

THE ROLE OF RECENT BIOMARKERS IN THE EARLY DIAGNOSIS OF DEMENTIA WITH LEWY BODIES

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ABSTRACT

Dementia with Lewy Bodies is one of the most challenging neurodegenerative conditions in older adults, frequently underdiagnosed due to its phenotypic overlap with Alzheimer's disease and Parkinson's disease. This study synthesizes the primary molecular, imaging, and neurophysiological biomarkers that enable the early detection and pathological differentiation of this condition during prodromal phases. Through a critical review of contemporary biological consensus criteria, the disruptive role of Alpha-Synuclein Seed Amplification Assays in cerebrospinal fluid and peripheral tissues is analyzed, showcasing high diagnostic specificity *in vivo*. Additionally, the contribution of iodine-123-metaiodobenzylguanidine myocardial scintigraphy in identifying postganglionic sympathetic denervation and dopamine transporter imaging in evaluating striatal neuronal loss is examined. In the neurophysiological spectrum, the value of quantitative electroencephalography in identifying the slowing of posterior background activity is highlighted, correlating with characteristic cognitive fluctuations. It is established that transitioning from a purely clinical diagnostic model to an integrated bio-clinical approach is essential for identifying the disease in its earliest stages. This advancement facilitates the timely enrollment of patients in clinical trials for disease-modifying therapies and optimizes early, targeted therapeutic management.

Keywords: Alpha-synuclein, Dementia with Lewy Bodies, Early diagnosis, Fluid biomarkers, Molecular imaging.

INTRODUCTION

Morbidity Dementia with Lewy bodies (DLB), also known as Lewy body dementia, is a progressive neurodegenerative disease and part of the spectrum of synucleinopathies, alongside Parkinson's disease and Parkinson's disease dementia.^{1,2} DLB is estimated to account for approximately 5–10% of all dementia cases and 15–20% of primary neurodegenerative dementias, making it the second most common cause after Alzheimer's disease.^{1,3} From a neuropathological perspective, the disease is characterized by the presence of intracellular aggregates of phosphorylated α -synuclein, Lewy bodies, distributed throughout the cerebral cortex, brainstem, limbic system, and subcortical structures, frequently in association with Alzheimer-type pathology.^{1,4,5} The pathophysiology of DLB involves conformational changes in α -synuclein, a protein encoded by the SNCA gene and normally involved in regulating neurotransmitter release

at presynaptic terminals.^{2,6} Under pathological conditions, α -synuclein undergoes phosphorylation, oxidation, and cleavage, forming insoluble oligomers and fibrils that accumulate in Lewy bodies and trigger mitochondrial dysfunction, oxidative stress, and neuronal death.^{1,4,6} Experimental evidence suggests a “prion-like” propagation mechanism, with trans-synaptic spread of pathogenic α -synuclein species between connected regions, which contributes to the progressive nature and anatomoclinical distribution of the disease.^{4,6,7} The co-occurrence of β -amyloid deposits and hyperphosphorylated tau, as well as vascular pathology, is frequent and influences the clinical phenotype and disease course.^{3,8,9}

Clinically, DLB presents a heterogeneous picture, but four core features are considered central: recurrent well-formed visual hallucinations, marked cognitive fluctuations, parkinsonism, and REM sleep behavior disorder.^{1,2} Clinical studies and international consensus statements also highlight the high prevalence of neuropsychiatric symptoms, autonomic dysfunction, neuroleptic hypersensitivity, and deficits in visuospatial functions, executive attention, and visuoperceptual processing.^{2,3,10} These manifestations partially overlap with those observed in Alzheimer's disease and psychiatric disorders, making early recognition of DLB difficult, particularly in prodromal stages or atypical presentations.^{3,11,12}

The consensus diagnostic criteria for Dementia with Lewy Bodies (DLB), established in 2017, stratify cases as probable or possible through the combination of core clinical features, suggestive manifestations, and biomarkers.^{1,2} Probable DLB is diagnosed in the presence of two core features or, alternatively, one core feature associated with a suggestive biomarker—such as reduced dopaminergic uptake on FP-CIT SPECT, occipital hypometabolism on FDG-PET, or abnormalities on cardiac MIBG scintigraphy.^{1,4,13} In contrast, the category of possible DLB includes cases with only one core feature or combinations of suggestive findings in the absence of biomarker support, a scenario frequently observed in clinical practice in services with restricted access to advanced diagnostic technologies.^{3,10}

Epidemiological studies in different countries report prevalence rates ranging from 0.5 to 4.5% among patients with dementia in tertiary centers and from 0.02 to 0.34% in the general population, with an annual incidence of approximately 1.5–3.5 cases per 100,000 person-years.^{1,3} The mean age at onset is between the sixth and seventh decades of life, with a slight predominance in males, and survival after diagnosis is approximately 6–8 years, although there is considerable interindividual variability.^{1,3,12} The presence of co-pathologies, such as Alzheimer's disease and vascular lesions, negatively influences prognosis and is associated with greater functional burden and a higher risk of institutionalization.^{3,4,9}

Despite advances in clinical criteria, the diagnosis of DLB remains challenging, with more than half of cases initially classified as Alzheimer's disease, Parkinson's disease, or psychiatric disorders.^{1,2,11} The reasons include symptomatic overlap with other dementias, phenotypic variability, limited availability of biomarkers, and still insufficient familiarity among healthcare professionals with DLB-specific criteria.^{3,10,11} In this context, fluid biomarkers, neuroimaging biomarkers, and biomarkers derived from Alzheimer-type pathology have emerged as promising tools for improving diagnostic accuracy, early detection, and prognostic stratification.^{1,4,6} α -Synuclein seed amplification assays in cerebrospinal fluid, analysis of phosphorylated α -synuclein in skin biopsies, plasma markers of neurodegeneration and neuroinflammation, as well as dopaminergic and metabolic functional neuroimaging techniques, constitute a growing panel of tests under evaluation.^{6,7,13,14}

OBJECTIVES

General objective:

Analyze the role of recent biomarkers in the early diagnosis of dementia with Lewy bodies,

highlighting their diagnostic accuracy, clinical applicability, and potential to differentiate it from other neurodegenerative dementias.

Specific Objectives:

- Identify the most promising fluid biomarkers (cerebrospinal fluid and blood) for the early diagnosis of DLB.
- Evaluate the diagnostic accuracy of neuroimaging biomarkers (FP-CIT SPECT, FDG-PET, MRI).
- Compare the sensitivity and specificity of biomarkers in differentiating DLB from Alzheimer's disease.
- Discuss the limitations and future perspectives for the clinical implementation of biomarkers.

METHODOLOGY

This is a narrative review of the literature aimed at analyzing the role of recent biomarkers in the early diagnosis of dementia with Lewy bodies. The literature search was conducted in the PubMed/MEDLINE database, as it is one of the main sources of information in the health sciences and provides broad coverage of studies in neurology and neurodegeneration.

English-language terms related to dementia with Lewy bodies and biomarkers were used, combining free-text descriptors and indexed terms. The strategy included expressions such as "dementia with Lewy bodies", "Lewy body dementia", "biomarkers", "alpha-synuclein", "neuroimaging", "cerebrospinal fluid", and "plasma biomarkers", combined with Boolean operators in order to retrieve studies evaluating fluid biomarkers (cerebrospinal fluid and blood) and neuroimaging biomarkers in individuals with suspected or diagnosed dementia with Lewy bodies.

Articles published between January 2005 and December 2025 in English, Portuguese, and French were included. The inclusion criteria comprised human studies addressing biomarkers applied to the diagnosis or differential diagnosis of dementia with Lewy bodies and presenting relevant quantitative data, such as sensitivity, specificity, diagnostic accuracy, or related measures. Observational studies (cross-sectional, case-control, and cohort studies) and systematic reviews or meta-analyses focusing on biomarkers were considered. Publications conducted exclusively in animal models or in vitro, studies without numerical data on diagnostic performance, studies dedicated only to Alzheimer's disease or other dementias without specific analysis of dementia with Lewy bodies, as well as isolated case reports and very small case series without structured statistical analysis, were excluded.

The initial search identified 844 records. After reviewing titles and abstracts, studies that did not meet the eligibility criteria were excluded, resulting in a subset of articles selected for full-text review. In this second stage, the inclusion and exclusion criteria were applied again, with detailed verification of the methodological design and outcomes of interest. At the end of the process, 41 articles were considered eligible and included in the narrative synthesis, and were organized into three analytical groups: fluid biomarkers, neuroimaging biomarkers, and systematic reviews/meta-analyses.

RESULTS AND DISCUSSION

The Fluid Biomarkers: Cerebrospinal Fluid and Blood

Fluid biomarkers have emerged as key tools in the evaluation of synucleinopathies, including DLB, because they directly reflect ongoing neuropathological processes.^{6,15} Traditional measurements of total α -synuclein in cerebrospinal fluid have shown limited ability to discriminate DLB from healthy controls, although reduced levels are associated with the presence of Lewy bodies and tissue deposition of the protein.^{1,6} In contrast, seed amplification assays, such as α -syn RT-QuIC and similar seed amplification

assay techniques, have demonstrated high sensitivity and specificity in detecting pathogenic α -synuclein and in differentiating DLB from Alzheimer's disease.^{6,14} Recent studies suggest that these methods may achieve diagnostic accuracy above 90%, including in prodromal stages, although interlaboratory standardization and automation are still required.^{4,6,14} The detection of phosphorylated α -synuclein in cutaneous nerve fibers obtained by skin biopsy has become established as a promising peripheral biomarker for synucleinopathies, including Parkinson's disease and DLB.^{4,6} Multicenter studies indicate high concordance between cutaneous α -synuclein deposits and the clinical diagnosis of DLB, with potential to complement cerebrospinal fluid assessment in settings in which lumbar puncture is contraindicated or refused.^{4,6,10} However, aspects such as technical standardization of the biopsy procedure, availability of specialized immunohistochemistry, and reproducibility across centers still limit routine use.^{4,6}

In the field of plasma biomarkers, increased levels of neurofilament light chain (NfL) indicate generalized axonal neurodegeneration and have been consistently associated with the severity and progression of dementias, including DLB.^{6,15} Although NfL has high sensitivity for detecting neurodegenerative processes, its specificity for DLB is limited, requiring interpretation together with other markers and clinical data.^{6,9,15} Glial fibrillary acidic protein (GFAP) is emerging as a marker of astrogliosis and inflammation, with studies reporting elevations in neurodegenerative dementias and suggesting possible complementary value in DLB.^{6,15}

Plasma biomarkers related to amyloid and tau pathology, such as p-tau181, p-tau217, and p-tau231, have shown excellent performance in identifying Alzheimer's disease and distinguishing it from other dementias.^{8,15,16} Although they are not specific to DLB, these markers are useful for identifying Alzheimer-type co-pathology in patients with synucleinopathies, which has diagnostic and prognostic implications.^{8,9,15} Recent reviews indicate that the combination of plasma phosphorylated tau biomarkers with NfL and GFAP may provide a robust panel for risk stratification in settings of mild cognitive impairment and suspected DLB.^{6,9,15}

In addition, cerebrospinal fluid studies have explored the activity of enzymes involved in neurotransmitter synthesis, such as DOPA decarboxylase, suggesting that its measurement may assist in distinguishing DLB from Parkinson's disease in multicenter cohorts^{4,6}. Although these findings are preliminary, they point to a possible role for enzymatic markers in the more refined characterization of the synucleinopathy spectrum.^{4,6,14} Overall, fluid biomarkers offer substantial potential for the early diagnosis of DLB, especially when integrated with neuroimaging markers and Alzheimer's disease biomarkers in the development of multimodal algorithms.^{1,6,15}

Neuroimaging Biomarkers

Neuroimaging biomarkers constitute a fundamental pillar in the diagnostic assessment of DLB, allowing in vivo visualization of dopaminergic, metabolic, and structural changes.^{1,13,17} Dopamine transporter scintigraphy using ¹²³I-FP-CIT (DaTSCAN) is the most established examination, demonstrating sensitivity of around 80–90% and specificity above 90% in differentiating DLB from Alzheimer's disease in studies and meta-analyses.^{1,13} These findings supported the inclusion of reduced striatal dopamine uptake as a suggestive biomarker in the consensus criteria for probable and possible DLB.^{1,2,13} However, the usefulness of DaTSCAN in the prodromal phase remains under investigation, with lower performance in very early stages or in presentations with mild parkinsonism.^{1,4,12}

Cardiac scintigraphy with metaiodobenzylguanidine (MIBG) evaluates myocardial sympathetic innervation, which is frequently impaired in synucleinopathies, and has shown good accuracy in distinguishing DLB and Parkinson's disease from Alzheimer's disease and other dementias.^{1,4,17} Studies indicate that the combination of MIBG with DaTSCAN may increase diagnostic confidence in uncertain cases, although issues related to

radiopharmaceutical availability and expertise in interpretation still limit its widespread use.^{1,4,10}

FDG-PET, in turn, demonstrates a characteristic metabolic pattern in DLB, with hypometabolism in occipital regions and relative preservation of the posterior cingulate compared with Alzheimer's disease^{1,17}. Meta-analyses indicate that this pattern may assist in differential diagnosis in mild stages, particularly when integrated with clinical data and other biomarkers.^{9,13,17} More recent PET techniques targeting amyloid and tau deposits have also been explored in DLB, mainly to assess the burden of Alzheimer-type co-pathology, although their specific role has not yet been fully established.^{4,8,9}

On magnetic resonance imaging, conventional measures of volume and cortical thickness show less marked changes compared with Alzheimer's disease, but group studies describe reduced volume in structures such as the insula and occipital lobe in prodromal DLB.^{1,17} Advances in diffusion imaging, particularly free-water diffusion MRI, have revealed a progressive increase in free water in multiple brain regions over 12 to 24 months in patients with DLB, associated with clinical progression and suggesting usefulness as a monitoring marker and possibly as a prodromal-phase marker.⁷ These findings point to the potential of advanced MRI techniques in longitudinal assessment and prognostic refinement.^{7,17}

In summary, neuroimaging biomarkers offer high accuracy for differentiating DLB from Alzheimer's disease and other dementias, particularly when dopaminergic, metabolic, and structural examinations are combined.^{1,13,17} However, barriers such as cost, unequal availability of PET and SPECT, and the need for protocol standardization remain relevant, especially in healthcare systems with limited resources.^{3,4,11}

Alzheimer's Disease Biomarkers in DLB

The coexistence of Alzheimer-type pathology in patients with DLB is common and has important clinical implications, as it may mask core features of DLB and make recognition of the synucleinopathy more difficult^{1,4}. Alzheimer's disease biomarkers, such as A β 42, A β 40, total tau (t-Tau), and phosphorylated tau (p-Tau) in cerebrospinal fluid, as well as their plasma counterparts, have proven to be relevant tools for identifying these mixed cases^{8,15,16}. Studies suggest that Alzheimer-compatible profiles in patients with a clinical picture suggestive of DLB are associated with greater cognitive impairment, poorer prognosis, and a higher likelihood of atypical presentation.^{4,9} Meta-analyses indicate that t-Tau and p-Tau181 have excellent discriminatory ability between Alzheimer's disease and DLB, while ratios involving A β 42 and A β 40 contribute to differential diagnosis in early stages.^{8,9,16} In individuals with mild cognitive impairment, the combination of Alzheimer's disease biomarkers with synucleinopathy markers, such as α -synuclein amplification assays, may increase accuracy in predicting future conversion to DLB or Alzheimer's disease.^{6,9,14} Thus, the systematic integration of these biomarkers into diagnostic algorithms allows better classification of patients with mixed or less typical phenotypes.^{1,4,9}

Diagnosis of the Prodromal Phase

In recent years, there has been growing interest in defining criteria for prodromal DLB, with a focus on risk syndromes such as isolated REM sleep behavior disorder, mild cognitive impairment with a visuospatial/attentional profile, and early forms of parkinsonism with subtle cognitive manifestations.^{1,2,12} The aim is to identify individuals in pre-dementia stages, in which clinical interventions and future disease-modifying therapies may have a greater impact.^{1,2}

Biomarkers play a central role in this phase, as certain findings may precede the onset of established dementia by several years.^{1,7,12} Cerebrospinal fluid α -synuclein amplification assays have shown positivity in individuals with idiopathic REM sleep behavior disorder, indicating a high

risk of conversion to DLB or Parkinson's disease.^{6,14} Likewise, abnormalities on DaTSCAN, reduced MIBG uptake, and free-water MRI changes have been described in prodromal cohorts, suggesting that a set of biomarkers may define distinct risk profiles.^{1,7,13}

Limitations and Challenges

Despite significant advances, several challenges limit the full incorporation of biomarkers into the routine diagnosis of DLB.^{3,4,11} First, many of the most promising tests, such as α -synuclein amplification assays and some plasma biomarkers, still lack widely standardized protocols, making it difficult to compare results across centers and establish universal cutoff values.^{4,6,14} Second, cost, the need for specialized infrastructure, and unequal availability of sophisticated examinations such as PET and SPECT restrict access in low- and middle-income countries and even in peripheral regions of high-income countries.^{3,11}

Another limitation concerns the clinical and neuropathological heterogeneity of DLB, which is frequently associated with Alzheimer's disease pathology, vascular disease, and other comorbidities, reducing the specificity of some biomarkers when considered in isolation.^{1,4,9} In addition, much of the evidence derives from studies conducted at tertiary centers and in selected cohorts, limiting the generalizability of the results to primary or secondary care settings.^{3,10,11} Finally, there is still no consensus regarding which minimum combinations of biomarkers should be recommended in different clinical scenarios, nor regarding the best way to integrate these results into diagnostic decision-making and risk stratification models.^{4,11}

CONCLUSION

Recent advances in biomarker research have significantly transformed the diagnostic approach to dementia with Lewy bodies. Fluid biomarkers, functional neuroimaging methods, and markers of Alzheimer-type co-pathology expand the capacity for early diagnosis and refine differential diagnosis. From a clinical perspective, the most promising trend is the combined use of these biomarkers in multimodal algorithms, rather than the isolated interpretation of each test. This integration may increase diagnostic confidence, especially in prodromal presentations, mixed phenotypes, or cases overlapping with Alzheimer's disease and Parkinson's disease. However, limitations related to laboratory standardization, cost, technological availability, and the need for validation in larger cohorts still restrict their universal adoption. Thus, the consolidation of these biomarkers in clinical practice will depend on the development of harmonized protocols, greater accessibility, and the definition of diagnostic strategies adapted to the realities of different healthcare systems.

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