing visual hallucinations or other psychiatric disorders – Neuropsychiatric Inventory¹²⁴; for measuring effects of comorbidities – Cumulative Illness Rating Scale¹¹⁸. Additional difficulty is to make a distinction, if it exists, between DLB and Parkinson's disease dementia. The question, whether DLB and PDD are different entities or the same one, is still debated. Although there are a few morphologic differences between them (e.g. cortical spreading of LBs or rate of neuronal loss in SN)¹²⁵, differential diagnosis is rather based on the temporal sequence of symptoms. If dementia occurs 1 year after the onset of extrapyramidal motor signs, it is considered as PDD, otherwise if dementia has proceeded or presented within 1 year after movement disorder, the diagnosis should be DLB¹²⁶. The latest McKeith diagnostic criteria define probable and possible DLB based on the clinical symptoms and biomarkers (Figure 2)²⁰. The presence of dementia, memory impairment and deficit of attention, executive functions and visuospatial orientation is essential for diagnosis. Core symptoms are frequently observed in DLB clinical syndrome; in the lack of at least one core feature, the probable DLB diagnosis

Essential symptoms	Supportive symptoms	Indicative biomarkers
<ul style="list-style-type: none"> Dementia Memory impairment Attention-, executive functions-, visuospatial orientation deficit 	<ul style="list-style-type: none"> Neuroleptic hypersensitivity Postural instability Repeated falls, syncope Autonomic dysfunctions (orthostatic hypotension, incontinency) Hypersomnia, Hyposmia Non-visual hallucinations Organized delusions Apathy, depression 	<ul style="list-style-type: none"> ↓DAT uptake of basal ganglia ↓MIBG scyntygraphy of myocardium PSG confirmed RBD
Core symptoms		Supportive biomarkers
<ul style="list-style-type: none"> Fluctuation of cognitive functions or attention Visual hallucinations Spontaneous parkinsonism REM sleep behaviour disorder 	<ul style="list-style-type: none"> Preservation of medial temporal lobe Generalized perfusion/metabolism ↓ on SPECT/PET and ↓occipital activity ± „cingulate island sign” Posterior slow-wave activity on EEG and periodic fluctuations 	
<p>Probable DLB: 2 or more core symptoms ± indicative biomarkers OR 1 core symptom + 1 or more indicative biomarker</p> <p>Possible DLB: 1 core symptom without indicative biomarker OR 1 or more indicative biomarker without core symptom</p>		

Figure 2.: Symptoms and biomarkers contribute to the diagnosis of probable or possible Dementia with Lewy bodies (DLB).

Essential symptoms are mandatory for diagnosis of DLB. Core clinical symptoms are characteristic to DLB, while supportive symptoms can confirm the decision by clinicians. Indicative biomarkers are frequently observed in DLB, while supportive biomarkers can facilitate the decision-making procedure. Important to note that clinicians cannot establish the diagnosis of probable DLB based on the biomarkers. (Recategorized or newly added features are highlighted in blue colour; REM = Rapid eye movement; DAT = Dopamine transporter; MIBG = Metaiodobenzylguanidine; PSG = Polysomnography; RBD = REM sleep behavior disorder; SPECT = Single-photon emission computed tomography; PET = Positron-emission tomography; EEG = Electroencephalography; ↓ = decrease). [Adapted from McKeith *et al.*²⁰]

cannot be established. The development of diagnostic techniques revealed that REM sleep behaviour disorder is more characteristic of LBD than it was previously thought. Therefore, McKeith *et al.* recategorized RBD from supportive to core features²⁰. Supportive features may help the clinicians; however, these symptoms are not specific to DLB and their presence is not required for the diagnosis of neither probable nor possible DLB. The refreshed criteria emphasize the importance of disease-specific biomarkers. One indicative biomarker itself is sufficient for possible DLB diagnosis. If one indicative biomarker associates with one core symptom, the diagnosis is probable DLB.

Therapy

There are two different therapeutic approaches: pharmacologic and non-pharmacologic. Although there is no curative treatment strategy, the adequate therapy may slow the disease progression with the chance of a better quality of life.

Non-pharmacologic interventions

At the first signs of DLB or mild NCD, installation of the below mentioned interventions are recommended.

Changes in the dietary habit, Mediterranean diet, and regularly performed social and mental tasks as well as physical activities could reduce the rate of progression¹²⁷. Personalized cognitive rehabilitation trainings with focus on the declined field, improve both quality of life and memory¹²⁸.

Pharmacologic treatments

The frequently noted extrapyramidal signs should be treated with the smallest effective dose of levodopa, to avoid the worsening of psychiatric symptoms¹²⁹. Selective serotonin reuptake inhibitors (SSRIs) are widely used and considered as effective medications for depression¹³⁰. In the case of REM sleep behaviour disorder, clonazepam and melatonin also have beneficial effect¹³¹. Acetyl-cholinesterase inhibitors (ChAT-I) have benefits in the treatment of psychiatric disturbances such as visual hallucination, delusions, behaviour disorders or apathy. Despite gastrointestinal side effects (i.e. vomiting, diarrhoea) these drugs are usually well tolerated²⁰. If ChAT-Is (rivastigmine, donepezil) are not effective, the use of atypical neuroleptic drugs (i.e. clozapine) might be inevitable, but typical neuroleptics should be avoided to minimize the possibility of severe neuroleptic hypersensitivity reaction¹³². ChAT-Is are more effective in patients

with DLB compared to patients with AD. These drugs improve the cognitive functions, reduce fluctuation, decrease the progression and in addition patients score better on neuropsychological tests¹³³. N-methyl-D-aspartate receptor (NMDA-R) antagonist memantine is also useful in the treatment of cognitive decline¹³⁴. Lucza *et al.* have suggested treatment with ChAT-Is in mild or mid-severe dementia and memantine combined with high dose of rivastigmine (13.5 mg) in severe dementia¹³⁵.

Summary

Despite the continuously growing incidence of dementia, which could be the most prevalent disease within 20 years in the industrialized world, our present knowledge is still insufficient to fully comprehend the underlying pathomechanism. This is particularly true for DLB, which is the second most common neurodegenerative dementia. Etiology of the disorder, its connection with aging, underlying pathomechanisms of clinical signs and imaging findings are still in need for further elucidation. Unfortunately, the definitive diagnosis is possible only by *post-mortem* histopathological examination and not by *in vivo* techniques (apart from a low percentage of cases). The concomitant Alzheimer's-type and vascular pathology raises issues regarding diagnostic clarity and accuracy¹³⁶. Future research should be multidisciplinary and should include pathological, proteomic, genetic and epigenetic approaches to identify the key factors of

the disease and reveal the correlation between clinical symptoms, radiological alterations and pathological findings. Development of imaging techniques brings the possibility of *in vivo* diagnosis, which implies adequate treatments in early stages, a crucial advancement to ensure better quality of life. Longitudinal cohort studies are also required to provide detailed prognostic information that are essential for planning a more effective and cost-efficient treatment protocol.

Author's contribution

Authors contributed equally to the work.

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