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Diagnosis of Dementia with Lewy Bodies: Fluctuations, Biomarkers, and beyond

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Abstract

Dementia with Lewy bodies (DLB), the second most common cause of dementia, remains a difficult condition to accurately diagnose and manage. Variable involvement of motor and cognitive functions, plus psychiatric and behavioral symptoms, contributes to the difficulty in managing DLB. Additionally, DLB can cause severe sleep disruption through REM sleep behavior disorder, autonomic symptoms, disruptions of olfaction/taste and mood, hallucinations, and more. In this chapter, advances and remaining challenges in the diagnosis of DLB are discussed, including a review of the current consensus criteria for DLB. The spectrum of disorders with Lewy bodies (LBs) are described including their wide-range of clinical presentations and overlap with Alzheimer's disease (AD) and Parkinson's disease with and without dementia. Particular consideration is given to advancements in quantification of cognitive fluctuations through improved clinical instruments, EEG, and other advanced biomarkers. Detection of DLB has improved, but establishing the "primary" pathology in cases with concomitant LB and AD remains difficult. Likelihood of a clinical DLB syndrome is thought to be a function of distribution of LBs and severity of AD-type pathology. Further work is needed to better understand LB disease subtypes and the underlying pathophysiological mechanisms to allow for more targeted and comprehensive therapies.

Keywords: dementia, Lewy body, quantitative EEG, cognitive fluctuations

1. Introduction

1.1 Background

Dementia with Lewy bodies (DLB) is now generally accepted to be the second most common cause of dementia [1–4] accounting for approximately 20% of cases in the Western world, second in prevalence to only Alzheimer's disease (AD) (which is usually accompanied by some degree of cerebrovascular disease) [5]. Yet, it remains a difficult condition to accurately diagnose and manage. Highly sensitive and specific biomarkers from blood or cerebrospinal fluid (CSF) have been elusive and lag behind recent progress in AD. Management is challenging due to variable involvement of motor and cognitive function plus psychiatric and behavioral

symptoms. Optimal management of motor parkinsonism is a very complex topic, worthy of textbook-length discussion, and DLB patients are generally not responsive (or only mildly responsive) to dopaminergic therapies. On top of this, DLB can cause severe disruption of sleep with REM sleep behavior disorder (RBD), autonomic symptoms, disruptions of olfaction/taste and mood, hallucinations, and more. Furthermore, these patients often have adverse effects of medications such as neuroleptic sensitivity, even to atypical antipsychotics, worsening of orthostatic hypotension by L-Dopa, and behavioral disinhibition to clonazepam and other benzodiazepines taken to treat RBD.

After reviewing the composition and regional distribution of Lewy bodies, this chapter will focus on the advances and remaining challenges in the diagnosis of DLB, rather than therapies and management, for which the reader is referred to other chapters in this volume. The spectrum of disorders with Lewy bodies will be described, with their wide range of clinical presentations and overlap with AD, as well as Parkinson's disease (PD) with and without dementia.

1.2 Scope and methods

This chapter reviews current consensus diagnosis criteria for dementia with Lewy bodies (DLB). This diagnosis can be challenging, especially if reliant on clinical criteria alone. Differentiation from PD with dementia (or without dementia) can be challenging and vague. Diagnosis in the setting of centers that focus on Alzheimer's disease or memory loss is particularly difficult as diagnostic criteria are less sensitive in these cohorts and some dementia cases with superimposed Lewy body (LB) pathology may only have a hint of the typical DLB or PD phenotype, or sometimes no attributable symptoms to their LB pathology. The 2017 DLB diagnostic criteria advanced the field by adding a category of "indicative biomarkers," and these are assigned equal diagnostic weight to the four core clinical features (fluctuating cognition, recurrent visual hallucinations, REM sleep behavior disorder (RBD), one or more cardinal features of parkinsonism).

This chapter will review the wide range of clinical presentations seen in Lewy body disease (motor, cognitive, and behavioral/psychiatric). The 2017 DLB diagnostic criteria will be reviewed in detail and the validation of these criteria and previous diagnostic criteria, for which there is greater neuropathological validation in the literature, will be critically reviewed. Advances in diagnosis will be reviewed, particularly in the areas of better quantification of fluctuations (made possible by electrophysiologic EEG studies and improved clinical instruments) and advanced biomarkers (including radionuclear imaging studies, polysomnography, CSF, and other biospecimens).

1.2.1 Literature search methods

This chapter was outlined by JMO. All coauthors participated in English literature searches conducted on PubMed and Google Scholar in January–February 2021. Search terms included: "incidence of Parkinson's disease," "prevalence of Parkinson's disease," "dementia with Lewy bodies epidemiology," "dementia with Lewy bodies REM sleep behavior disorder," "alpha-synucleinopathy," "dementia with Lewy bodies neuropathology," "dementia with Lewy bodies diagnosis," "Parkinson's disease dementia diagnosis," "dementia with Lewy bodies vs. Parkinson's disease dementia," "dementia with Lewy bodies clinical course," "serum and CSF biomarkers in synucleinopathy," "genetics of dementia with Lewy bodies," "dementia with Lewy bodies phenocopies," "imaging in dementia with Lewy bodies," and "electrophysiology and EEG in dementia with Lewy bodies."

1.3 Lewy bodies: What? Where? Why?

In 1912, Frederic Lewy described eosinophilic neuronal inclusion bodies in cases of “paralysis agitans” or idiopathic PD [6]. Lewy bodies (LBs) were initially found in a restricted distribution involving primarily the substantia nigra, locus caeruleus, dorsal vagus motor nucleus, and substantia innominata. Recent advances have shown that neocortical LBs are also commonly present in PD, as well as in other neurological disorders associated with cognitive and behavioral abnormalities. This family of disorders is now considered “synucleinopathies” but commonly overlaps with AD pathology, particularly among cases presenting with dementia or cognitive impairment.

Lewy bodies are intracytoplasmic eosinophilic inclusions that have slightly different appearances in the brain stem and basal forebrain (“classical” or brain stem-type LBs) than in the cerebral neocortex. The brain stem or classical-type LBs typically are large (>15 μm diameter) and have an eosinophilic core surrounded by a less densely staining peripheral halo. These LBs are usually single and round. Ultrastructurally, brain stem LBs have a dense osmiophilic core of granular and vesicular material and a concentric rim of radially or haphazardly arranged 8- to 10-nm diameter fibrils [7–10]. These fibrils are composed of abnormally phosphorylated neurofilament proteins aggregated with ubiquitin and α -synuclein (αS) [11]. The classical LB has been described in monoaminergic and cholinergic neurons [12, 13].

Neocortical LBs, in contrast, are smaller and more difficult to discern on hematoxylin and eosin staining than those found in the brain stem. They are more homogeneous with no distinct core and have comparatively loosely arranged fibrils and granular material [14–18]. In the 1980s, identification of neocortical LBs was greatly facilitated by immunohistochemical staining with antiubiquitin antibodies [16]. Advances in the 1990s resulted in the development of antibodies that stain αS [19], which are now the gold standard for identifying LBs and other synuclein pathology such as Lewy neurites. αS is expressed in a number of neuronal and nonneuronal cell types such as cortical neurons, dopaminergic neurons, noradrenergic neurons, endothelial cells, and platelets. Its functions have been found to include the binding of fatty acids, the regulation of certain enzymes and transporters, the modulation of synaptic plasticity, and the production and regulation of neurotransmitter vesicles, including those for dopamine and acetylcholine [20, 21]. The filamentous ultrastructural character of the LB and its immunohistochemical profile suggest that disturbed neurofilament metabolism or transportation is important in LB formation [22].

Braak described an orderly progression of LBs and alpha-synuclein pathology in PD [23] from olfactory and brain stem to subcortical motor to cortical regions, with cortical involvement in the later stages 5 and 6. Most, but not all, cases follow this orderly progression, but some dementia series find cases that seem to skip the more primitive brain regions and instead can have cortical or limbic predilection, where other neurodegenerative pathology is also usually present. The overlap of LBs with AD pathology (senile plaques and neurofibrillary tangles) is particularly common, especially in cases of “plaque-predominant” AD, who usually have only intermediate Braak stage tau pathology [24, 25]. Cortical LBs have a predilection for the cingulate gyrus, insular, and frontotemporal cortex, a distribution that correlates with mesolimbic dopaminergic projections [25–27].

1.4 Epidemiology

The epidemiology of PD is much better understood than that of DLB. The prevalence of PD reaches ~1% in the U.S. by age 70 in males and 75 in females [28].

This prevalence then roughly doubles with every 10 years of aging and is expected to rise by ~25% in the U.S. population over the next 10 years. Criteria to diagnose DLB have shifted over the last two decades. Both clinical and biomarker indices have been reassigned and refined. Epidemiological studies of DLB are rare and difficult to distinguish from PD with dementia (discussed below under Clinical Presentations). The literature of the last 40 years has used a plethora of terms to refer to the spectrum of patients with Lewy body disease. These terms have included “senile dementia of the Lewy body type” [29], “Lewy body variant of Alzheimer’s disease” [30], “diffuse Lewy body disease, common form, with plaques and/or tangles” [31], “Alzheimer’s disease with Lewy bodies” [32], and “Parkinson’s disease in Alzheimer’s disease” [33] to refer to patients with dementia and/or concomitant AD pathology. Other terms such as “diffuse Lewy body disease, pure form” or “idiopathic PD” have been used to describe those without AD pathology. “Dementia with Lewy bodies” is now the preferred term, and current diagnostic criteria are discussed below. However, the neuropathology in these patients is heterogeneous. Also, one should keep in mind that DLB prevalence underestimates how common Lewy body pathology is with advanced aging, as it does not include those with mild cognitive impairment (MCI), pure motor parkinsonism, or Parkinson’s disease with dementia. The clinical phenotypic heterogeneity and evolving diagnostic criteria further complicate the epidemiological study of DLB. Studies, especially community based with autopsy verification, are few and far between. Most studies of DLB prevalence have been based on selected dementia cohorts and are discussed under Pathological Validation below. In a longitudinal cohort of Olmsted, Minnesota, of 542 cases of parkinsonism, prevalence was 11.8% for DLB and 8.5% for PDD [34]. To truly reflect DLB prevalence, more population-based studies with diagnostic standardization are needed. The prevalence of subcortical LBs with aging is even higher, reported to be about 5–10% in “normal” older subjects over 50 years old, and appears to rise with increasing age [35]. When neurological or psychiatric symptoms are rigorously excluded, prevalence of LBs appears to still be ~4% in those above 70 years old [36].

1.4.1 Age of onset and survival

DLB primarily affects the elderly, with nearly all cases presenting at 60 years of age and older. In contrast, ~4% of PD cases present before age 50 and many of the “diffuse Lewy body disease (DLBD), pure form” cases described by Kosaka and colleagues had juvenile parkinsonism for decades before developing dementia [37]. Mean age of onset in a representative clinically diagnosed DLB cohort was 75.8 years (female = 77.2, male = 72.4) with mean survival time of only 5.5 years from symptom onset [38]. Cases with “Lewy body variant” (AD + LB pathology) had a mean survival of 7.7 years from onset of cognitive symptoms, ~1.5 years shorter than AD cases in an ADRC-autopsied cohort [39]. Clinicopathological studies of Lewy body density did not find correlations with age of onset, or with various other clinical features such as presence/absence of cognitive fluctuations, visual hallucinations, delusions, recurrent falls, or parkinsonism [40]. Age of onset is significantly later in DLB and PDD, relative to PD without dementia [41].

2. Clinical presentations

Diagnosing DLB often presents a particular challenge given the disease’s wide range of symptomatology and high rate of comorbidity with AD and cerebrovascular disease (CVD). Associated signs and symptoms include various combinations of motor, cognitive, and psychiatric changes as described below. The common overlap

of some of the most frequent symptoms (specifically visual hallucinations (VH), extrapyramidal signs (EPS), and RBD) is well illustrated in Mayo Clinic's DLB sample (see **Figure 1**, adapted from Ferman et al. [42]).

2.1 Cognition

As in other types of dementias, the diagnosis of DLB requires cognitive decline to be sufficiently severe as to prevent the ability to function independently. Current DSM-V criteria for dementia require “evidence of significant cognitive decline from a previous level of performance” that “interfere[s] with independence in everyday activities” most often described clinically as a loss of independence with instrumental activities of daily living such as paying bills or managing medications. Though previous editions of the DSM required a clear decline in at least two cognitive domains, this is no longer the case and DLB (along with other types of dementias) may be diagnosed based on decline in a single domain (along with functional decline). This represents an advance in the diagnosis of frontal and subcortical dementias, which typically present with dysexecutive deficits. When frontal-executive functions are significantly impaired, there is usually an impact on social, occupational, or independent function and a “single domain dementia” is therefore an appropriate diagnosis. Although patients with DLB often present with memory complaints and are frequently misdiagnosed with AD [43], neuropsychological testing tends to uncover relatively more pronounced impairments in attention, executive function, and visual processing in these patients compared with those with AD and normal cohorts. Patients with DLB tend to perform more poorly on tests of processing speed, divided attention, and perceptual discrimination than their counterparts with AD, who typically have more difficulty with short-term memory and object naming [44].

One of the core features of DLB is frequent fluctuations in cognition and/or alertness, which is discussed further below. Fluctuations can be particularly difficult to recognize, however, and can mimic seizures, delirium, and other transient alterations of alertness. Other cognitive differences between DLB and AD may be subtle and tend to be lost as the diseases progress. This increases the need to assess for motor and psychiatric changes, as well as the judicious deployment of biomarker testing (discussed below). Of note, functional limitations due to cognitive decline in patients who present with parkinsonism may be difficult to tease out from the downstream effects of motor changes.

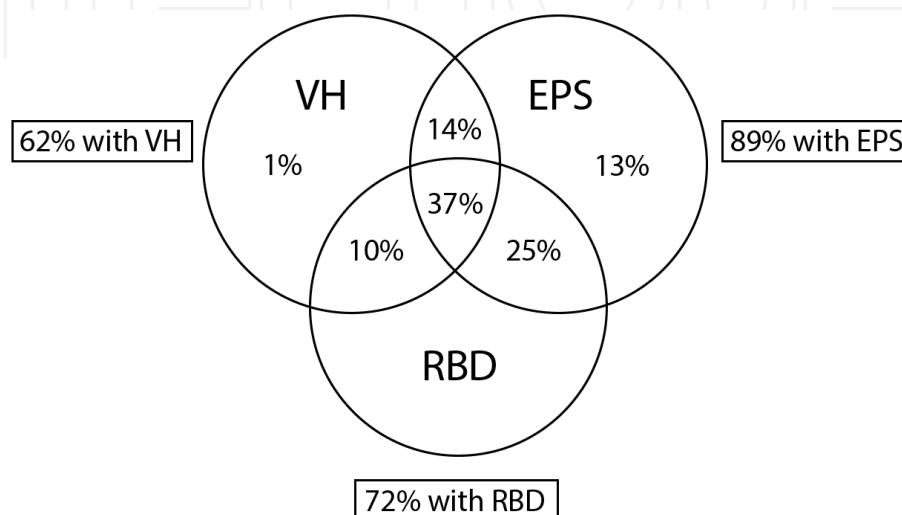


Figure 1.
Frequency of clinical features. Adapted from Ferman et al. [42] Neurology.

Contrary to James Parkinson's original description of the "senses and intellects" being "uninjured" [45], dementia is now recognized to occur fairly commonly in PD. The reported frequency of dementia in PD has varied widely—from 8% [46] to 81% [47] in early studies, owing largely to different populations, methodologies, and criteria for "dementia" [48]. Although mild cognitive impairment is very common in PD (and has been demonstrated in over 90% of PD patients [49]), many are unlikely to satisfy criteria for dementia. Most studies that required functional decline due to cognitive deficits have found dementia prevalence in PD to be between ~25 and 40% [47, 50].

2.2 Motor

The presence of Lewy bodies is associated with motor changes in both idiopathic Parkinson's disease and DLB. In contrast to idiopathic PD in which patients present with motor changes that precede significant cognitive decline, patients with DLB experience cognitive decline around the same time as motor symptoms/changes. Both conditions present with EPS, though DLB patients more often have "atypical" parkinsonian features such as a lack of resting tremor. The presence of one or more "cardinal" signs of parkinsonism (bradykinesia, rest tremor, or rigidity) is considered a core feature of DLB [51]. Other parkinsonian features are considered supportive for the diagnosis of DLB; these include postural instability, shuffling gait, frequent falls, dysautonomia, hypersomnia, and hyposmia. It has been long known that among PD patients, those with prominent postural instability and gait disorder (PIGD) have greater risk of cognitive deterioration than those with a tremor-dominant pattern of motor parkinsonism. Severity of motor impairment also predates dementia risk in PD [52]. In patients with possible CVD and atypical parkinsonism, neuroimaging is useful to rule out vascular causes of parkinsonism such as lacunar infarcts in the basal ganglia, or severe white matter lesions affecting motor tracts, speed, and balance.

2.3 Sleep

Another core clinical feature of DLB is the presence of REM sleep behavior disorder (RBD), which may begin years before the onset of other DLB symptoms. In RBD, patients recurrently manifest abnormal movements and/or vocalizations during REM sleep due to loss of atonia, which can be confirmed by polysomnogram. These episodes are often associated with a subjective experience of being chased or attacked within the dream and may result in injuries to self or bed partner. Caregivers, especially bed partners, will often report sleep disturbances and sleep-related injuries, as a consequence of DLB patients acting out their dreams [53]. Parkinsonism may arise at onset of RBD, or later in the course of the disease. RBD may precede diagnosis of DLB by several years or even decades. RBD should be differentiated from similar sleep disturbances in elderly patients such as confusional awakenings, periodic limb movements, and obstructive sleep apnea, which can be done via polysomnography. A wide range of sleep disturbances have been associated with PD, including reduced sleep spindle density, which appears to confer on increased risk of developing dementia [54–56].

2.4 Psychiatric

Compared to those with AD, DLB patients are particularly prone to depression and apathy that occurs earlier in the disease and is associated with increased caregiver burden and decreased quality of life [57]. It is not unusual to have primary

psychiatric presentations of DLB, which may account for ~10–15% of cases [37]. Note that parkinsonian features such as masked facies and bradykinesia may initially be thought to represent a dysthymic affect and psychomotor retardation and attributed to a depressive disorder. While it is important to address psychiatric issues in this population, the lack of specificity of these symptoms makes this less useful clinically for the diagnosis of DLB. Notably, however, the development of recurrent, well-formed visual hallucinations [58] is a rather specific core feature of DLB. In fact, a patient with dementia who develops recurrent, detailed visual hallucinations (not due to delirium or other known causes) makes a strong case for the diagnosis of DLB. Less specific, but still suggestive of DLB, are nonvisual hallucinations and systematized delusions, including Capgras syndrome. Besides increasing caregiver burden, the neuropsychiatric symptoms accompanying DLB increase medical care expenses [59]. Psychiatric symptomatology in DLB is thought to cause lower quality of life and self-sufficiency [60].

Importantly, patients with Lewy body disorders tend to exhibit significant neuroleptic sensitivity and are at higher risk of extrapyramidal side effects. With the increasingly common use of atypical antipsychotics over conventional ones, this criterion has become less sensitive but remains an important consideration when managing a patient with agitation or psychotic features who may have an underlying Lewy body disorder. The management of such changes is best achieved through behavioral and environmental manipulations, such as verbal de-escalation and reassurance, setting a daily routine, regulating sleep, and regular exercise. Other nonpharmacological interventions include sensory and cognitive stimulation therapies such as acupressure, music therapy, and animal-assisted therapy, but these are less well understood in the DLB population. Nonpharmacological interventions have shown mixed results in their effectiveness but remain the first line of treatment given their low risk of adverse effects and their potential cost-effectiveness [61]. There is evidence that such interventions improve quality of life of dementia patients and their caregivers [62]. If behavioral symptoms are still not adequately controlled, a trial of low-dose atypical antipsychotic such as quetiapine or olanzapine may be appropriate with close monitoring of side effects including dystonia, orthostatic hypotension, and fall risks. It is also worth noting that the use of cholinesterase inhibitors (donepezil or rivastigmine) is associated with improvement in both cognitive and neuropsychiatric symptoms [63] and should be prioritized in the long term with the goal of minimizing administration of antipsychotics.

3. Current diagnostic criteria

The clinical diagnosis of DLB relies first on the presence of dementia as defined in the Cognition section of Clinical Presentations (adapted from McKeith et al. [51]). There are four identified “core” clinical features: (1) fluctuating cognition; (2) recurrent visual hallucinations; (3) RBD; and (4) at least one spontaneous cardinal feature of parkinsonism (bradykinesia, rest tremor, or rigidity). Two of these core features are sufficient to diagnose “probable” DLB. If only one core feature is present, probable DLB can be diagnosed with at least one of three indicative biomarkers: (1) reduced dopamine transporter uptake in basal ganglia on SPECT or PET, (2) low uptake of 123iodine-MIBG in myocardial scintigraphy, or (3) confirmation of REM sleep without atonia on polysomnography. These are discussed in the Section 5. In the absence of any core features, the presence of an indicative biomarker fulfills the criterion for diagnosing “possible” DLB. Possible DLB can also be diagnosed when a single core feature is present without any indicative biomarkers. “Supportive” clinical features and supportive biomarkers are consistent with DLB

and may help with diagnostic evaluation but are of unclear diagnostic specificity. Supportive clinical features may include neuroleptic sensitivity, postural instability, frequent falls, severe autonomic dysfunction, urinary incontinence, hyposmia, and other psychiatric symptoms. Supportive biomarkers can be evaluated with CT/MRI (relative preservation of medial temporal lobe structures, indicating a higher likelihood of AD pathology), SPECT/PET (abnormal generalized uptake with reduced occipital activity), as well as EEG (prominent posterior slow-wave activity with fluctuations). Biomarkers are further described below. In patients who present with dementia and parkinsonism, the 1-year rule is recommended to differentiate between DLB and PDD. Cognitive decline in DLB should precede (or occur within 1 year of) motor changes. When dementia begins at least 1 year after motor changes, PDD is thought to be more likely. This rule is rather arbitrary and generally more useful in research settings. As mentioned above, Lewy body diseases are likely on a continuum rather than distinct subtypes, and there is a lack of neuropathological data to support the arbitrary distinction of the 1-year rule [3, 64], or a separation of DLB from PDD.

3.1 Differential diagnosis

It should be noted that historically, lower specificity has been found for cases meeting criteria for “Possible DLB” [65]. To reduce the false diagnosis of DLB, clinicians should be cautious when the only core feature is atypical parkinsonism. Careful history is critical to exclude prior exposure to phenothiazines (including prochlorperazine and metoclopramide) as atypical antipsychotics, which are sometimes tried liberally to control behavioral symptoms in dementia. Furthermore, the differential diagnosis of other dementias with atypical parkinsonism needs to be considered closely including vascular parkinsonism, corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), multiple system atrophy (MSA), Hallervorden-Spatz (now termed PKAN), Fahr’s disease, and other disorders affecting the basal ganglia and its connections.

Other dementias to consider in the differential diagnosis include Alzheimer’s disease, vascular dementia, and “mixed” AD/vascular dementia, which has been the most common reason for false-positive diagnoses of DLB in the UC Davis ADRC’s multiethnic cohort. False-positive diagnoses can occasionally be made in the setting of delirium, which may mimic symptoms of DLB (e.g., fluctuations in alertness and psychosis). The classic triad of cognitive decline, urinary incontinence, and gait disorder in normal-pressure hydrocephalus (NPH) may be present as features of DLB. Notably absent from patients with NPH are the psychotic manifestations typical of DLB. Finally, Creutzfeldt-Jakob disease can also present similar to DLB with prominent visual disturbances and motor changes, but generally with very rapid progression.

4. Fluctuations

4.1 Clinical instruments and studies

Cognitive fluctuations (CF) are spontaneous episodes of impaired attention and reduced arousal [66]. CF have been designated as a core clinical feature since the earliest consensus diagnostic criteria in 1996 [67] and remain a core clinical criterion in the current (Fourth consensus report of the DLB Consortium) diagnostic criteria discussed below [51]. Despite their importance, CF are difficult to operationalize and detect on clinical history. While some U.K. studies have

found prevalences of up to 90% in DLB [68], many U.S. centers have reported much lower prevalences [69, 70], especially among cases with concomitant AD [71]. Many caregivers report day-to-day fluctuations (e.g., “bad days”) and some do not seem to detect subtler episodes of mildly reduced attention. Differentiating CF from delirium caused by infection or concurrent medical conditions, or from the effects of sedating medications, can prove difficult in clinical populations. Ferman et al. [42] found that the presence of three symptoms of neuropsychiatric fluctuation including daytime drowsiness, daytime sleep of 2 hours or more, staring episodes, or episodes of disorganized speech was found in 63% of DLB patients (n = 70) [42]. Thus, asking about “excessive daytime sleepiness” can often be more fruitful than asking about “fluctuations in alertness,” which can be overly vague and difficult to discriminate normal vs. excessive changes in alertness. Walker and colleagues have introduced two clinical scales designed to quantify such issues: the One Day Fluctuation Assessment Scale and the Clinician Assessment of Fluctuation (CAF). The CAF has been well validated and is commonly used in clinical trial assessments of CF. It should be scored by an experienced clinician with significant exposure to DLB or PD patients, which poses a barrier to its more widespread use in the community, primary care, or general neurology practices. Biomarkers that can quantify CF would clearly be of value by: (1) increasing our sensitivity to CF, and thereby improving diagnostic sensitivity; (2) allowing insights into the physiological mechanisms that underlie CF, as this could point the way toward treatments that reduce CF and their associated disability; (3) reducing the need for specialized raters; and (4) objective measures could be used across cultures and reduce the subjective aspects of current clinical rating scales.

4.2 Electrophysiological studies

Electroencephalography (EEG), a time-honored technique used in the assessment of alertness, level of consciousness, and the stages of sleep, has also showed much promise in the assessment of CF. EEG is a noninvasive, inexpensive, and widely available technology with unsurpassed temporal resolution. It offers high signal-to-noise ratio and portability and is more easily tolerated by dementia patients than MRI or PET scanning. Walker et al. [68] found DLB patients to have significantly greater CF than AD or vascular dementia patients, and the EEG also showed greater variation in the mean frequency and increased fluctuations over time, apparent even on a second-to-second basis within 90-second samples of EEG data. Further work with quantitative EEG (qEEG) has suggested several biomarkers for DLB, as well as for PD dementia. Bonanni and colleagues [72] found slower dominant frequency over the posterior scalp in DLB (n = 36) and PD dementia patients with CF (n = 16). A follow-up study by this group [73] showed reduced dominant frequency and increased dominant frequency variability can be detected before the diagnosis of DLB, when patients are in the MCI stage, and these EEG patterns confer an increased risk for conversion from MCI to dementia, that is, the loss of functional independence. Stylianou et al. have added to this literature by showing abnormalities in theta activity in DLB, with more variability in theta range dominant frequency and greater prevalence of slow theta activity [74]. This body of work has led to the Consensus DLB Diagnostic Criteria adding EEG as a supportive biomarker in 2017 particularly when “prominent posterior slow-wave activity with periodic fluctuations in the pre-alpha/theta range” is present. A prealpha dominant frequency intermixed with alpha/theta/delta activities in pseudoperiodic patterns may have >90% predictive value in differentiating DLB from AD [75].

5. Biomarkers

Direct biomarker evidence of Lewy body pathology is not yet clinically available for the diagnosis of DLB. In 2017, the fourth consensus report of the DLB consortium categorized available biomarkers into “indicative” and “supportive” categories based on available evidence and diagnostic specificity [51]. Below, we discuss the validity and potential pitfalls of these tests as well as future biomarkers still under development.

5.1 Indicative biomarkers

Indicative biomarkers include (1) reduced dopamine transporter (DAT) uptake in the basal ganglia demonstrated by SPECT or PET; (2) abnormal (low) 123iodine-MIBG uptake on myocardial scintigraphy; and (3) Polysomnographic (PSG) confirmation of REM sleep without atonia.

Reduced nigrostriatal DAT uptake by SPECT or PET imaging is reflective of dopaminergic neuron dysfunction due to α S deposition and has a specificity of 90% and sensitivity of 78% in distinguishing DLB from AD [76]. However, parkinsonism and reduced DAT uptake may also be seen in disorders such as PSP, MSA, CBD, and frontotemporal dementia; therefore, caution must be exercised in diagnosing dementia patients with probable DLB when parkinsonism is the only core clinical feature present. Occasionally, normal DAT uptake may also be seen in autopsy-confirmed DLB due to limited nigral neuron loss or a balanced loss of dopamine across the whole striatum [77].

Evaluation of imaging biomarkers typically relies on visual interpretations and manual selection of regions of interest and can leave it susceptible to interrater and intrarater variability. The advent of automated imaging processing software such as GE Healthcare's DaTQUANT potentially increases the predictive yield over that of manual DAT-SPECT interpretation and combining with the use of two other imaging modalities (MRI and FDG-PET) has been shown to increase the concordance (c-statistic) rate of predicting DLB to 0.996 [78].

Low 123Iodine-MIBG myocardial scintigraphy uptake has a specificity of 87% and sensitivity of 69% in discriminating probable DLB from probable AD. Abnormal MIBG uptake results from reduced postganglionic sympathetic cardiac innervation due to α S deposition, as such other causes of peripheral neuropathies, including diabetes mellitus, and cardiac conditions such as heart failure and recent ischemic heart disease, and certain medications such as labetalol and tricyclic antidepressants may also reduce MIBG uptake [79].

REM sleep behavior disorder is a parasomnia characterized by a loss of normal skeletal muscle atonia during REM sleep with prominent motor activity during dreaming, including punching, kicking, talking, and moving purposefully. Onset is typically after the age of 50 and can precede the manifestation of a neurodegenerative syndrome by years or decades. PSG confirmation of REM sleep without atonia, along with a history of dementia and RBD, has a predictive accuracy of 98% for the presence of a synucleinopathy. Rarely, PSG-confirmed cases may be associated with nonsynucleinopathies such as AD or CBD (3 cases out of 82 total patients) [80].

5.2 Supportive biomarkers

Supportive biomarkers include (1) relative preservation of medial temporal lobe (MTL) structures on CT/MRI scan; (2) generalized low uptake on SPECT/PET perfusion/metabolism scan with reduced occipital activity and/or the “cingulate

island sign” on FDG-PET imaging; and (3) prominent posterior slow-wave activity on EEG with periodic fluctuations in the prealpha/theta range.

DLB patients demonstrate less MTL atrophy compared to AD. Absent or minimal medial temporal atrophy on MRI has a sensitivity of 64% and specificity of 68% for separating AD from DLB [81]. For clear DLB cases, concurrent MTL atrophy may signal additional AD pathology and predict a more rapid clinical course.

On FDG-PET, DLB patients demonstrate occipital hypometabolism and relative preservation of posterior cingulate metabolism compared to AD, the latter has been coined the “cingulate island sign.” Occipital hypometabolism in DLB has a sensitivity of 70% and specificity of 74% in distinguishing DLB from AD [82]. Relative preservation of cingulate island metabolism on FDG-PET has been associated with lower Braak tangle stage at autopsy and predicted better clinical trajectory in DLB [83].

Quantitative EEG analysis of DLB patients using multiple methods has been shown to reliably identify DLB with a correct classification rate of 90%. Posterior slow-wave activity and the presence of prealpha- (5.5–7.5 Hz) or theta- (>4 Hz–8 Hz) dominant frequencies are associated with DLB [75].

In an anonymous survey of 22 DLB center of excellence investigators, MRI and DAT-SPECT were the most ordered biomarkers (90% and 86.4%, respectively). Myocardial scintigraphy and EEG use were the rarest (13.6% and 9.1%, respectively). Insurance coverage of DAT-SPECT is variable among U.S. insurers; some consider the use “investigational” for the indication of distinguishing DLB from AD, while others cover it for the indication of clinically uncertain DLB [84]. MIBG compounds for diagnosis of neurological indications is considered off-label use in the U.S. by the FDA but are more widely available in Europe [85].

5.3 Future biomarkers (in development)

Genetic testing and peripheral tissue and CSF biomarkers for the diagnosis of DLB are an area of ongoing research. Genome-wide association studies (GWAS) in DLB have demonstrated variations in glucocerebrosidase (GBA) and α -synuclein gene (SNCA) alleles as risk factors for DLB and PD, while APOE E4 is a shared risk allele in DLB and AD [86, 87]. Common genetic variants including the H1G haplotype of microtubule-associated protein (MAPT) and in the scavenger receptor class B member 2 (SCARB2) loci confer a higher risk of DLB compared to controls, whereas the H2 MAPT haplotype and a common variant in the butyrylcholinesterase (BuChE) loci have been associated with a decreased risk of DLB. Additional genetic variants such as the parkin (PARK2), PTEN-induced putative kinase 1 (PINK1), granulin (GRN), triggering receptor expressed on myeloid cells 2 (TREM2), and SNCB alleles have also been associated with DLB but are often of unclear pathogenicity [88]. At the current time, the Fourth Consensus Report suggests that it is premature to recommend genetic testing in a clinical setting, either for confirmation of diagnosis or for prediction of disease [51].

Direct assays of alpha-synuclein (α S) oligomers are being developed for CSF and peripheral nerve biopsies. In the CSF, abnormal α S aggregates can be measured taking advantage of the seeding-nucleation process of α S aggregation, where misfolded oligomers seed the polymerization of monomeric proteins. One such process uses a combination of protein misfolding cyclic amplification assays (PMCA) and thioflavin (ThT) fluorescence; in this method, DLB and PD result in the highest levels of ThT fluorescence and reliably differentiates these diseases from MSA (100% sensitivity and 93% specificity) and healthy controls [89]. Plasma and serum α S levels have been demonstrated to reliably differentiate between PD and normal controls with a c-statistic of 0.992 (plasma) and 0.917 (serum) with regard

to the clinical diagnosis. Its diagnostic capacity for diagnosing DLB remains to be seen [90]. Studies of cutaneous α S aggregation in the skin nerve fibers using skin biopsies and in gastrointestinal specimens using colonic biopsies are also under investigation [91].

Alternative fluid biomarkers under development include CSF levels of DJ-1, a ubiquitous protein involved in inhibition of α S aggregation; mutations in the DJ-1 gene (PARK7) can also cause early-onset PD [92]. Results have been mixed: one study demonstrated CSF DJ-1 levels were lower in PD compared to AD and normal controls and had a sensitivity of 90% and specificity of 70% in distinguishing PD from controls [93]. Another demonstrated higher CSF DJ-1 levels in MSA compared to PD and normal controls, with a sensitivity and specificity of 78% in distinguishing MSA from PD [94]. Others include β -glucocerebrosidase activity, CSF neurofilament light chain (NF-L), and combination testing with AD biomarkers amyloid and tau [92].

6. Pathological validation

Initial criteria for the pathologic diagnosis of DLB required the presence of brain stem or cortical Lewy bodies; this was subsequently expanded to include five subtypes based on the region of LB deposition, including diffuse neocortical, limbic (or transitional), amygdala-predominant, brain stem-predominant, and olfactory bulb-only variants [95]. In one prospective study, 84% of patients with clinically probable DLB ($n = 43$) had diffuse cortical LB, 14% demonstrated the limbic/transitional subtype at autopsy, and the one remaining patient had mixed PSP/AD pathology [96].

Over 50% of DLB cases have concurrent Alzheimer's pathology (neocortical tau and β -amyloid) on autopsy. Diffuse, rather than neuritic, plaques make up the preponderance of amyloid burden in DLB [97], and the presence of amyloid could contribute to faster progression of dementia [98]. The presence of neocortical tangles affects the phenotypic expression of DLB; combined diffuse Lewy body disease (DLBD) and neocortical tangles were associated with comparable memory-naming impairment but worse baseline attention-visual processing than AD. Dementia trajectory was also the fastest for this combined pathology group, compared to transitional LBD without neocortical tangles, which had the slowest progression of the clinical DLB patients. In general, a clinical diagnosis of DLB was highly likely when the distribution of α S pathology was greater than tau and less likely when the distribution of tau pathology was greater than α S [99]. In an ADRC series of cases autopsied within 3 years of last cognitive assessment, both the presence of Lewy bodies and advanced Braak neurofibrillary tangle stage were associated with more severe dementia [100]. Lewy bodies appeared to be a major determinant of dementia severity in "Lewy body variant" cases with milder AD pathology (Braak III-IV), but not in those with severe AD pathology (Braak V-VI; see **Figure 2**). It may be that advanced AD-related neurodegeneration facilitates LB formation and, reciprocally, that neocortical LBs promote secondary beta-amyloid deposition and AD pathology.

Illustrating the spectrum of Lewy body disorders, coexistence of LB pathology in AD patients results in higher Unified Parkinson's Disease Rating Scale (UPDRS) scores compared to pure AD patients [101]. Matching cases diagnosed with DLB, AD, and LBV in the NACC database on MMSE scores, Kaur et al. found UPDRS scores increased with cognitive impairment in all three patient groups. Thus, total UPDRS scores may be useful for indicating likelihood of dual pathology in dementia cohorts [102]. On qEEG measures, DLB and AD copathology also demonstrates

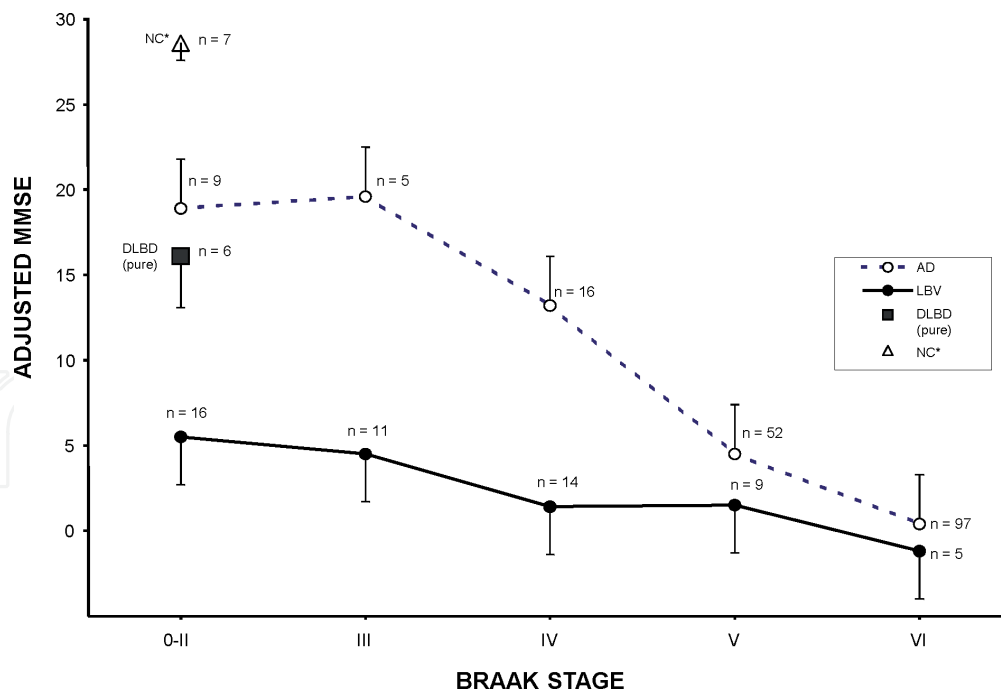


Figure 2. Dementia severity by Braak stage in AD and LBV. NC*—normal controls; last MMSE (unadjusted) plotted. Mean age = 82.9 years. Excluded if met NIA or CERAD neuropathological criteria for possible AD. All other groups (AD, LBV, pure DLBD) had MMSE adjusted using 3 pt/yr correction estimate.

greater reduction of posterior alpha, beta, and gamma frequencies compared to pure AD cases but is similar to the qEEG findings in pure DLB [103].

In summary, the likelihood of a clinical DLB syndrome is thought to be a function of both the distribution of Lewy bodies and the severity of AD-type pathology; this probability is positively correlated with LBs and negatively correlated with NIA-Alzheimer’s Association Braak staging of neurofibrillary tangles (i.e., higher Braak stages were associated with a lower probability of clinical DLB in diffuse cortical and transitional LB pathology, and vice versa). Brain stem, amygdala-predominant, and olfactory bulb-only subtypes had a low probability of clinical DLB regardless of Braak staging [104, 105]. A separate research criteria for the diagnosis of prodromal DLB have been proposed, compatible with current criteria of other prodromal neurodegenerative disorders including AD and PD; further validation studies are underway [106].

7. Conclusions and future directions

In conclusion, this chapter has attempted to summarize the recent advances in both clinical diagnostic criteria and biomarkers with higher sensitivity or specificity to DLB. It should be noted that these advances have improved in the detection of DLB, but the attribution of which disease process is “primary” remains difficult in cases with concomitant LB and AD pathology. Clinical criteria alone have good specificity but limited sensitivity to many of these cases, where the AD phenotype may be more evident in the so-called LBV of AD cases. Adding biomarkers has increased sensitivity further, but the specificity of the biomarkers may be less than the specificity of clinical criteria.

Further work is clearly needed to parse the “mixed” dementias, both among neurodegenerative diseases where “quadruple proteinopathy” cases are increasingly recognized [107], plus the common coexistence of cerebral vascular disease, which makes AD with CVD arguably the most common dementia in the U.S. [108].

Another limitation of DLB criteria is that while it captures well a subgroup of patients with poor prognosis and who need the most care, it does not capture the full spectrum of phenotypes attributable to LBs. The validation of prodromal DLB criteria is a current important focus of the field, and the capture of PD dementia cases in population-based studies with comparisons to DLB prevalence is important for an understanding of this relative impact on the public health. Further advances may be possible with better detection of olfactory deficits (anosmia being common in PD, DLB, and LBV), autonomic dysfunction, and subclinical motor dysfunction.

We have emphasized recent advances in the detection of CF both with clinical instruments and qEEG. Further applications and work in this area are needed, as CF are disabling and the electrophysiological mechanisms may be treatment-responsive. In this digital age, advances in EEG analytic methods, for example, statistical pattern recognition (SPR) [109, 110], artificial intelligence, and machine learning with support vector machine EEG classifiers [111], hold promise in detecting LBs, perhaps independent of clinical presentation (PD, DLB, LBV), or alternatively as a “digital fingerprint” for disease subtypes. Future investigations are encouraged to characterize the physiological abnormalities using more comprehensive biomarker approaches (e.g., biofluids, PSG, EEG, PET, autonomic and olfactory testing), while capturing a broader range of phenotypes. Further neuropathologic studies to validate the disease subtypes are also needed, for which careful phenotyping will allow increased ability to detect less widespread LB disease (e.g., olfactory and brain stem) and ultimately stage patients accurately during life. One recent clinicopathologic study found different clinical phenotypes in transitional Lewy body disease (TLBD) than in DLBD, and neurofibrillary tangles were associated with faster decline and less sensitivity of the consensus criteria (48–70% vs. 87–96% in LB disease cases without tangles) [99].

We expect that, as in any disease, a better understanding of its subtypes and underlying pathophysiological mechanisms will allow future treatments for DLB and the other synucleinopathies that are more targeted and comprehensive. While symptomatic treatments for PD and DLB are quite well developed and tested, future advances will increasingly address prevention and presymptomatic treatments that are disease-modifying. Such advances would have a truly major impact on the public health of our elderly population.

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