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Case Report

Prodromal Dementia with Lewy Bodies: A Case Series of the 3 Prodromal Types from Clinical Practice

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Abstract
Prodromal dementia with Lewy bodies (DLB) refers to a state prior to the onset of dementia with clinical signs or symptoms that may indicate the future development of DLB. Prodromal symptoms can include not only cognitive deficits but also a mix of clinical features including sleep disorders, autonomic dysfunction, and neuro-psychiatric disturbances. While diagnostic criteria for the subtypes of prodromal DLB were recently published, they are largely used in research settings. However, these criteria have important implications for clinical practice. Recognition of prodromal DLB stages can lead to identifying deficits sooner, improved patient and family counseling, and advance care planning. This case series presents examples of the 3 subtypes of prodromal DLB – mild cognitive impairment onset, delirium onset, and psychiatric onset – to help clinicians identify individuals who may be on a trajectory to develop DLB.

Introduction

Dementia with Lewy bodies (DLB) is a common cause of dementia, often coexisting with Alzheimer disease pathology. DLB is characterized by cognitive impairment, affecting daily function (dementia) and core symptoms including fluctuation of attention, parkinsonism, hallucinations, and rapid eye movement sleep behavior disorder (RBD) [1]. Prodromal DLB

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refers to a state prior to dementia onset with clinical signs or symptoms that may indicate the future development of DLB [2]. Prodromal symptoms in DLB can present decades before dementia [3]. They include cognitive deficits and clinical features such as sleep disorders, autonomic dysfunction, and neuro-psychiatric disturbances [3].

Research diagnostic criteria for prodromal DLB subtypes were published in 2020 [2]. These criteria also have important implications for clinical practice, including for non-specialists, as only one-third of patients are referred to dementia specialists in the first 5 years post-diagnosis [4]. Many individuals with dementia do not receive a specific diagnosis (e.g., DLB, Alzheimer disease) at all [3]. Additionally, DLB may be initially misdiagnosed in over 70% of cases and numerous office visits are often needed to reach the correct diagnosis [4].

Early diagnosis – including at prodromal stages – can potentially lead to improved patient and family counseling, advance care planning, avoidance of contraindicated antipsychotic administration, earlier symptomatic treatment, and connection to DLB clinical trials. Improved treatment may result in improved patient and caregiver quality of life and reduced hospitalizations, as well as appropriate use of available resources [5].

The research criteria for prodromal DLB describe three phenotypes: mild cognitive impairment (MCI) onset, delirium onset, and psychiatric onset [2]. Research regarding MCI-onset DLB (MCI-LB) was more robust than for the other phenotypes and allowed for development of diagnostic criteria mimicking those for DLB (Table 1) [2].

However, clinicians should also be aware of delirium- and psychiatric-onset presentations. Case reports described the occurrence of delirium as a presenting symptom of DLB, even in individuals without cognitive impairment [6]. Delirium-onset prodromal DLB should be particularly suspected in individuals with delirium without identified provoking factors, with prolonged or recurrent delirium, or who later develop progressive cognitive decline [2]. Challenges to diagnosing delirium-onset DLB include the fact that cognitive fluctuations and hallucinations (core clinical features of DLB and MCI-LB) can be present in non-DLB delirium. Additionally, parkinsonism seen in individuals with delirium can relate to antipsychotic medication use. In cases where physical findings are unclear (e.g., psychomotor retardation vs. parkinsonism), atypical clinical features, such as the presence of recurrent visual hallucinations occurring before cognitive impairment, may prove helpful [7]. The diagnostic value of a history of RBD and/or use of MCI-LB biomarkers in suspected delirium-onset prodromal DLB are currently uncertain.

Psychiatric-onset prodromal DLB is considered when an individual has predominant psychiatric symptoms, usually either late-onset major depressive disorder or late-onset psychosis (which may include visual hallucinations, other hallucinations, and delusions). The psychiatric disturbance may be severe enough to warrant hospitalization and can be difficult to treat. Unfortunately, psychiatric-onset prodromal DLB is not easily distinguished from late-onset psychosis unrelated to Lewy body disease based on the psychiatric phenomenology or neuropsychological profile alone. DLB is commonly diagnosed only as these individuals are followed over time. Caution is needed when assessing individuals with late-onset psychiatric disease for DLB features as RBD may be caused by antidepressant medications and parkinsonism can reflect psychomotor retardation or be induced by antipsychotic medications. Mild cognitive disturbance can be present, but assessment may be confounded by the psychiatric disorder, and cognition may fluctuate. The utility of biomarkers in this setting is currently unknown. This case series presents examples of the 3 subtypes of prodromal DLB to help clinicians identify individuals who may be on a trajectory to develop DLB.

Table 1. Research criteria for the diagnosis of MCI with Lewy bodies

Required criterion: mild cognitive impairment as defined by (must have all 3) 1. subjective cognitive complaint (from patient, informant, or clinician), 2. impairment in 1 or more domains (typically attention-executive or visual processing), 3. preserved or minimally affected independence in functional abilities
Probable MCI-LB: MCI (as above) + presence of ≥2 core clinical features (±proposed biomarker) *OR* 1 core clinical feature + ≥1 proposed biomarker(s)
Possible MCI-LB: MCI (as above) + presence of 1 core clinical feature (no indicative biomarker) *OR* ≥1 indicative biomarkers (no core clinical features)

Core clinical features	Proposed biomarkers
1. Fluctuating cognition with variations in alertness and attention	1. Reduced basal ganglia dopamine transporter uptake (SPECT or PET; e.g., DaT scan)
2. Recurrent visual hallucinations	2. Abnormal (low uptake) ^{123}iodine-MIBG myocardial scintigraphy
3. REM sleep behavior disorder	3. Polysomnographic confirmation of REM sleep without atonia
4. Parkinsonism (presence of one or more: bradykinesia, rest tremor, rigidity)	
Supportive clinical features*	**Potential biomarkers***
1. Severe sensitivity to antipsychotic agents	1. Quantitative EEG showing slowing and dominant frequency variability
2. Postural instability	2. Relative preservation of medial temporal lobe structures on structural imaging
3. Repeated falls	3. Insular thinning and gray matter volume loss on MRI
4. Syncope or other transient episodes of unresponsiveness	4. Low occipital uptake on perfusion/metabolism scan
5. Prolonged or recurrent delirium	
6. Autonomic dysfunction, e.g., constipation, orthostatic hypotension, urinary incontinence	
7. Excessive daytime sleepiness/hypersomnia	
8. Decreased smell/hyposmia	
9. Hallucinations in other modalities, including sense of passage or presence	
10. Systematized delusions	
11. Apathy, anxiety, depression	

Adapted from: McKeith et al. [2].

MCI-LB, mild cognitive impairment with Lewy bodies; SPECT, single-photon emission computed tomography; PET, positron emission tomography; MIBG, metaiodobenzylguanidine; EEG, electroencephalography. *Supportive clinical features and potential biomarkers may help raise suspicion of MCI-LB and/or add weight to suspected diagnosis but are not formally part of the criteria.

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Case #1: Mild Cognitive Impairment Onset

Initial Presentation

A 75-year-old gentleman with a history of benign prostatic hypertrophy, hypertension, hyperlipidemia, chronic kidney disease, and diabetic polyneuropathy was referred for evaluation. He had a 10-year history of dream enactment, which resulted in multiple injuries requiring stitches. He underwent two sleep studies showing REM sleep without atonia. His wife described gradual onset of cognitive changes over 5 years. He had difficulty with calculations, previously a simple task for him. She also raised concerns about word-finding difficulties, short-term memory problems, and excessive daytime sleepiness. He described a 3-year history of visual distortions and illusions but denied formed visual hallucinations. His wife managed finances. While he continued to drive short distances, his wife had concerns about his distractibility while driving. However, he remained otherwise functionally intact, completing all activities of daily living independently.

On examination, he demonstrated mild hypomimia and hypophonia as well as mild bradykinesia in the left hand, but no other parkinsonian features. His Montreal Cognitive Assessment (MoCA) score was 21/30, with points missed in multiple sections, including visuospatial/executive function, language, and delayed recall improved with cueing. MRI brain demonstrated nonspecific mild-moderate cerebral atrophy for age.

Diagnosis and Follow-Up Course

The patient met criteria for MCI-onset prodromal DLB given the presence of executive MCI, RBD, and mild parkinsonism. He also had supportive features of postural instability, transient episodes of unresponsiveness, and hypersomnolence (Table 1). He progressed over the subsequent year, with worsening confusion and cognitive fluctuations. His wife reported he got lost in unfamiliar places, RBD was more prominent, and he developed formed visual hallucinations. He demonstrated more functional impairment over time, and neuropsychological testing was suggestive of multidomain major neurocognitive disorder with particular limitations in executive and visuospatial function. He met criteria for DLB given dementia, cognitive fluctuations, RBD, formed visual hallucinations, and parkinsonism (he had all four core features where only two are required for DLB diagnosis).

Case #2: Delirium Onset

Initial Presentation

A 65-year-old retired computer repairman and active pilot with an unremarkable medical history underwent MRI after mentioning mild memory problems to a new primary care physician. He had a 1-year history of thrashing in his sleep and a 3-month history of new-onset panic attacks. The MRI showed a fourth ventricular mass which was resected (pathology: subependymoma). Immediately post-operatively, he was markedly confused with fluctuating attention, initially attributed to post-operative delirium and benzodiazepine withdrawal. He also had visual hallucinations, poor spatial perception, and leaning to the left with ambulation. Cognitive impairment, hallucinations, and new-onset myoclonus persisted during inpatient rehabilitation, where he was treated with aripiprazole, divalproex, donepezil, escitalopram, quetiapine, and clonazepam. He was admitted to the neurology hospital service directly from his 1-month neurosurgery follow-up appointment.

On admission, neurological examination was notable for masked facies, a left hand resting tremor, bradykinesia, rigidity, myoclonus, and hyperreflexia. He was lethargic, perseverative, and unable to follow some commands. Speech was halting, but he was able to repeat. He had

near-constant hallucinations and delusions, calling the police from his hospital room. Basic laboratories were unremarkable. MRI showed post-surgical changes including meningeal enhancement. Computerized tomography of the chest/abdomen/pelvis was negative for malignancy. Cerebrospinal fluid (CSF) studies showed elevated white blood cells (86; lymphs 46%, monos 54%), red blood cells 25, protein 124, glucose 40, felt to be consistent with post-surgical findings versus inflammation. CSF cultures, RT-QuIC, and a paraneoplastic CSF autoantibody panel were negative. Electroencephalography demonstrated nonspecific slowing. The inpatient differential diagnosis included prolonged post-operative delirium, prodromal DLB, or encephalitis (for which he received IVIG, though changes were ultimately felt to be post-surgical rather than inflammatory/infectious). All central nervous system-acting medications were gradually stopped, starting with the antipsychotics.

Diagnosis and Follow-up Course

Once the patient's delirium improved to the point where he no longer required restraints, he returned to inpatient rehabilitation. Off all CNS-acting medications and with rehabilitation, he improved but never fully returned to his pre-operative baseline. His parkinsonism initially improved dramatically, but he had residual post-operative neurological findings that can occur after 4th ventricular tumor resections (skew deviation, oscillopsia, oculopalatal tremor, mild left hemi-ataxia). In contrast, his cognitive impairment, hallucinations, and parkinsonism were not easily attributable to this localization [8]. He remained easily distractible and had daily hallucinations, but with retained insight. Anxiety and depression persisted. His cognition gradually improved but then worsened again via MoCA screening (Table 2). Neuropsychological testing 13 months after hospitalization showed deficits primarily in processing speed and fronto-executive domains but he declined follow-up testing. Four years after the resection, he demonstrated persistent daily hallucinations and parkinsonism (Table 2) and continued deterioration in cognitive function with particular deficits in fronto-executive and visuospatial domains.

While the diagnostic significance of a history of dream enactment in a person with delirium is not yet established, the wife's report of a 1-year history of thrashing during nightmares could suggest that this patient had a developing synucleinopathy at his initial presentation. This is further supported by mild pre-operative memory concerns (prompting the MRI), new-onset anxiety and panic attacks, a couple of illusions in the patient's peripheral vision the month prior to surgery, and the suggestion of severe and acute drug-induced parkinsonism in the context of antipsychotic use during his rehabilitation admission. The prolonged delirium was also consistent with delirium-onset DLB. Four years later, he met criteria for DLB with dementia, persistent formed visual hallucinations, symptoms suggestive of RBD, and mild parkinsonism with supportive features of anxiety and depression.

Case #3: Psychiatric Onset

Initial Presentation

The family of a 78-year-old woman with a medical history of chronic obstructive pulmonary disease, hyperlipidemia, obstructive sleep apnea, restless leg syndrome, urinary incontinence, depression, and anxiety reported a 1-year history of auditory and visual hallucinations. The patient described hearing a man and a woman talking as well as seeing adults, children, and animals. She had delusions of spousal infidelity and stealing. Initially quetiapine controlled visual hallucinations, but auditory hallucinations persisted. She had some insight into the visual hallucinations but no insight into the auditory hallucinations or delusions. A prior trial of risperidone led to markedly worse hallucinations and insomnia. Her

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Table 2. Progression of cognition in parkinsonism in a case of suspected delirium-onset prodromal DLB

Time post-hospitalization	1 month	3 months	22 months (1 year, 10 months)	30 month (2 years, 6 months)	36 months (3 years)	42 months (3 years, 6 months)	54 months (4 years, 6 months)	60 months (5 years)
Motor UPDRS		13	25	28	18	16	18	29
MoCA	22	26	25			18	20	20

This table shows the course of the parkinsonism and MoCA scores following the hospitalization for Case 2. The parkinsonism has fluctuated over time. Cognition initially improved post-hospitalization but subsequently worsened.
UPDRS: Unified Parkinson's Disease Rating Scale, MoCA: Montreal Cognitive Assessment.

husband reported that she had cognitive fluctuations with intermittent loss of attention and difficulty concentrating. She had difficulty with multitasking and word finding.

Initial clinical exam was notable for subtle parkinsonism with mild right-sided rigidity, hypomimia, and stooped posture. Her MoCA score was 21/30 with deficits in visuospatial/executive function and delayed recall.

Diagnosis and Follow-Up Course

The late-onset anxiety, depression, and psychosis (visual and auditory hallucinations, delusions) that responded variably to medication were suggestive of psychiatric-onset DLB. This was further supported by mild cognitive changes, cognitive fluctuations, mild parkinsonism, and sensitivity to antipsychotic agents.

On follow-up visits, delusions persisted and became more severe. She accused her spouse of being hypnotized and having speakers in his mouth. She also described pain shooting over her skin and something crawling on her head. Clozapine for psychosis had no significant benefit (doses up to 150 mg/day). Modest benefits were achieved with off-label pimavanserin. Cognition has remained largely stable clinically but due to the severity of her psychosis, with many delusions centered on her husband, the patient now resides in a memory care facility.

Discussion

These 3 cases from a specialty clinic illustrate patient presentations that should make a clinician consider prodromal DLB. While prodromal DLB often cannot be confirmed without longitudinal follow-up, early consideration of prodromal DLB is critical in order to assess for core and supportive clinical features, inform biomarker assessment, avoid antipsychotics (e.g., for delirium, late-onset psychosis), and to guide follow-up assessments and patient and family counseling.

When considering the possibility of prodromal DLB, clinicians should assess for core and supportive DLB features, which are largely identical to the core and supportive features for MCI-LB (Table 1). As noted above, the diagnostic value of core DLB features is less certain in the presence of confounders such as delirium (associated with fluctuations, psychosis), conditions, or medications that can cause RBD (e.g., antidepressants), psychomotor slowing mimicking parkinsonism, or potential antipsychotic-induced parkinsonism. In suspected delirium-onset prodromal DLB, persistence of core features after delirium resolution and addressing confounders (e.g., cessation of antipsychotics as seen in Case 2) can further support suspected prodromal DLB. While supportive features (Table 1) do not play a formal role in the diagnosis of either DLB or MCI-LB, the presence of these features – particularly multiple features – should raise additional suspicion of a prodromal DLB process.

In the absence of associated clinical conditions (e.g., untreated obstructive sleep apnea) or provoking medications, a history of RBD symptoms is particularly important to assess when considering prodromal DLB. Longitudinal studies suggest that over 70% of individuals with isolated RBD will develop a synucleinopathy (DLB, Parkinson disease, or multiple system atrophy) during 12 years of follow-up [7]. Clinical history of RBD is obtained through bed partner reports of dream enactment and use of validated scales, though formal diagnosis is made through polysomnography with a finding of REM sleep without atonia.

Biomarkers could be helpful in some cases of suspected prodromal DLB. For MCI-LB, biomarkers proposed as helpful are dopamine transporter imaging (DaT scans), ^{123}iodine-MIBG myocardial scintigraphy, and polysomnography to assess for REM sleep without atonia [2, 9]. However, MIBG myocardial scintigraphy is not available for this indication in the USA. Polysomnography and DaT scan are likely most helpful in cases where the presence of RBD and/or parkinsonism are uncertain from the history and examination. The role of "proposed biomarkers" (Table 1) in MCI-LB and any biomarker in delirium- or psychiatric-onset prodromal DLB is less certain, but studies suggest possible uses for FDG-PET and MIBG myocardial scintigraphy in these scenarios [2]. New commercially available tests for alpha-synuclein in CSF [10] and skin biopsies [11] became available after the publication of the prodromal DLB criteria. These are likely to become increasingly useful in situations where prodromal DLB is being considered as they would provide evidence of the synuclein pathology that is associated with DLB.

One important reason to identify prodromal DLB is to help assess the risks of antipsychotic administration. Research previously found that >80% of individuals with DLB receiving typical antipsychotics had adverse reactions, half of which were severe [12]. Severe sensitivity to antipsychotic agents is a supportive clinical feature in both DLB [1] and MCI-LB criteria (Table 1) [2]. The frequency of antipsychotic sensitivity in prodromal DLB is uncertain. In DLB, non-pharmacologic strategies are recommended as a first-line approach for psychosis, followed by cholinesterase inhibitors and then cautious antipsychotic use. When antipsychotics are required, quetiapine, clozapine, and pimavanserin are felt to be safest [12].

Identification of potential prodromal DLB necessitates ongoing follow-up to assess for symptoms that would further confirm this diagnosis or suggest the development of DLB. Patients and families should be counseled regarding the diagnosis and encouraged to participate in advance care planning. Limited data are available to guide counseling regarding expected progression, but in studies of individuals with MCI-LB, the median time from the first study visit to a dementia diagnosis was 2 years in one study [13] and the average was 2.7 ± 1.7 years in another [14].

In conclusion, recently published prodromal DLB criteria target research settings but have clinical care implications. Identifying MCI-LB, late-onset psychiatric disturbance, and unprovoked or severe delirium should prompt clinicians to assess for additional DLB features and monitor for development of these over time. Identification of these phenotypes should also prompt avoidance of antipsychotics and initiation of advance care planning. Research is needed to assess the validity of these phenotypes, refine diagnostic criteria for both research and clinical settings, and investigate the role that existing and emerging biomarkers can play in identifying prodromal DLB. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000533378).

Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from all the patients next of kin for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Melissa Armstrong devised the project and selected the patients represented in the manuscript. Tracy Tholanikunnel wrote the manuscript with support from Melissa Armstrong and Ben Chapin.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

References

1 McKeith IG, Boeve BF, Dickson DW, Halliday G, Taylor JP, Weintraub D, et al. Diagnosis and management of dementia with Lewy bodies. Fourth consensus report of the DLB consortium. Neurology. 2017;89(1):88–100.
2 McKeith IG, Ferman TJ, Thomas AJ, Blanc F, Boeve BF, Fujishiro H, et al. Research criteria for the diagnosis of prodromal dementia with Lewy bodies. Neurology. 2020 Apr 28;94(17):743–55.
3 Savica, R, Boeve, BF, Mielke, MM. When do α-synucleinopathies start? An epidemiological timeline: a review. JAMA Neurol. 2018 Apr 1;75(4):503–9,
4 Galvin JE, Duda JE, Kaufer DI, Lippa CF, Taylor A, Zarit SH. Lewy body dementia: the caregiver experience of clinical care. Parkinsonism Relat Disord. 2010 Jul;16(6):388–92.
5 Galvin JE, Duda JE, Kaufer DI, Lippa CF, Taylor A, Zarit SH. Lewy body dementia: caregiver burden and unmet needs. Alzheimer Dis Assoc Disord. 2010 Apr-Jun;24(2):177–81.
6 Gore RL, Vardy E, O'Brien JT. Delirium and dementia with Lewy bodies: distinct diagnoses or part of the same spectrum? J Neurol Neurosurg Psychiatry. 2015;86(1):50–9.
7 Postuma RB, Iranzo A, Hu M, Högl B, Boeve BF, Manni R, et al. Risk and predictors of dementia and parkinsonism in idiopathic REM sleep behaviour disorder: a multicentre study. Brain. 2019;142(3):744–59.
8 Ferguson SD, Levine NB, Suki D, Tsung AJ, Lang FF, Sawaya R, et al. The surgical treatment of tumors of the fourth ventricle: a single-institution experience. J Neurosurg. 2018;128(2):339–51.
9 Armstrong MJ, Irwin DJ, Leverenz JB, Gamez N, Taylor A, Galvin JE. Biomarker use for dementia with Lewy body diagnosis: survey of US experts. Alzheimer Dis Assoc Disord. 2021 Jan-Mar 01;35(1):55–61.
10 Bongianni M, Ladogana A, Capaldi S, Klotz S, Baiardi S, Cagnin A, et al. α-Synuclein RT-QuIC assay in cerebrospinal fluid of patients with dementia with Lewy bodies. Ann Clin Transl Neurol. 2019;6(10):2120–6.
11 Mammana A, Baiardi S, Quadalti C, Rossi M, Donadio V, Capellari S, et al. RT-QuIC detection of pathological α-synuclein in skin punches of patients with Lewy body disease. Mov Disord. 2021;36(9):2173–7.
12 McKeith I, Fairbairn A, Perry R, Thompson P, Perry E. Neuroleptic sensitivity in patients with senile dementia of Lewy body type. BMJ. 1992;305(6855):673–8.
13 Wyman-chick KA, O'Keefe LR, Weintraub D, Armstrong MJ, Rosenbloom M, Martin PK, et al. Prodromal dementia with Lewy bodies: evolution of symptoms and predictors of dementia onset. J Geriatr Psychiatry Neurol. 2021;35(4):527–34.
14 Van de Beek M, van Steenoven I, van der Zande JJ, Barkhof F, Teunissen CE, van der Flier WM, et al. Prodromal dementia with Lewy bodies: clinical characterization and predictors of progression. Mov Disord. 2020;35(5):859–67.