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Research criteria for the diagnosis of prodromal dementia with Lewy bodies

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Abstract

The prodromal phase of dementia with Lewy bodies (DLB) includes (1) mild cognitive impairment (MCI), (2) delirium-onset, and (3) psychiatric-onset presentations. The purpose of our review is to determine whether there is sufficient information yet available to justify development of diagnostic criteria for each of these. Our goal is to achieve evidence-based recommendations for the recognition of DLB at a prodromal, symptomatic stage. We propose operationalized diagnostic criteria for probable and possible mild cognitive impairment with Lewy bodies, which are intended for use in research settings pending validation for use in clinical practice. They are compatible with current criteria for other prodromal neurodegenerative disorders including Alzheimer and Parkinson disease. Although there is still insufficient evidence to propose formal criteria for delirium-onset and psychiatric-onset presentations of DLB, we feel that it is important to characterize them, raising the index of diagnostic suspicion and prioritizing them for further investigation.

Introduction

Dementia with Lewy bodies (DLB) accounts for 7.5% or more of all dementias in older people.¹ It is characterized by dementia together with varying combinations of the core clinical features of parkinsonism, REM sleep behavior disorder (RBD), fluctuating cognition/alertness, and visual hallucinations.² There is a variable progression of α -synuclein aggregation many years before the full DLB syndrome develops,^{e1} which likely determines the pattern of early clinical changes. Prodromal DLB refers to a prodromal stage with signs or symptoms indicating that DLB will subsequently develop and encompasses not only cognitive deficits but also a variable mixture of noncognitive clinical features including motor symptoms and signs, sleep disorders, autonomic dysfunction, and neuropsychiatric disturbance.³ Because these first clinical manifestations can occur 15 years or more before dementia onset, precise early diagnosis of DLB presents particular challenges, individuals being extremely difficult to distinguish from those with the first manifestations of Parkinson disease (PD) or multiple system atrophy (MSA), which are also α -synuclein-related syndromes,⁴ or of other dementing disorders, particularly Alzheimer disease (AD).

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Glossary

AD = Alzheimer disease; DAT = dopamine transporter; DLB = dementia with Lewy bodies; FTD = frontotemporal dementia; MCI = mild cognitive impairment; MCI-LB = MCI with Lewy bodies; MIBG = meta-iodobenzylguanidine; MSA = multiple system atrophy; NCD = neurocognitive disorder; PD = Parkinson disease; PSG = polysomnography; QEEG = Quantitative EEG; RBD = REM sleep behavior disorder; RSWA = REM sleep without atonia; VH = visual hallucination; VRH = ventilatory response to hypercapnia.

Reliable identification of prodromal DLB would enable early intervention while pathologic burden is circumscribed and before clinical symptoms become debilitating. It would assist clinicians to streamline care, anticipate treatment options known to be effective in DLB,^{e2} and to avoid or minimize iatrogenic adverse events with the goal of fewer office and emergency department visits.^{e3} Importantly, early diagnosis would help patients and families to plan and to implement early nonpharmacologic interventions, (e.g., exercise and behavioral strategies). It would also facilitate selection for trials of targeted therapies as these become available.

Methods

We performed electronic searches of MEDLINE, PubMed, and EMBASE databases using the combination of a number of medical subject headings, Emtree subject headings, and free-text terms (“dementia with Lewy bodies”, “Lewy body dementia”, “Lewy body disease”, “prodromal”, “delirium”, “psychosis”, “mild cognitive impairment”, “rapid eye movement sleep behavior disorder” for clinical categories, and “neuropsychological test”, “dopamine transporter imaging”, “positron emission tomography”, “meta-iodobenzylguanidine myocardial scintigraphy”, “nuclear magnetic resonance imaging”, “electroencephalography”, “cerebrospinal fluid”, “rapid eye movement sleep without atonia” for biomarkers). All relevant articles were retrieved, placing restrictions on fields (free-text terms searched exclusively in the title or abstract of the articles) and date (last 5 years). Except for book chapters, all publication types (original articles, reviews, editorials, and letters) were considered. Because the focus of this review was on prodromal DLB, studies on the broader, less specific category of Lewy body disease (which comprises both DLB and PD) were also considered. We then used Refworks to remove duplicates and share the resulting 3570 records among the lead authors. Of all full-text articles assessed for eligibility after the abstract screening phase, those eventually included either as listed or as e-references were selected based on their relevance (data available from Dryad, e-references, doi:10.5061/dryad.1c59zw3rv). Seminal papers on the topic were included regardless of publication date. The preliminary findings and recommendations were presented for discussion and feedback at a session of the International Lewy Body Dementia Conference in Las Vegas, NV, USA, in June 2019, following which further revision and review took place.

How does prodromal DLB usually present?

One or more of the core clinical features characteristic of fully developed DLB may develop before dementia and are usually accompanied by mild cognitive complaints.⁵ Spontaneous parkinsonism often develops within the prodementia stage but is not present in all patients.^{3,6} RBD is a parasomnia that typically occurs years, and even decades, before the onset of dementia or parkinsonism and may presage any of the α -synucleinopathies.^{4,7,e4} In patients with mild cognitive deficits who later develop dementia, both parkinsonism and RBD strongly predict a later transition to DLB rather than to AD or other dementia types.^{6,8} Delirium can occur during the prodementia stage of DLB⁹ as can fluctuations of cognition and arousal³ that may give rise to a diagnosis of delirium. Visual hallucinations (VHs) either spontaneous or provoked by illness or medication are more likely to occur compared with normal controls or prodromal AD.^{10,11} There are also case reports of delusions, hallucinations, depression, and anxiety as presenting features of DLB.¹² Based on such observations, 3 prototypic prodromal DLB syndromes have been proposed¹³ as (1) mild cognitive impairment (MCI), (2) delirium-onset, or (3) psychiatric-onset.

MCI with Lewy bodies

The National Institute on Aging and Alzheimer’s Association criteria for MCI^{14, e5} provide a standardized approach to diagnosis and form the basis for our proposed MCI with Lewy body (MCI-LB) criteria. They require a cognitive complaint from the patient or from an informant or clinician who knows them and has observed a decline. Also required are deficits in one or more cognitive domains that are greater than would be expected from normal aging, do not represent lifelong patterns of lower cognitive function, and are not associated with acute medical or neurologic insults. Although people with MCI may be less efficient or less capable at performing tasks they have performed previously, their cognitive deficits should not be sufficient to interfere with their typical daily functioning. In other words, there should be an overall preservation of their prior level of independence with minimal interference in day-to-day functional abilities, which, by definition, does not constitute a dementia.

Objective cognitive impairment is optimally based on standardized assessment with scores on neuropsychological measures that are typically 1 to 1.5 SDs below the mean for their age and education matched peers on culturally appropriate normative data (i.e., for the impaired domain(s), when available). It is emphasized that these ranges are guidelines

and not cutoff scores.¹⁴ Impairment on neuropsychological tests may also be demonstrated by significant decline demonstrated on serial testing or significant decline from estimated premorbid abilities.^{e5} Cognitive impairment may additionally be categorized as single or multiple domain, and as amnestic or nonamnestic, which may help to classify potential subgroups as they relate (1) to biomarkers and pathologic correlates, and (2) to differences in the rate of decline and progression to dementia, each of which may be important in the conduct of clinical trials. A further refinement to describe the cognitive profile of MCI-LB may be provided by using the MDS level II criteria for PD-MCI.^{15,e6,e7}

The cognitive presentation of MCI-LB

The cognitive pattern of MCI-LB is similar to DLB and typically includes disproportionate attention/executive and visual processing deficits and relatively preserved memory and object naming.^{16,e8,e9} Impairment on tasks of attention, processing speed, and verbal fluency typically constitute the attention/executive deficits, and tasks of visual discrimination, assembly, and figure drawing typically constitute the visual perceptual and spatial deficits.^{5,6,17-19}

Diagnostic criteria for DLB emphasize that prominent or persistent memory impairment may not necessarily occur in the early stages,² but patients and carers frequently offer memory complaints as a presenting symptom.²⁰ Of 49 patients with MCI who progressed to DLB, 27% had multidomain amnestic MCI, but only 6% had single-domain amnestic MCI,³ similar to other reports.^{19,21} When patients with MCI-LB have memory impairment, attention and/or visual processing deficits also tend to be present³ and may precede the memory difficulties. Patients with RBD who later developed DLB had attention/executive deficits up to 6 years before the diagnosis of dementia and memory deficits up to 2 years before the diagnosis.²² The basis for verbal memory impairment in DLB or MCI-LB may be related to slowed processing speed and deficits in working memory and retrieval that characterize the attention and executive deficits,^{e10} consistent with hippocampal preservation in MCI-LB compared with MCI-AD.^{23,e11} However, impaired memory in DLB may also be related to the extent of coexisting AD-related pathology,^{e9} characterized by greater hippocampal atrophy on imaging^{e12} and greater CA1 hippocampal subfield pathology on autopsy.^{e13} Similar to other subtypes of MCI, a proportion of patients may revert to being cognitively normal, although they remain at a greater risk of the eventual development of dementia.^{e14} Some instability of an MCI-LB diagnosis is to be expected given inherent fluctuating cognition, worsening with neuroleptics or anticholinergics, or improvement with levodopa-carbidopa or cholinesterase inhibitors.

In summary, the performance pattern of MCI-LB is best characterized as single- or multidomain nonamnestic MCI, or as multidomain amnestic MCI, whereas single-domain amnestic MCI is more likely to represent MCI-AD. The MCI-LB cognitive pattern is often seen in patients with 1 or more core DLB features,⁵ although these may develop

later.^{3,18} Nonamnestic MCI seldom develops into AD but is associated with a greater risk of transition to DLB^{10,21} with a ten-fold risk compared with amnestic MCI.³ Because a substantial subset of patients with DLB have coexisting AD-related pathology that may influence their cognitive profile, MCI-LB still should be considered an important part of the differential diagnosis in amnestic subjects.

Operationalization of MCI-LB

The scheme suggested in table 1 for the identification of MCI-LB allows a diagnosis of either possible or probable MCI-LB based on the number of qualifying clinical features or biomarkers. The terms possible and probable refer to the likelihood of underlying LB disease and not to the MCI syndrome. Structured diagnostic instruments may assist identification of the core clinical features of DLB that precede, coincide with, or follow the onset of cognitive difficulties.²⁴⁻²⁶ Cognitive fluctuations may be of lesser amplitude or frequency than in more severe disease. Passage and sense of presence hallucinatory phenomena may precede the development of recurrent, well-formed and detailed VH. Clinical features supportive of DLB may occur secondary to other causes reducing their diagnostic specificity, but they can be useful indicators of underlying LB disease, particularly when they persist over time or occur in combination.

Use of the possible MCI-LB category may raise diagnostic suspicion prompting further clinical and biomarker investigation. Some possible MCI-LB combinations will likely prove better predictors than others, for example, multidomain nonamnestic MCI plus clinically well-defined RBD is anticipated to be more predictive of progression to DLB than single-domain amnestic MCI plus a history of cognitive fluctuation. The utility of different combinations of clinical features and biomarkers remains to be established.

MCI-LB and PD-MCI

Uncertainty may occur in deciding how patients exhibiting both MCI and parkinsonism are best categorized. PD-MCI will usually be the most appropriate diagnosis when PD is diagnosed before significant cognitive decline occurs. The adoption of a 1-year rule similar to that used to separate DLB and PD dementia may be helpful to distinguish some MCI-LB and PD-MCI cases if the onset and order of mild symptoms of parkinsonism and cognitive decline can be clearly established. If not, an initial diagnosis of prodromal LB disease may be preferable, recognizing that this will require revision as the full clinical picture evolves. Individuals with poor global cognitive test performance identified in community samples have been reported to be at a greater risk of developing PD over subsequent years,^{e15,e16} but poor cognitive test scores are not equivalent to MCI, and this increased risk was no longer statistically significant when individuals with subtle motor signs at baseline were excluded.^{e15} There are data to suggest that patients with MCI-LB may have greater cognitive impairment than those with PD-MCI,²⁷ but this is not easily operationalized to differentiate individual subjects. The cognitive deficits of PD-MCI can be heterogeneous,^{e17} with

Table 1 Research criteria for the clinical diagnosis of probable and possible MCI-LB

| |
|--|
| Essential for a diagnosis of MCI-LB is MCI defined by the presence of each of the following: |
| Concern by the patient, informant, or clinician regarding cognitive decline. |
| Objective evidence of impairment in 1 or more cognitive domains. The cognitive impairment may include any domain, but is more likely to be associated with attention-executive and/or visual processing deficits. |
| Preserved or minimally affected performance of previously attained independence in functional abilities, which do not meet the criteria for dementia. |
| Core clinical features |
| Fluctuating cognition with variations in attention and alertness. |
| Recurrent visual hallucinations. |
| RBD. |
| One or more spontaneous cardinal features of parkinsonism: these are bradykinesia (defined as slowness of movement and decrement in amplitude or speed), rest tremor, or rigidity. |
| Proposed biomarkers |
| Reduced dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET. |
| Polysomnographic confirmation of REM sleep without atonia. |
| Reduced meta-iodobenzylguanidine (MIBG) uptake on myocardial scintigraphy. |
| Probable MCI-LB can be diagnosed if: |
| Two or more core clinical features of DLB are present, with or without the presence of a proposed biomarker, or |
| Only 1 core clinical feature is present, but with 1 or more proposed biomarkers. |
| Probable MCI-LB should not be diagnosed based on biomarkers alone. |
| Possible MCI-LB can be diagnosed if: |
| Only 1 core clinical feature of DLB is present, with no proposed biomarkers, or |
| One or more of the proposed biomarkers is present, but there are no core clinical features. |
| Supportive clinical features |
| Severe sensitivity to antipsychotic agents; postural instability; repeated falls; syncope or other transient episodes of unresponsiveness; prolonged or recurrent delirium; autonomic dysfunction, e.g., constipation, orthostatic hypotension, urinary incontinence; hypersomnia; hyposmia; hallucinations in other modalities including passage, and sense of presence phenomena; systematized delusions; apathy, anxiety, and depression. |
| Potential biomarkers of MCI-LB |
| Quantitative EEG showing slowing and dominant frequency variability. |
| Relative preservation of medial temporal lobe structures on structural imaging. |
| Insular thinning and gray matter volume loss on MRI. |
| Low occipital uptake on perfusion/metabolism scan. |
| MCI plus supportive clinical features or potential biomarkers are insufficient to diagnose MCI-LB but may raise suspicion of it and prompt biomarker investigation and may add weight to an existing MCI-LB diagnosis. |
| MCI-LB is less likely in the presence of any other physical illness or brain disease including cerebrovascular disease, sufficient to account in part or in total for the clinical picture, although these do not exclude an MCI-LB diagnosis and may serve to indicate mixed or multiple pathologies contributing to the clinical presentation. |
| Abbreviations: DLB = dementia with Lewy bodies; MCI = mild cognitive impairment; MCI-LB = MCI with Lewy bodies. These should be used in conjunction with the corresponding article text, which gives further information about core and supportive clinical features and the use of biomarkers as they apply to MCI-LB. |

disproportionately affected attention/executive function,²² visuospatial skills,^{e18} and memory.²⁸ Similar to MCI-LB, there is evidence that nonamnestic MCI is more common than amnestic MCI and that multidomain amnestic MCI is more common than single-domain amnestic MCI.²⁹

Biomarkers for prodromal DLB

Direct measures of α -synuclein pathology would offer definitive diagnosis at an early stage; several are under development, but none is yet validated or available for use antemortem. Surrogate biomarkers of LB disease must

therefore be used, as is the case for the diagnosis of DLB itself.² We propose biomarkers for the diagnosis of prodromal DLB, where there is either sufficient, good quality, published evidence of adequate diagnostic specificity in prodromal DLB or this can be reasonably extrapolated from fully developed DLB or related disorders. We categorize biomarkers for which only limited data are available as potential biomarkers, recognizing that such distinctions are likely to require revision as new data become available.

Proposed biomarkers

Reduced dopamine transporter (DAT) uptake in basal ganglia demonstrated by SPECT or PET

The utility of DAT imaging in discriminating DLB from AD is already well established² and its sensitivity in distinguishing MCI with LB (MCI-LB) from MCI with AD was 54% and specificity 89%,³⁰ when MCI-LB was defined by the presence of 1 core clinical feature of DLB in patients with MCI. A higher sensitivity of 61% was achieved when 2 core clinical symptoms were present.³⁰ Reduced striatal DAT uptake therefore seems suggestive of prodromal DLB in a person with MCI, but normal striatal DAT uptake does not exclude it.

Polysomnographic confirmation of REM sleep without atonia

The association between RBD and synucleinopathy is highly specific, (e.g., a multicenter autopsy study found that of 80 subjects with polysomnography [PSG]-confirmed RBD and a coexisting neurodegenerative disorder, only 2 had a disease unrelated to α -synuclein deposition).^{e4} These data imply that a patient presenting with MCI and having PSG-confirmed RBD, that is, a history of probable RBD plus clear documentation of REM sleep without atonia (RSWA) on PSG, also has a high probability of an underlying prodromal synucleinopathy. Because around a quarter of patients with DLB do not report symptoms of RBD and/or have normal REM sleep atonia on PSG, a normal PSG does not exclude a prodromal DLB diagnosis.³¹

Reduced meta-iodobenzylguanidine uptake on myocardial scintigraphy

Reduced meta-iodobenzylguanidine (MIBG) uptake is an indicative biomarker for DLB² and has also been reported to occur in a small series of patients with late-onset psychiatric disorder and PSG-confirmed RBD,³² reinforcing its association with underlying α -synucleinopathy. Of 2 patients with amnesic MCI with low MIBG uptake, one developed DLB after 2 years; the other had no clinical follow-up reported.^{e19} VHs and/or RBD were reported among 7 of 13 patients with MCI with reduced MIBG uptake, the majority of whom also had autonomic symptoms suggestive of LB disease, but they were not followed to determine conversion to DLB.^{e20} Despite a paucity of longitudinal data,^{e21} there seems to be sufficient evidence that abnormal MIBG myocardial scintigraphy in a patient with MCI supports a prodromal DLB diagnosis, but further studies are required.

Potential biomarkers

These are biomarkers consistent with underlying LB disease, which may help the diagnostic evaluation, but for which there is still insufficient evidence of diagnostic sensitivity and specificity in early disease. This will change as new evidence emerges, at which point these, or other candidates, may become considered as indicative of prodromal DLB.

Quantitative EEG showing slowing and dominant frequency variability

EEG slowing has been reported as predictive of dementia in both PD^{e22} and RBD,^{e23} posterior slow wave activity with periodic fluctuations in the pre-alpha range being supportive of DLB.² Quantitative EEG (QEEG) methods show that a dominant frequency <8 Hz and dominant frequency variability >1.5 Hz is typical of DLB, and in a 3-year, follow-up study, 83% of subjects with MCI with this pattern at presentation converted to DLB. If these findings are replicated, QEEG may represent a powerful predictor of progression from MCI to DLB.³³

Relative preservation of medial temporal lobe structures on structural imaging

Absent or minimal medial temporal lobe atrophy is consistent with DLB, but not sufficiently specific to differentiate it from AD.² Lewy body disease with RBD is characterized by preserved hippocampal volumes,³⁴ and hippocampal preservation in patients with MCI supports progression to DLB instead of AD dementia with a sensitivity of 85% and a specificity of 61%.²³ Suboptimal specificity may be due to the variability of hippocampal atrophy in AD³⁵ and contribution of other pathologic processes such as TAR DNA binding protein 43 (TDP43).^{e24}

Insular thinning and gray matter volume loss

Insular cortical thinning occurs in prodromal DLB relative to healthy controls using MRI T1 sequences, with gray matter atrophy predominantly affecting the anterior cingulum and medial frontal structures. This contrasts with more extensive loss of gray matter in the temporal, frontal, and parietal regions of subjects with prodromal AD. Insular cortical thinning may therefore differentiate patients with prodromal DLB not only from healthy controls but also from their prodromal AD counterparts.³⁶ No group differences in insular volumes are seen between DLB and AD at the dementia stage, so longitudinal studies are required to determine its precise value as an early diagnostic marker of DLB.³⁷ Insula is also involved early in frontotemporal dementia (FTD), being the first cortical area to show atrophy in presymptomatic GRN, MAPT, or C9ORF72 mutation carriers^{e25} and unlikely therefore to be helpful in differentiating DLB from FTD.

Low occipital uptake on perfusion/metabolism scan

Occipital hypometabolism on FDG-PET is associated with DLB,³⁸ and together with relative preservation of posterior cingulate metabolism (the cingulate island sign)^{e26} is a supportive biomarker of DLB.² How frequently the cingulate

island sign is seen in prodromal DLB remains to be established; significantly reduced posterior cingulate metabolism may be a useful indication of the concurrence of additional neurofibrillary tangle pathology.^{e27}

Other biomarkers

There is currently no α -synuclein radioligand with sufficient evidence supporting its utility for imaging DLB or any other α -synucleinopathy, nor have any diagnostically applicable biofluid, peripheral tissue, or genotypic biomarkers been established.² CSF measures cannot reliably discriminate between DLB and AD,³⁹ although the measurement of CSF α -synuclein aggregates using seeding aggregation assays such as protein misfolding cyclic amplification and real-time quaking-induced conversion is providing encouraging preliminary results and may be extended to more accessible biofluids including saliva, plasma, serum, or urine.^{e28} Combining CSF markers may be useful; for example, addition of CSF phospho-tau to α -synuclein significantly improved the differential diagnosis between MCI-LB and MCI-AD increasing sensitivity and specificity both > than 95%.^{e29} Other direct or indirect biomarker candidates that may occur early include identification of phosphorylated α -synuclein deposits in peripheral nervous tissue from skin biopsy,⁴⁰ gait analysis,^{e30} and abnormalities in color vision discrimination.^{41,42}

The figure shows a framework for considering a wider range of biomarkers in the setting of prodromal DLB determining the extent to which AD-related pathology is contributing to the dementia syndrome and influencing clinical trajectories in these patients.^{43,44,e31,e32} $A\beta_{42}$ declines earlier in AD than DLB, whereas $A\beta_{40}$ levels increase alone in AD. A low

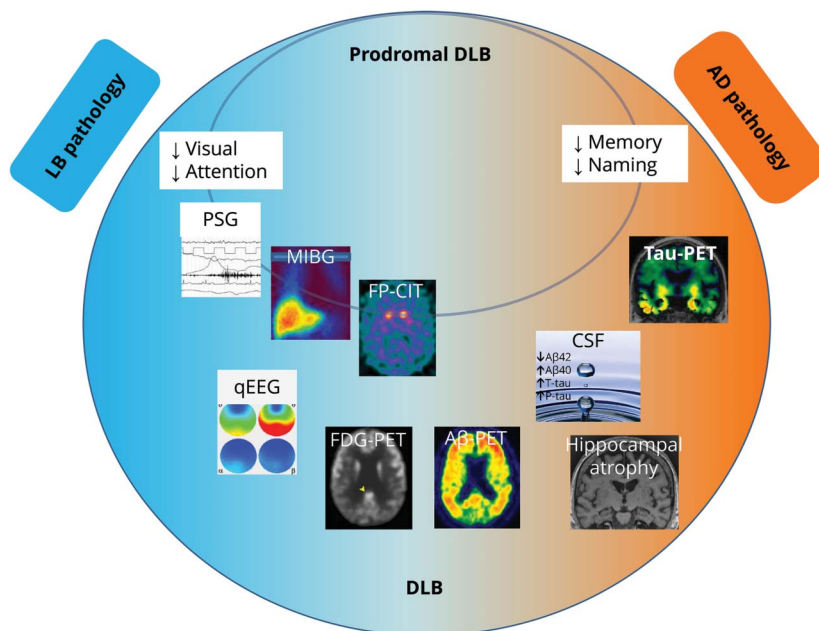
$A\beta_{42}/A\beta_{40}$ ratio may therefore differentiate patients with prodromal AD from patients with prodromal DLB better than individual measures.⁴³ There is also evidence showing different frequencies and topographies of abnormal uptake on amyloid and tau PET imaging in DLB vs AD.⁴⁵

Delirium-onset DLB

Cognitive fluctuations, or pronounced variations in alertness and arousal, are a core feature of DLB, apparent as marked fluctuations in cognitive ability or function, detectable by observation or informant report, and measurable using sensitive cognitive and electrophysiologic measures.^{e33} The occurrence of delirium (sometimes referred to as acute confusional state) as an early presenting feature of DLB has been described in numerous case reports and series,^{e34} including in those with no apparent previous history of cognitive impairment.^{46,e35} Whether this represents a greater vulnerability to delirium in subjects with DLB, or the misdiagnosis of severe fluctuations with clouding of consciousness as delirium, or a combination of both is unclear.

Recognition that DLB may first present as delirium is important because most guidelines for behavioral disturbances in delirium recommend antipsychotics as first-line pharmacologic treatment. Delirium or marked fluctuations in consciousness were reported by 43% of caregivers before DLB diagnosis,⁴⁷ and previous episodes of delirium were much more frequent in patients with DLB compared with patients with AD (25% vs 7%), with 1 in 4 of those with DLB having repeated delirium.¹¹ In the majority of these, potential provoking causes were present. A similarly higher incidence of delirium was found for subjects with DLB compared with

Figure Multimodal biomarkers for prodromal DLB



Reduced dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET; PSG-confirmed REM sleep without atonia and MIBG myocardial scintigraphy are proposed as biomarkers of prodromal DLB. Multimodality biomarkers are also important in characterizing patients with prodromal DLB, in whom the pathologic mechanisms of cognitive impairment include both LB and AD pathologies and who may have abnormalities associated with both. Medial temporal lobe uptake on tau PET, medial temporal lobe atrophy on MRI, and high levels of uptake on amyloid PET and positive CSF biomarkers of AD-related pathology may characterize patients with prodromal DLB with significant AD pathology. It is expected that biomarker abnormalities detected in the earliest stages will remain abnormal as disease progresses, with additional biomarkers showing changes later during the progression from prodromal to dementia phase DLB. DLB = dementia with Lewy bodies; MIBG = meta-iodobenzylguanidine.

subjects with AD in the year before diagnosis (17.6 v 3.2/100 person-years),⁹ and admissions for delirium were more common in those already diagnosed with DLB than for other dementias. Prolonged delirium may also raise the index of suspicion for DLB.^{e36} In an FDG-PET imaging study of prolonged delirium, 32% of subjects were found to have a DLB like pattern, a high proportion in regard both to the known prevalence of the disease and to that of their matched cognitively impaired control group (4%).^{e37}

The similarities between the marked fluctuations in DLB and disturbances of attention and consciousness in delirium have been noted and reviewed,⁴⁶ but there is as yet little understanding of a shared neurobiological basis. There have been few pathologic studies, and although in an epidemiologic-based autopsy cohort, there was no link between delirium and LB pathology at autopsy,^{e38} a significantly increased risk of postoperative delirium in those with peripheral α -synuclein pathology has been described.⁴⁸ Delirium has been suggested to be more common in those subjects with DLB with later age at onset,^{e39} but further evidence is needed.

In summary (table 2), it is clear that DLB can present with delirium, and in patients diagnosed with delirium, a careful search for other DLB features should be made with a low threshold for undertaking DLB biomarker examinations, especially in those with recurrent, unexplained, or prolonged delirium. The extent to which delirium presentations of DLB have the biomarker abnormalities associated with established DLB or other prodromal DLB presentations is unclear,

although the PET imaging study cited above supports this,^{e37} as does a report of reduced DAT uptake in a patient with acute, unexplained delirium.⁴⁹ The link between delirium and DLB is an important area for future research, to clarify the relationship between the 2, and to establish which factors associated with delirium should raise the index of suspicion for underlying prodromal DLB.

Psychiatric-onset DLB

Early clinicopathologic studies suggested that DLB may present as a primary psychiatric disorder,^{50,51} but subsequent focus on the cognitive and motor aspects of DLB has limited the documentation of such cases outside of a few centers.^{12,32,52–54,e36} Late-onset major depressive disorder and late-onset psychosis are the most frequently reported presentations differing markedly from the construct of mild behavioral impairment^{e40} and sometimes sufficiently severe to require hospitalization. Symptoms include hallucinations in visual and in other modalities and systematized delusions including Capgras syndrome,⁵⁵ apathy, anxiety, and depression. Psychiatric-onset DLB cases are not easily differentiated from non-LB late-onset psychosis cases on the basis of primary psychiatric phenomenology or neuropsychological profile alone.⁵⁴ Psychomotor retardation such as slowed speech, thinking, and body movements can resemble the bradykinesia of parkinsonism. The occurrence of rest tremor or rigidity is more helpful than bradykinesia to suspect prodromal DLB in patients with depressive disorder,⁵³ but psychotropic-induced parkinsonism may complicate diagnosis. Atypical clinical features may prove valuable pointers

Table 2 Summary of key features of delirium-onset DLB

Patients with DLB are more susceptible to delirium than people with Alzheimer disease, and this delirium may occur as their presenting complaint before dementia develops.

Such episodes may be provoked by multiple factors including surgery, infections/sepsis, fever, or other systemic illness, or secondary to use, or sudden withdrawal of, alcohol or psychoactive drugs.

Prodromal DLB should be particularly suspected in patients

- in whom adequate provoking factors for the delirium are not found.
- with prolonged or recurrent delirium
- who later develop progressive cognitive decline or subsequent dementia

Core clinical features of DLB are likely to be of more limited diagnostic weight in a patient with delirium because

- cognitive fluctuation and clouding of consciousness can also occur in non-DLB delirium, i.e., are not diagnostically specific for DLB in this situation
- visual hallucinations may occur in non-DLB delirium, particularly drug-induced or provoked by alcohol abstinence
- motor parkinsonism present may be due to antipsychotic medications used to treat delirium
- the diagnostic significance of a history of RBD in a person with delirium is not yet established

Identification of delirium-onset DLB

- may be assisted by use of MCI-LB biomarkers, but further research evidence of this is required
- is important to inform the management plan including the avoidance or minimization of antipsychotic and anticholinergic agents

Abbreviations: DLB = dementia with Lewy bodies; MCI = mild cognitive impairment; MCI-LB = MCI with Lewy bodies; RBD = REM sleep behavior disorder.

to underlying LB pathology, particularly the presence of recurrent VH¹² when these occur before cognitive impairment becomes evident. As with all α -synucleinopathies, RBD may be a useful indicator, although a relationship between antidepressant usage and subsequent RBD onset is a potential confounder.^{e41} Although the primary psychiatric manifestations are often accompanied by mild cognitive deficits,⁵⁴ cognitive evaluation and interpretation of performance can be difficult when psychiatric symptoms are prominent. The frequency of cognitive fluctuations in psychiatric-onset LB cases has not been determined.

Initial reports suggest that ¹²³I-MIBG scintigraphy may be helpful in psychiatric-onset DLB.^{52,53,56} Eighteen of 35 patients with a first onset of major depressive disorder >50 years and with bradykinesia developed a clinical diagnosis of DLB after 6 years of follow-up. All 18 had an abnormal ventilatory response to hypercapnia (VRH), indicative of severe autonomic dysfunction, whereas none of the 17 patients with a normal VRH converted to DLB within the study period. For the converters, the most common presentation was with psychotic and melancholic features simultaneously. The frequency of hypersensitivity to antipsychotics, antidepressants, and anti-anxiety drugs was higher in converters than in non-converters.⁵³ Further studies need to confirm these findings and to determine the value of other DLB biomarkers in psychiatric-onset cases.^{32,52,56}

In summary, it is not yet clear how to identify patients with prominent late-onset psychiatric symptoms who may have underlying LB disease and subsequently progress to DLB. It is

premature to try to construct formal criteria for psychiatric-onset DLB, but clinicians in mental health and other settings need to be aware that this possibility exists, not least because of the risk of severe antipsychotic sensitivity reactions with increased morbidity and mortality. The small available literature including reports such as those cited above does provide some useful guidance, summarized in table 3, but requires replication and further investigation.

Idiopathic REM sleep behavior disorder

RBD is characterized by abnormal dream enactment behavior during REM sleep, accompanied by loss of muscle atonia during REM sleep (REM sleep without atonia or RSWA) on PSG. For the purpose of a prodromal DLB diagnosis, a clinical history of RBD is obtained in the same way as for DLB,² that is, a clear complaint of dream enactment by a bedpartner or other witness, with no evidence of sleep disorders that may mimic RBD on clinical interview. Conditions known to mimic or masquerade as RBD include non-REM parasomnias (sleep walking, sleep talking, or other behaviors that emerge from non-REM sleep stages), obstructive sleep apnea, confusional arousals, or nocturnal seizures. In the absence of PSG, the risk of a false-positive clinical diagnosis of RBD is reduced by using optimized sleep questionnaires, which can have sensitivity and specificity over 90%.^{e42}

RBD may be considered as idiopathic until it is associated with another ongoing neurologic condition, the most frequent being an α -synucleinopathy (PD, DLB, or MSA). In a recent large study, 73.5% of patients with RBD converted to an overt neurodegenerative syndrome after 12-year follow-up, 56.5% developing parkinsonism, and 43.5% dementia as their first

Table 3 Summary of key features of psychiatric-onset DLB

Is characterized by predominant psychiatric symptoms that typically correspond to late-onset major depressive disorder or late-onset psychosis, which may feature hallucinations in visual and in other modalities, and systematized delusions including Capgras syndrome

- may also present with apathy, anxiety, and depression
- may be sufficiently severe to require hospitalization
- the frequency of LB disease as a cause of late-onset psychiatric disorder is not known

When assessing for core clinical features of DLB in a patient with a primary psychiatric presentation:

- bradykinesia may be mimicked by psychomotor retardation, which is commonly seen in depressive disorders
- parkinsonism may be induced by antipsychotic medications used to treat psychiatric disorder
- RBD (and REM sleep without atonia) may be induced by antidepressant medications
- mild cognitive disturbance may be present but is not predominant and may fluctuate
- formal neuropsychological testing may be confounded by the psychiatric mental state
- the frequency and character of cognitive fluctuations is unknown

Identification of psychiatric-onset DLB

- may be assisted by use of MCI-LB biomarkers, but further research evidence of this is required
- is important to inform the management plan including the avoidance or minimization of antipsychotic and anticholinergic agents

Abbreviations: DLB = dementia with Lewy bodies; MCI = mild cognitive impairment.

disease manifestation. Among many predictive markers tested, only the cognitive variables differed at baseline between those converting to primary dementia vs parkinsonism.⁷ Other multicenter studies confirm that the only clinical feature that predicts dementia vs parkinsonism first is neuropsychological performance; those with RBD who exhibit cognitive changes are more likely to evolve first into MCI or DLB.^{22,e4} Thus, although RBD may be regarded an early manifestation of α -synucleinopathy, it is not possible to clearly distinguish whether an individual presenting with RBD will develop dementia first, that is, evolve into a primary DLB diagnosis, or parkinsonism first, that is, a primary PD/MSA diagnosis. Any MCI subtype associated with PSG-confirmed RBD is highly likely to represent underlying LB disease. Although idiopathic RBD is a useful model to study the early stages of LB disease progression, it is not necessarily representative of the whole spectrum of patients with PD and DLB, a significant minority of whom do not have RBD.⁴²

Autonomic dysfunction/anosmia and other nonspecific prodromal LB disease symptoms

Patients with DLB frequently report a history of autonomic dysfunction at first clinic attendance, with 25%–50% complaining of one or more among constipation, orthostatic dizziness, urinary incontinence, erectile dysfunction, increased sweating, or increased saliva.^{56,57} In a cohort of patients with pure autonomic failure, 34% converted to an overt α -synucleinopathy over 6 years of follow-up; this was to DLB (52%), PD (24%), or MSA (24%).⁵⁸ However, because there are many other causes for autonomic dysfunction in older people, these symptoms, either alone or in combination, have low positive predictive value.⁵⁹ The situation is similar for hyposmia, which also frequently occurs early in prodromal DLB and PD,⁴² but which can have many other causes in this age group.

Conclusions and future direction

Diagnosis of DLB at the dementia stage depends on identifying fully expressed core clinical features, which may be mild or absent at the prodromal stage when biomarker evidence may also be weaker and may even differ from that found at the dementia stage. Several new biomarker candidates, direct and indirect, are in development, and we will continue to review these to update our recommendations as soon as sufficient evidence accumulates. We recognize that the clinical phenotype of neurodegenerative disorders reflects interaction between several rather than a single brain pathology, and it is therefore likely that multiple biomarkers of individual pathologies (e.g., α -synuclein, β -amyloid, and tau), or of disease surrogates (e.g., metabolic imaging/EEG), will be required.

Although we have described the 3 prodromal DLB syndromes separately, they are unlikely to be mutually exclusive, and there may be substantial overlap. We propose operationalized criteria only for MCI-LB because the evidence base from our systematic review, albeit relatively limited, is sufficient to

support recommendations that are immediately applicable and testable. Our recommendations should be used alongside guidance about the prodromal manifestations of PD,^{15,59} MSA,⁶⁰ and AD¹⁴ with which there is overlap. Notwithstanding the potential benefits of early diagnosis, we are also mindful of the importance of avoiding incorrect (false-positive) diagnosis of prodromal DLB and the potential negative consequences this could have for an individual. We suggest that the predictive validity of different categories and combinations of our proposed criteria should be clarified by prospective studies before they are adopted for widespread clinical use and that they will enable standardization for inclusion in research studies and clinical trials.

Some published guidance about the early clinical diagnosis of DLB does already exist. DSM5 recommends a diagnosis of mild neurocognitive disorder (NCD) with LB “for individuals who present with the core or suggestive features at a stage when cognitive or functional impairments are not of sufficient severity to fulfill criteria for major NCD”.^{e43} This is based, however, on the 2005 version of DLB guidelines and requires updating. *ICD-11* takes a similar approach toward diagnosing mild NCD at a syndromic level and lists both Lewy body disease and PD as possible causes.^{e44}

The diagnostic position for other prodromal manifestations of DLB, that is, delirium-onset and psychiatric-onset, is less clear than for MCI. Operationalization of specific criteria for these syndromes is not yet justified, and the reliable differentiation of the minority of delirious and psychiatrically ill patients who have underlying LB pathology, from the majority who do not, will probably only be achieved when routinely applicable biomarkers are developed. LB disease is seldom, if ever, currently considered as part of the differential diagnosis of delirium or late-onset psychiatric disorder, and we hope that the information we provide in the text and accompanying boxes will raise clinicians’ awareness of that possibility.

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Appendix (continued)

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Continued

Appendix (continued)

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| Pietro Tiraboschi, MD | Istituto Neurologico "Carlo Besta", Milan | Design and conceptualization of the study, acquisition of data, analysis and interpretation of the data, and drafting and revising the manuscript for intellectual content. |

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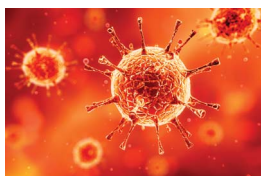
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