REM Sleep Behavior Disorder Associated with Dementia with Lewy Bodies

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6.1 The RBD-DLB Association

RBD has been associated with numerous cases of dementia with Lewy bodies [1–36]. Additionally, several reports involving idiopathic RBD patients followed prospectively (and see below) have shown that phenoconversion to DLB occurs with equal, and perhaps greater, frequency than Parkinson's disease.

6.2 RBD and Diagnostic Criteria for DLB

The classic clinical features of spontaneous parkinsonism, recurrent and fully formed visual hallucinations, and fluctuations in cognition have been the "core" criteria for DLB since the original diagnostic classification system was developed [29, 37, 38]. The presence of two or more of these three core criteria satisfied the diagnosis of clinically probable DLB, and one of these criteria was fitting for clinically possible DLB [38]. The data available at the 3rd Consensus Conference for the Diagnostic Criteria for DLB led to the inclusion of RBD as a "supportive" criterion for DLB, which meant that the presence of RBD plus only one of the core criteria was sufficient for the clinically probable DLB designation [38].

A considerable body of additional evidence supporting the association of RBD plus DLB, regardless of other coexisting features, had accumulated after 2005 when the 3rd criteria were published [10–13, 15, 19, 21, 23–25, 28, 29, 32–35, 39, 40]. This elevated the presence of RBD as a fourth core feature for the diagnosis of DLB in the recently published 4th Consensus Conference for the Diagnostic Criteria for DLB [30]. There was ample debate among the panel of coauthors on whether PSG confirmation of RBD should be required for the RBD criterion or whether a strong

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Table 6.1 Key elements of the updated criteria for the clinical diagnosis of dementia with Lewy bodies

Presence of dementia
• Deficits on measures of attention, executive functions, and visuospatial functions are typically prominent, whereas memory impairment is more variable
Core clinical features
• Fluctuating cognition
• Recurrent well-formed visual hallucinations
• REM sleep behavior disorder, which usually precedes cognitive decline
• Parkinsonism
Supportive clinical features
• Many are described, with a new feature being hypersomnia
Indicative biomarkers
• Polysomnographic confirmation of REM sleep without atonia
• Reduced dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET
• Reduced uptake of 123iodine-MIBG myocardial scintigraphy
Probable DLB—Dementia plus either
• Two or more core clinical features regardless of the presence of indicative biomarkers
• Only one core clinical feature but with one or more indicative biomarkers present
Possible DLB—Dementia plus either
• Only one core clinical feature with no indicative biomarkers present
• One or more indicative biomarkers present but there are no core clinical features

Adapted from McKeith et al. (2017) [30]

and convincing history of recurrent dream enactment behavior consistent with probable RBD was sufficient. Since the clinical diagnostic criteria were designed to be simple and practical for routine clinical use, and due to the expense and lack of availability of PSG in many clinical settings, the consensus of the authors was to consider probable RBD as sufficient. However, PSG evidence of REM sleep without atonia—along with reduced uptake on dopamine transporter SPECT or PET imaging and reduced uptake on cardiac MIBG scintigraphy—were identified as "indicative biomarkers." Other aspects of DLB phenomenology were also added or explained in more detail. For example, hypersomnia was added as a supportive feature, and the qualitative aspects of the neuropsychological profile were characterized—prominent impairment in the domains of attention/executive functioning and visuospatial functioning [30]. The key features of the updated criteria are shown in Table 6.1.

6.3 Prodromal DLB

The development of DLB surely evolves over a transitional state from normal aging to dementia in most individuals. The transitional state that is dominated by changes in cognition is known as mild cognitive impairment (MCI), and several groups have characterized MCI retrospectively and prospectively in those with clinical DLB +/− underlying Lewy body disease [41–43]. Molano et al. analyzed the clinical and

neuropsychological data on all patients who were diagnosed with MCI, prospectively followed, and eventually underwent neuropathologic examination and had limbic +/− neocortical LBD [41]. Eight subjects were identified, seven of whom developed DLB prior to death, and one died characterized as MCI. RBD preceded cognitive symptom onset in six cases by a median of 10 years. Each of the MCI subtypes was represented, with seven of the eight patients having impairment in the attention/executive functioning and/or visuospatial functioning domains. As exemplified by most of these cases, RBD was the initial clinical feature, followed by cognitive decline, then the MCI diagnosis, and subsequent development of parkinsonism, visual hallucinations, and/or fluctuations with eventual neuropathologic evidence of Lewy body disease. Another analysis showed that those patients with the nonamnestic subtype of MCI are more likely to evolve to DLB than the amnestic subtype (which is more likely to evolve to Alzheimer's disease dementia) [44].

Other prodromal DLB phenotypes would be predicted to include isolated visual hallucinations, isolated depression, pervasive apathy, and recurrent delirium. There has not been sufficient prospective data with large numbers of patients with these phenotypes to develop a clear picture of these clinical characterizations.

RBD is the disorder that precedes and continues through most of these prodromal DLB cognitive and neuropsychiatric syndromes. A schematic depiction of the RBD-MCI-DLB continuum is shown in Fig. 6.1.

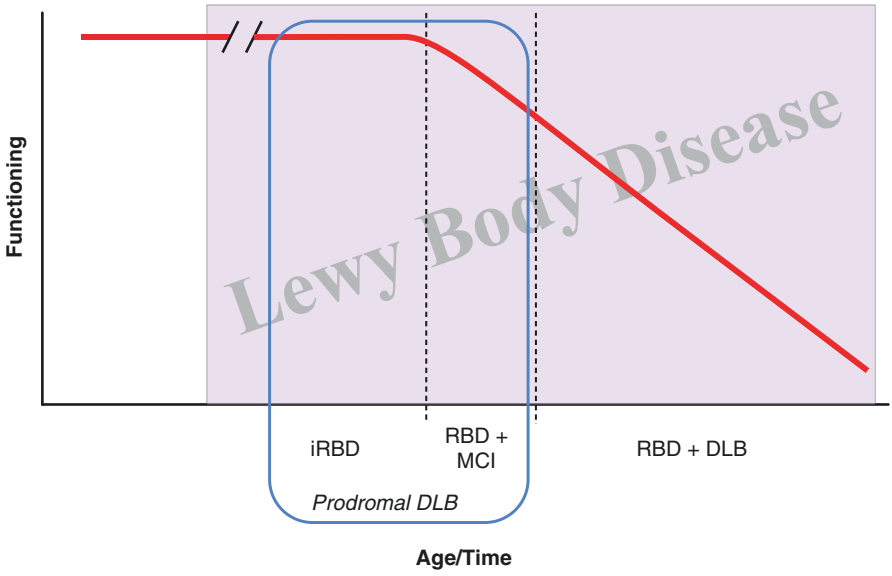

Fig. 6.1 The RBD-MCI-DLB continuum**.** This schematic representation of the RBD to MCI to DLB continuum, showing RBD followed by RBD plus MCI (with the phenotypes of idiopathic RBD and then RBD plus MCI reflecting "prodromal DLB"). Abbreviations: *RBD* REM sleep behavior disorder, *iRBD* idiopathic RBD, *MCI* mild cognitive impairment, *DLB* dementia with Lewy bodies

6.4 Analyses in Patients with Idiopathic RBD Pertinent to Dementia

There are several studies published to date which involved patients with iRBD who have been followed prospectively. The seminal paper by Schenck et al. which launched the interest in the RBD-neurodegenerative disease association showed that among 29 iRBD patients who they followed longitudinally, almost 40% developed a parkinsonian disorder at a mean interval of 3.7 years after the diagnosis of RBD and at a mean interval of 12.7 years after the onset of RBD [45]. Several have since developed cognitive impairment or dementia, with DLB features being present in most [26, 46]. Other groups of investigators have shown a similar profile of iRBD developing MCI or DLB [11, 13, 23, 33, 47–52].

Evidence of impairment on neuropsychological assessment has been documented in iRBD patients by several groups [53–55].The pattern of impairment—with deficits largely in attention, executive functioning, and visuospatial functioning and more variable performance in learning and memory—is similar to that described in MCI [56] and DLB [2, 19, 39, 44, 57].

Findings on several biomarkers in iRBD patients have also been consistent with those with DLB or PD. These include slowing on background electroencephalography [58–60], (99m)Tc-ethylene cysteinate dimer (ECD) SPECT [61], ioflupane SPECT [23, 48, 62–65], and fluorodeoxyglucose positron emission tomography (FDG-PET) [27, 66–69].

6.5 Application of the Braak Staging System for Parkinson's Disease to the Evolution of RBD to Dementia with Lewy Bodies

Braak et al. have proposed a staging system for the neuropathologic characterization of the phenotype of Parkinson's disease (PD), and this system may be applicable to the timing of the evolution of RBD in the context of evolving Lewy body disease regardless if the clinical phenotype evolves as PD or DLB [7, 11–13, 64, 70–74]. This staging system proposes a temporal sequence of α-synuclein pathology in the brain beginning mainly in the medulla (and olfactory bulb) and gradually ascending to more rostral structures [70, 71]. Dysfunction in the sublaterodorsal nucleus (SLD) +/− magnocellular reticular formation (MCRF) and associated networks (Stage 2) could lead to REM sleep without atonia (RSWA) and RBD. This temporal sequence of pathology could explain why RBD precedes parkinsonism and cognitive decline (Stages 3 and 4) and dementia (Stages 4–6) in many patients with Lewy body pathology. A schematic representation of this evolution from Stage 2 to Stages 5/6 is shown in Fig. 6.2.

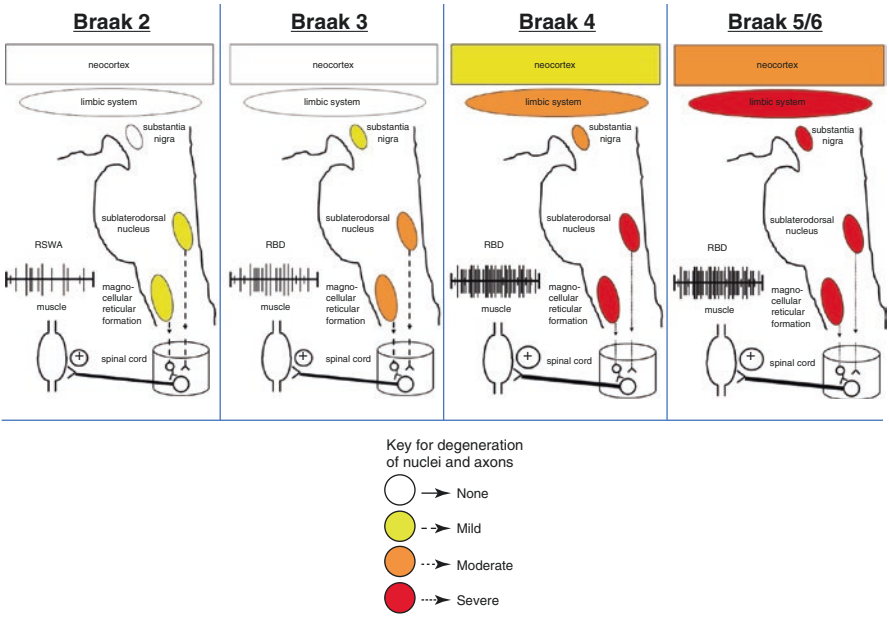

Fig. 6.2 Electrophysiologic-neurodegenerative correlations according to the Braak staging system. Schematic of the key brainstem nuclei—the sublaterodorsal nucleus and magnocellular reticular formation—and their corresponding degrees of degeneration associated with REM sleep without atonia according to Braak Stages 2–5/6. Note that overt parkinsonism and/or cognitive impairment would not be expected until at least Stage 4, but RSWA (Stage 2) and RBD (Stage 2 or 3) would occur earlier in the course. This temporal sequence of degenerative changes could explain why RBD precedes parkinsonism and dementia in many patients with Lewy body pathology. Abbreviations: *RSWA* REM sleep without atonia

6.6 The Bigger Picture in the RBD-MCI-DLB Continuum

One can then synthesize the electrophysiologic changes in REM sleep tone, the neurodegenerative changes according to the Braak staging system, and biomarker findings based on neocortical (e.g., FDG-PET) and nigral (e.g., ioflupane SPECT) integrity along this clinical RBD-MCI-DLB continuum (Fig. 6.3). This is a hypothetical model that is testable, realizing that this would require ample numbers of iRBD patients who undergo comprehensive clinical, neuropsychological, polysomnographic, and neuroimaging studies longitudinally. Yet if even some of these assumptions prove to be relatively accurate, then the ability to use biomarkers for predicting future outcomes would be enhanced. For example, those iRBD patients who demonstrate progressive but subtle changes on clinical and neuropsychological markers while also showing progressive changes in neocortical FDG metabolism

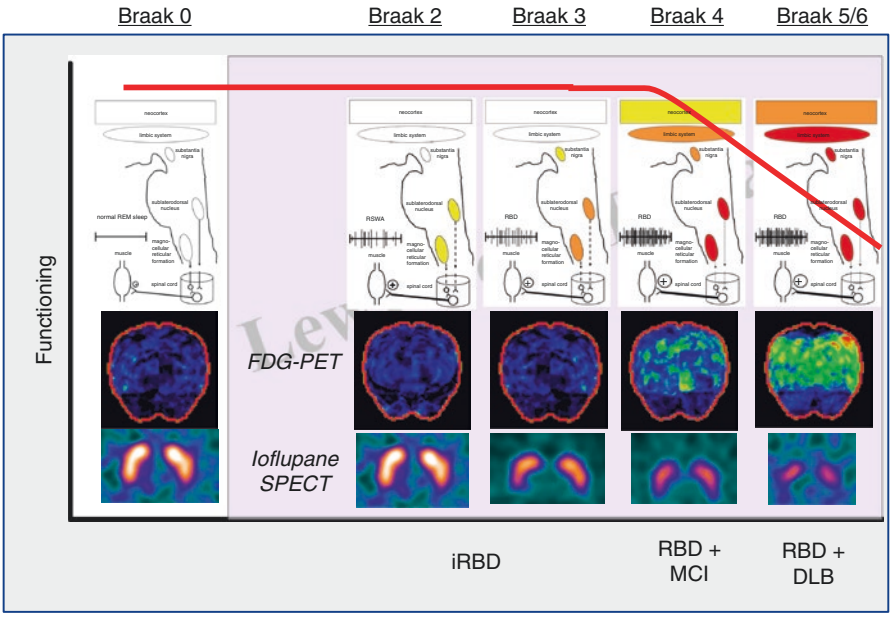

Fig. 6.3 Electrophysiologic changes in REM sleep tone, the neurodegenerative changes according to the Braak staging system, and biomarker findings based on neocortical and nigral integrity along this clinical RBD-MCI-DLB continuum. Braak Stage 0 is not associated with any clinical symptoms nor Lewy body pathology. Degenerative changes in Stage 2 would involve the sublaterodorsal nucleus and magnocellular reticular formation and potentially result in mild REM sleep without atonia but perhaps minimal if any dream enactment behavior. Overt RBD would be predicted by Stage 3, and sufficient degenerative changes may be present in the substantia nigra that could be reflected on ioflupane SPECT, but no overt parkinsonism would be evident yet. The limbic and neocortical structures are spared, and therefore FDG-PET should still show normal metabolism. Cognitive changes and associated occipital hypometabolism may be evident in Stage 4, and overt cognitive impairment plus parkinsonism would be expected in Stages 5 and 6 with corresponding changes on FDG-PET and ioflupane SPECT. Importantly, many MCI patients and a significant minority of DLB patients do not have any degree of parkinsonism early in the course, and even despite overt RBD, the findings on ioflupane SPECT may be normal. This suggests that the MCI and DLB phenotypes are associated with relative sparking of the substantia nigra in a minority of patients, and hence the classic Braak staging system may not be consistently applicable to all patients in the evolution of RBD to MCI to DLB

+/− nigrostriatal uptake on ioflupane SPECT will likely phenoconvert to MCI and subsequently DLB. Those iRBD patients who demonstrate progressive but subtle changes on clinical (especially motor measures) +/− neuropsychological markers while also showing progressive changes in nigrostriatal uptake on ioflupane SPECT but minimal to absent changes on FDG-PET will likely phenoconvert to mild parkinsonism and subsequently overt PD. And perhaps the degrees of change on many of these measures would predict the timing of phenoconversion. As explained in the figure caption for Fig. 6.3, this hypothetical model may not be applicable to all RBD

patients in the evolution to MCI and DLB due to relative sparing of the substantia nigra—at least in the early course of this evolution.

If funding is adequate to perform natural history studies with multimodal measures such as those suggested here, the scientific community will become increasingly prepared for future disease-modifying therapeutic trials to delay the onset or prevent overt DLB (or PD) in those with iRBD.

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Note Added in Proof: Two recent pertinent publications: 1. Savica R, Boeve BF, Mielke MM. When do α-synucleinopathies start? An epidemiological timeline: A review. JAMA Neurol 2018;75(4):503-509. doi: 10.1001/jamaneurol.2017.4243. 2. Marchand DG, Postuma RB, Escudier F, De Roy J, Pelletier A, Montplaisir J, Gagnon JF. How does dementia with Lewy bodies start? Prodromal cognitive changes in REM sleep behavior disorder. Ann Neurol 2018; doi: 10.1002/ana.25239.

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