Title: Research criteria for the diagnosis of prodromal dementia with Lewy bodies.

Abstract

The prodromal phase of dementia with Lewy bodies (DLB) includes (i) mild cognitive impairment (MCI), (ii) delirium, and (iii) 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 pre-dementia, symptomatic stage. We propose operationalized diagnostic criteria for probable and possible mild cognitive impairment with LB (MCI-LB), which are intended for use in research settings and which are compatible with current criteria for other prodromal neurodegenerative disorders including Alzheimer's and Parkinson's disease. While there is still insufficient evidence to propose formal criteria for delirium-onset, and psychiatric-onset presentations of DLB, we feel it important to characterise them, raising the index of diagnostic suspicion and prioritising them for further research investigation. (140 words).

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 behaviour 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 pre-dementia stage with signs or symptoms indicating that DLB will subsequently develop, and encompasses not only cognitive deficits but also a

variable mixture of non-cognitive clinical features including motor symptoms and signs, sleep disorders, autonomic dysfunction and neuropsychiatric disturbance.[3] Since these first clinical manifestations can occur 15 years or more before dementia onset, precise early diagnosis of DLB presents particular challenges, individuals being indistinguishable from those with the first manifestations of Parkinson's disease (PD) or multiple system atrophy (MSA) which are also α-synuclein related syndromes,[4] or of other dementing disorders particularly AD.

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 room visits.[e3] Importantly, early diagnosis would help patients and families to plan and to implement early non-pharmacologic interventions, (e.g. exercise and behavioral strategies). It would also facilitate selection for trials of targeted therapies as these become available.

How does prodromal DLB usually present?

One or more of the core clinical features characteristic of fully developed DLB may develop before dementia, and is usually accompanied by mild cognitive complaints.[5] Spontaneous parkinsonism often develops within the pre-dementia stage but is not present in all patients.[3, 6] REM sleep behavior disorder (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 pre-dementia stage of DLB[9] as can fluctuations of cognition and arousal[3] that may give rise to a diagnosis of delirium. Visual hallucinations (VH) either spontaneous or provoked by illness or medication, are more likely to occur compared to 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, three prototypic prodromal DLB syndromes have been proposed[13] either as (i) mild cognitive impairment (MCI), (ii) delirium, or (iii) psychiatric-onset In order to investigate these further we conducted a systematic review; our search strategy and selection criteria are detailed in Appendix 1.

BOX 1 HERE.

MCI with Lewy bodies (MCI-LB).

The NIA-AA criteria for MCI [e5, e6] provide a standardized approach to diagnosis and form the basis for our proposed 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 standardised assessment with scores on neuropsychological measures that are typically 1 to 1·5 standard deviations 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 cut-off scores.[e5] Impairment on neuropsychological tests may also be demonstrated by significant decline demonstrated on serial testing or significant decline from estimated premorbid abilities.[e6] Cognitive impairment may additionally be categorised as single or multiple domain, and as amnestic or non-amnestic, which may help to classify potential subgroups as they relate to biomarkers and pathological correlates, and differences in rate of decline and progression to dementia which will 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.[14,e7,e8]

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.[15,e9,e10] 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.[5,6,16-18]

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.[19] Of 49 patients with MCI who progressed to DLB, 27% had multi-domain amnestic MCI but only 6% had

single-domain amnestic MCI[3], similar to other reports.[18, 20] MCI-LB patients with memory impairment also tend to have attention and/or visual processing deficits, (e.g. patients with RBD who later developed DLB had attention/executive deficits up to six years before the diagnosis of dementia, and memory deficits up to two years before the diagnosis).[21] Impaired verbal memory performance in DLB may be related to slowed processing speed and deficits in working memory and retrieval that characterize the attention and executive deficits,[e11] consistent with hippocampal preservation in MCI-LB compared to MCI-AD.[22,e12] Impaired memory in DLB may also be related to the contribution of comorbid AD-related pathology [e10], lower memory scores in DLB being associated with greater hippocampal atrophy [e13] and greater CA1 hippocampal subfield pathology.[e14]

Similar to other subtypes of MCI, a proportion of patients may revert to cognitively normal, although they remain at greater risk for the eventual development of dementia.[e15] 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 characterised as non-amnestic MCI and, to a lesser extent, multi-domain amnestic MCI, while single domain amnestic MCI is specific to MCI-AD. The MCI-LB cognitive pattern is often seen in patients with one or more core DLB features[5] although these may develop later.[3, 17] Non-amnestic MCI rarely develops into AD but is associated with a greater risk of transition to DLB [10, 20] with a ten-fold risk compared with amnestic MCI.[3] Since a substantial subset of DLB patients have co-existing AD-related pathology that may influence their cognitive profile, MCI-LB still should be considered an important part of the differential diagnosis in amnestic cognitive profile 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 upon 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.[23-25] 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 multi-domain non-amnestic 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 remain to be established.

TABLE 1 HERE

Table 1

Research criteria for the clinical diagnosis of probable and possible mild cognitive impairment with LB (MCI-LB)*

Essential for a diagnosis of MCI with LB (MCI-LB) is mild cognitive impairment defined by the presence of each of the following:

Concern by patient, informant or clinician regarding cognitive decline

Objective evidence of impairment in one 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 criteria for dementia.

Core clinical features

Fluctuating cognition with variations in attention and alertness.

Recurrent visual hallucinations.

REM sleep behavior disorder.

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:

a Two or more core clinical features of DLB are present, with or without the presence of a proposed biomarker, or

b Only one core clinical feature is present, but with one or more proposed biomarkers .

Probable MCI-LB should not be diagnosed based on biomarkers alone.

Possible MCI-LB can be diagnosed if:

a Only one core clinical feature of DLB is present, with no proposed biomarkers, or

b 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

Legend Table 1: Research criteria for the clinical diagnosis of probable and possible mild cognitive impairment with LB. (MCI-LB) *These should be used in conjunction with the corresponding manuscript text which gives further information about core and supportive clinical features, and the use of biomarkers as they apply to MCI-LB.

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. Although primary research suggests that patients with MCI-LB have more severe cognitive impairment in attention, executive, memory and visuospatial domains than those with PD-MCI,[26] these variations are not easily operationalized to discriminate individual subjects. The adoption of the one-year rule 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 have been reported to be at greater risk of developing PD over subsequent years[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. Cognitive changes in prodromal PD predominantly affect executive function[21] with memory function as the second most commonly affected domain,[27] not the multi-domain non-amnestic pattern predictive of DLB.

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 ante-mortem. 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. Biomarkers for which only limited data are available are categorised as potential biomarkers, recognising 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 established[2] and its sensitivity in distinguishing MCI with LB (MCI-LB) from MCI with AD was 54% and specificity 89%[28], when MCI-LB was defined by the presence of one core clinical feature of DLB in MCI patients. A higher sensitivity of 61% was achieved when two core clinical symptoms were present.[28] Reduced striatal DAT uptake therefore appears 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 (RSWA).

The association between RBD and synucleinopathy is highly specific, (e.g. a multicentre autopsy study found that, of 80 subjects with polysomnography [PSG]-confirmed RBD and a coexisting neurodegenerative disorder, only two had a disease unrelated to α-synuclein deposition).[,e4] These data imply that a patient presenting with MCI and having PSG-confirmed RBD i.e. a history of probable RBD plus clear documentation of RSWA on PSG, also has a high probability of an underlying

prodromal synucleinopathy. Since around a quarter of DLB patients 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.[29]

Reduced meta iodobenzylguanidine (MIBG) uptake on myocardial scintigraphy. Reduced MIBG uptake is an indicative biomarker for DLB[2] and has also been reported to occur in a small series of patients with late-onset psychiatric disorder and PSG-confirmed RBD,[30] reinforcing its association with underlying α-synucleinopathy. Of two amnestic MCI patients with low MIBG uptake, one developed DLB after two years; the other had no clinical follow up reported. [e17] Visual hallucinations and/or RBD were reported among seven of 13 MCI patients 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. [e18] Despite paucity of longitudinal data [e19] there seems to be sufficient evidence that abnormal MIBG myocardial scintigraphy in an MCI patient 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 [e20] and RBD,[e21] posterior slow wave activity with periodic fluctuations in the pre-alpha range being supportive of DLB.[2] Quantitative electroencephalogram (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 MCI subjects 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.[31]

Relative preservation of medial temporal lobe structures on structural imaging.

Absent or minimal medial temporal lobe (MTL) 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,[32] 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%.[22] Suboptimal specificity may be due to the variability of hippocampal atrophy in AD[33], and contribution of other pathologic processes such as TAR DNA binding protein 43 (TDP43). [e22]

Insular thinning and grey matter volume loss.

Insular cortical thinning occurs in prodromal DLB relative to healthy controls using MRI T1 sequences, with grey matter atrophy predominantly affecting the anterior cingulum and medial frontal structures. This contrasts more extensive loss of grey matter in the temporal, frontal, and parietal regions of prodromal AD subjects. Insular cortical thinning may therefore differentiate prodromal DLB patients not only from healthy controls, but also from their prodromal AD counterparts.[34] 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.[35] Insula is also involved early in frontotemporal dementia (FTD), being the first cortical area to show atrophy in pre-symptomatic GRN, MAPT, or C9ORF72 mutation carriers [e23] 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 [36] and together with relative preservation of posterior cingulate metabolism (the cingulate island sign),[e24] 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.[e25]

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 bio-fluid, peripheral tissue or genotypic biomarkers been established.[2] CSF measures cannot reliably discriminate between DLB and AD[37], although the measurement of CSF α-synuclein aggregates using seeding aggregation assays, such as Protein-Misfolding Cyclic Amplification (PMCA) and Real-Time Quaking-Induced Conversion (RT-QuIC) is providing encouraging preliminary results and may be extended to more accessible bio-fluids including saliva, plasma, serum, or urine. [e26] 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%[.e27] Other direct or indirect biomarker candidates which may occur early include identification of phosphorylated α-synuclein deposits in peripheral nervous tissue from skin biopsy[38], gait analysis, and abnormalities in colour vision discrimination.[39, 40]

Figure 1 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.[41, 42,e28,e29] Aβ42 declines earlier in AD than DLB whereas Aβ40 levels increase alone in AD. A low Aβ42/Aβ40 ratio may therefore differentiate prodromal AD from prodromal DLB patients better than individual measures.[41] There is also evidence showing different frequencies and topographies of abnormal uptake on amyloid and tau PET imaging in DLB vs AD.[43]

FIGURE 1 HERE

Multimodal biomarkers for prodromal DLB

Legend:
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. Multi-modality biomarkers are also important in characterizing patients with prodromal DLB, in whom the pathological 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, as well as positive CSF biomarkers of AD-related pathology may characterize prodromal DLB patients 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.
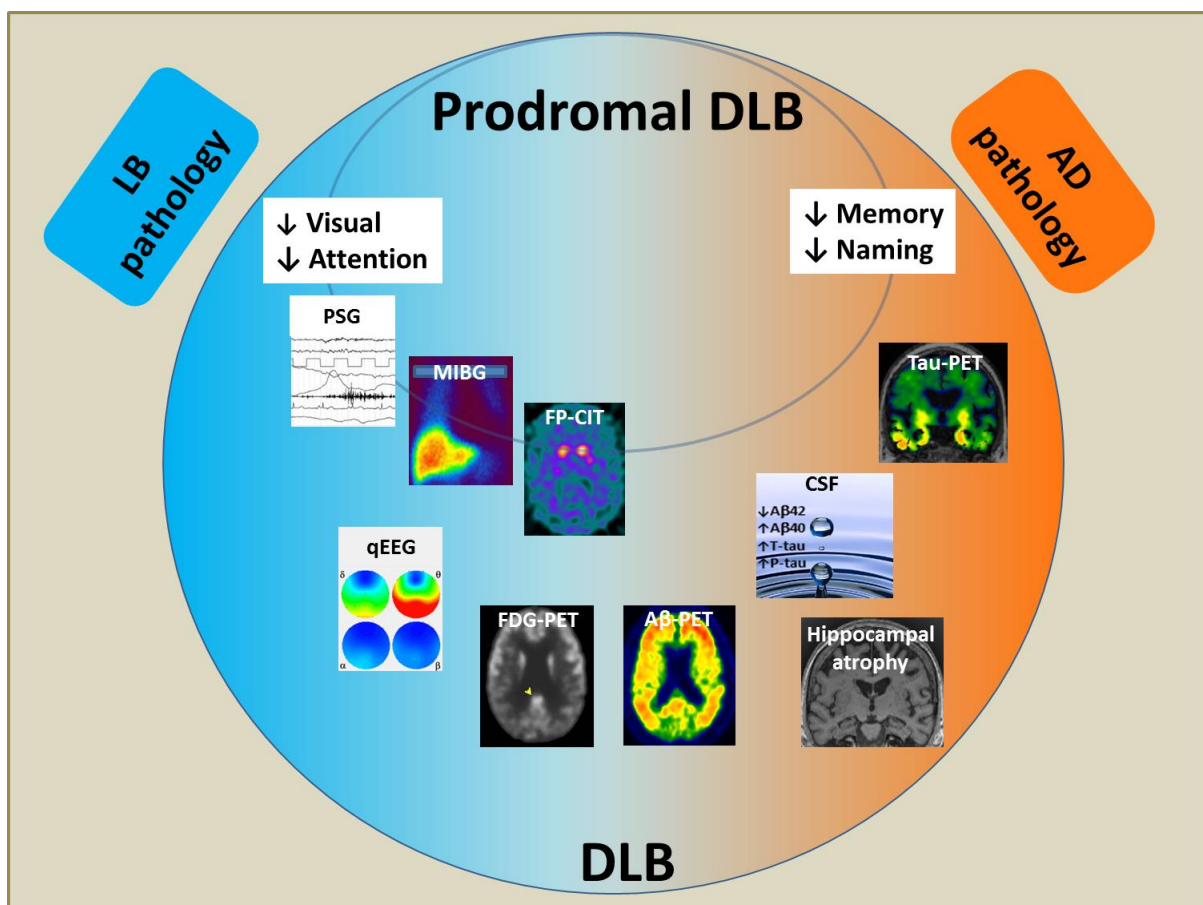
Delirium-onset DLB

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 measureable using sensitive cognitive and electrophysiological measures.[e30] 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,[e31] including in those with no apparent prior history of cognitive impairment.[44,e32] 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 behavioural disturbances in delirium recommend antipsychotics as first line pharmacological treatment. Delirium or marked fluctuations in consciousness were reported by 43% of caregivers prior to DLB diagnosis,[45] and previous episodes of delirium were much more frequent in DLB compared with AD patients (25% vs 7%), with one in four 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 DLB compared to AD subjects 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.[e33] 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%).[46]

The similarities between the marked fluctuations in DLB and disturbances of attention and consciousness in delirium have been noted and reviewed, [44] but there is as yet little understanding of a shared neurobiological basis. There have been few pathological studies, and although in an epidemiological based autopsy cohort there was no link between delirium and LB pathology at autopsy,[e34] a significantly increased risk of post-operative delirium in those with peripheral α-synuclein pathology has been described.[47] Delirium has been suggested to be more common in those subjects with DLB with later age of onset, [e35] but further evidence is needed.

In summary, 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, though the PET imaging study cited above supports this,[46] as does a report of reduced DaT uptake in a patient with acute, unexplained delirium.[48] The link between delirium and DLB is an important area for future research, to clarify the relationship between the two and to establish which factors associated with delirium should raise the index of suspicion for underlying prodromal DLB.

TABLE 2 HERE

> **Table 2 : Delirium-onset DLB**
>
> Patients with DLB are more susceptible to delirium than people with Alzheimer's 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 minimisation of antipsychotic and anticholinergic agents

Psychiatric-onset DLB

Early clinicopathological studies suggested that DLB may present as a primary psychiatric disorder[49, 50] but subsequent focus on the cognitive and motor aspects of DLB limited documentation of such cases outside of a few centres.[12, 30, 51-53, e36] Late-

onset major depressive disorder or late-onset psychosis are the most frequently reported presentations differing markedly from the construct of mild behavioural impairment (MBI),[e37] and sometimes sufficiently severe to require hospitalization. Symptoms include hallucinations in visual and in other modalities; systematized delusions including Capgras syndrome,[54] 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.[53] 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.[52] Psychotropic-induced parkinsonism may also complicate diagnosis. Atypical clinical features may prove valuable pointers to underlying LB pathology, particularly the presence of recurrent VH[12] when these occur before cognitive impairment becomes evident. As with all α-synucleinopathies, RBD may be a useful indicator although a relationship between anti-depressant usage and subsequent RBD onset is a potential confounder.[e39] Although the primary psychiatric manifestations are often accompanied by mild cognitive deficits,[53] 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 ^{123}I-MIBG scintigraphy may be helpful in psychiatric-onset DLB.[51, 52, 55] Eighteen of 35 patients with a first onset of major depressive disorder >50 years and with bradykinesia, developed a clinical diagnosis of DLB after six 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, antidepressant and anti-anxiety drugs, was higher in converters than in non-converters.[52] Further studies need to confirm these findings and to determine the value of other DLB biomarkers in psychiatric-onset cases.[30, 51, 55]

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, which requires replication and further investigation.

TABLE 3 HERE.

Table 3: Psychiatric-onset DLB

Is characterised 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 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 minimisation of antipsychotic and anticholinergic agents

Rapid eye movement (REM) sleep behaviour disorder

RBD is characterised by abnormal dream enactment behaviour during REM sleep, accompanied by loss of muscle atonia during REM sleep (REM sleep without atonia, or RSWA) on polysomnography (PSG). 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%.[e39]

RBD is strongly associated with the α-synucleinopathies and therefore qualifies as a prodromal presentation of each of these. For an individual patient in the early stages of idiopathic RBD, it is impossible to clearly distinguish whether they will later develop dementia first i.e. a primary DLB diagnosis, or parkinsonism first i.e a primary PD/MSA diagnosis. In a recent large study 73·5% of RBD patients converted to an overt neurodegenerative syndrome after 12-year follow-up, 56·5% developing parkinsonism and 43·5% dementia as their first disease manifestation. Amongst many predictive markers tested, only the cognitive variables differed at baseline between those converting to primary dementia versus parkinsonism.[7] Other multicentre studies confirm that the only clinical feature that predicts dementia versus parkinsonism first is neuropsychological performance; those with RBD who exhibit cognitive changes are more likely to evolve first into MCI / DLB. [21,e4] 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 PD and DLB patients, a significant proportion of whom do not have RBD.[40]

Autonomic dysfunction /anosmia and other non-specific prodromal LB disease symptoms.

DLB patients frequently report a history of autonomic dysfunction at first clinic attendance with 25 – 50% complaining of one of more among; constipation, orthostatic dizziness, urinary incontinence, erectile dysfunction, increased sweating or increased saliva. [55, 56] In a cohort of patients with pure autonomic failure, 34% converted to an overt α-synucleinopathy over six years of follow-up; this was either to DLB (52%), PD (24%), or MSA (24%).[57] However, since there are many other causes for autonomic dysfunction in older people, these symptoms, either alone or in combination, have low positive predictive value.[58] The situation is similar for hyposmia which also frequently occurs early in prodromal DLB and PD,[40] but which can have many other causes in this age group.

Conclusions and future direction.

Diagnosis of DLB at the dementia stage depends upon 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 in dementia. Several new biomarker candidates, direct and indirect, are in development and we will continue to review these in order 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 three prodromal DLB syndromes separately, they

are unlikely to be mutually exclusive and there may be substantial overlap. We propose operationalized research criteria only for MCI-LB since the evidence base from our systematic review, albeit relatively limited, is sufficient to support recommendations that are immediately applicable and testable. Their predictive validity needs to be established, as does the value of distinguishing between possible and probable categories. Our recommendations refer specifically to prodromal DLB and should be used alongside guidance about the prodromal manifestations of PD,[14, 58], MSA[59] and AD [e5] with which there is overlap. 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".[e40] This is based upon the 2005 version of DLB guidelines and requires updating. ICD11 takes a similar approach towards diagnosing mild NCD at a syndromic level and lists both Lewy body disease and PD as possible causes.[e41] The diagnostic position for other prodromal manifestations of DLB, i.e. 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 possible 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 hope that the information we provide in the text and accompanying boxes will raise clinicians' awareness of those possibilities.

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decision to submit it for publication. The corresponding author (IMK) had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Authors Contributions.

Ian McKeith: design or conceptualization of the study, major role in the acquisition of data, analysis or interpretation of the data, drafting or revising the manuscript for intellectual content. Tanis Ferman: design or conceptualization of the study, major role in the acquisition of data, analysis or interpretation of the data, drafting or revising the manuscript for intellectual content. Alan J Thomas: design or conceptualization of the study, major role in the acquisition of data, analysis or interpretation of the data, drafting or revising the manuscript for intellectual content. Frédéric Blanc: design or conceptualization of the study, major role in the acquisition of data, analysis or interpretation of the data, drafting or revising the manuscript for intellectual content. Bradley Boeve: design or conceptualization of the study, major role in the acquisition of data, analysis or interpretation of the data, drafting or revising the manuscript for intellectual content. Hiroshige Fujishiro: design or conceptualization of the study, major role in the acquisition of data, analysis or interpretation of the data, drafting or revising the manuscript for intellectual content.

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