Viewpoints

REM Sleep Behavior Disorder and Prodromal Neurodegeneration – Where Are We Headed?

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Abstract

Rapid eye movement (REM) sleep behavior disorder (RBD) is characterized by dysfunction of systems that produce the normal REM atonia of sleep, such that patients appear to act out their dreams. The most important implication of research into this area is that patients with idiopathic RBD are at very high risk of developing synuclein-mediated neurodegenerative disease (Parkinson’s disease [PD], dementia with Lewy bodies [DLB], and multiple system atrophy), with risk estimates that approximate 40–65% at 10 years. Thus, RBD disorder is a very strong feature of prodromal synucleinopathy. This provides several opportunities for future research. First, patients with REM sleep behavior disorder can be studied to test other predictors of disease, which could potentially be applied to the general population. These studies have demonstrated that olfactory loss, decreased color vision, slowing on quantitative motor testing, and abnormal substantia nigra neuroimaging findings can predict clinical synucleinopathy. Second, prospectively studying patients with RBD allows a completely unprecedented opportunity to directly evaluate patients as they transition into clinical neurodegenerative disease. Studies assessing progression of markers of neurodegeneration in prodromal PD are beginning to appear. Third, RBD are very promising subjects for neuroprotective therapy trials because they have a high risk of disease conversion with a sufficiently long latency, which provides an opportunity for early intervention. As RBD research expands, collaboration between centers will become increasingly essential.

Keywords: REM Sleep Behavior Disorder, Parkinson’s disease, Dementia with Lewy bodies, prodromal

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Introduction

Rapid eye movement (REM) sleep behavior disorder (RBD) is characterized by dysfunction of systems that produce the normal REM atonia of sleep, such that patients appear to act out the content of their dreams.¹ Generally, diagnosis requires a polysomnogram to confirm the loss of REM sleep atonia and to rule out potential confounders, such as apnea. Symptomatic treatment, with clonazepam or melatonin, is usually successful.

Of special interest is the connection between RBD and neurodegeneration. Although it has been associated with diverse neurodegenerative disorders, RBD is most prominently caused by synucleinopathies – Parkinson’s disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy.

Studying RBD within established clinical synucleinopathies has provided numerous important insights; for example, RBD may be a marker of a certain PD subtype, as well as a risk factor for dementia in...
In the case of established dementia, RBD can be useful as a strong diagnostic marker for DLB as the underlying pathology. However, the most important implication of this research is that RBD can anticipate the full development of synucleinopathies; that is, RBD is a prodromal marker of PD. This has been confirmed in four sleep center cohort studies and one population-based study – in these studies, risks for development of neurodegeneration were approximately 25–40% at 5 years and 40–65% at 10 years. Approximately half of RBD patients develop parkinsonism (most commonly PD), and half develop dementia. However, studies suggest considerable overlap between conditions, with most patients demonstrating both cognitive impairment and parkinsonism in the first years after diagnosis. Such a high risk of disease provides an unprecedented opportunity to directly observe prodromal stages of neurodegenerative disease.

The potential for the future of RBD research is vast; however, three aspects of the relationship between RBD and prodromal PD are of particular promise. First, the potential to test disease predictors; second, the ability to directly observe the evolution of prodromal PD; and third, the potential to develop neuroprotective therapies.

Testing disease predictors

Neurodegenerative diseases such as PD almost always begin gradually and have a long prodromal interval, during which time RBD can be a prominent feature. However, idiopathic RBD patients rarely present to clinics for evaluation. This limits our ability to use idiopathic RBD as a marker for prodromal neurodegeneration in the general population. This may eventually change – several screening tools to assess RBD in the general population have been developed, some of which have reported sensitivity and specificities greater than 80%. Moreover, even before large-scale assessment of idiopathic RBD is performed, known RBD patients can be studied to test other prodromal neurodegenerative markers. By investigating RBD, predictive/diagnostic markers can be directly tested before diagnosis of neurodegenerative disease.

Several studies have assessed potential markers of neurodegeneration in patients with RBD. They have demonstrated that patients with idiopathic RBD have a higher prevalence of autonomic dysfunction, depression, subcortical motor problems, mild cognitive changes, olfactory loss, and color vision loss. In addition, there are numerous abnormalities in potential ancillary markers, including dopaminergic functional neuroimaging, transcranial substantia nigra ultrasound, electroencephalogram spectral analysis, whole-brain glucose utilization, diffusion-weighted magnetic resonance imaging, and MRI volumetry. All of these features have also been found early in the course of neurodegenerative synucleinopathies; their documentation in RBD suggests that they may be present before full motor PD or DLB develops.

There is now direct evidence from prospective studies that at least some of these markers can identify prodromal PD. In prospective studies assessing olfaction in idiopathic RBD, those with abnormal olfaction at baseline had a 65% risk of developing neurodegenerative disease, compared to a 14% risk in those with normal olfaction. Similarly, those with abnormal color vision had a 74% risk of neurodegenerative synucleinopathy compared to 26% in those with normal test results (subsequent studies have suggested that color vision correlates closely with posterior visuoperceptual dysfunction, and may therefore be a more useful marker of DLB). Prospective studies assessing dopaminergic single-photon emission computed tomography (SPECT) imaging found that 6/8 (75%) of persons who developed neurodegenerative disease had abnormal imaging 2.3 years before diagnosis, compared to 31% of those who were still disease free. Transcranial ultrasound was normal at baseline in 5/8 (62.5%), compared to 29% of those who were still disease free. Finally, patients with RBD who eventually developed disease showed evidence of hippocampal hyperperfusion on whole-brain glucose utilization SPECT (a common finding in early dementia), compared to those who did not develop disease (Thanh, in press).

Therefore, studies in patients with RBD have already provided direct evidence that dopaminergic imaging, olfaction, color loss, and whole-brain glucose utilization can identify prodromal neurodegenerative disease. As research continues, this list of proven markers will likely continue to expand.

Watching PD develop

The above studies included mainly patients with idiopathic RBD and compared those who developed disease to those remained disease free. Although this approach allows one to ‘prove’ that a given marker predicts PD, there are limitations. First, the comparison group (disease-free RBD) can be problematic – as the longest duration studies are being reported, it is clear that the risk of developing synucleinopathy approaches 65–80%. Therefore, the large majority of patients with ‘idiopathic’ RBD may in fact have prodromal disease. In long-term cohort studies, it becomes increasingly difficult to find a ‘disease-free’ comparison group, and even when these are defined, it may really be a matter of disease stage rather than disease state. This implies that it may be more informative to compare baseline findings in RBD patients who eventually developed disease to age-matched controls. Another limitation is that RBD is predominantly related to pontomedullary dysfunction and is therefore likely a marker of Braak Stage II. This could imply that many Stage I markers (e.g., autonomic dysfunction, olfaction) may already be at ‘floor’ levels by the time a patient presents with RBD. If this is the case, many still-idiopathic patients would already be maximally abnormal on the marker, resulting in false negative results when ‘disease vs. disease-free’ comparisons are used. Finally, although it is useful to provide evidence that a marker can predict disease, there are many other important questions to answer, such as how do markers evolve in prodromal disease, when do they become abnormal, and when can a patient in prodromal PD stages be identified?

Some recent studies are tackling these more complex questions by measuring change in prodromal disease markers over prospective periods. A recent study compared the evolution of motor changes in patients with idiopathic RBD who had developed parkinsonism to
age-matched controls.\textsuperscript{16} This analysis estimated that prodromal parkinsonism first becomes detectable approximately 4.5 years before overt disease onset. Hypomimia and hypophonia may begin first, followed by limb bradykinesia, rigidity, and finally tremor. Using a cutoff on the Unified Parkinson Disease Rating Scale Part III of ≥3 points (excluding action tremor), prodromal parkinsonism could be identified 2 years before clinical disease diagnosis with a sensitivity of 94% and a specificity of 97% (longer prodromal intervals had much lower sensitivity). Perhaps of even more significance for future screening programs, simple non-expert quantitative motor testing demonstrated abnormalities approximately 6–9 years before diagnosis of parkinsonism and could identify parkinsonism with approximately 80% sensitivity and specificity up to 3 years before disease diagnosis. Simply comparing ‘disease-free RBD’ to ‘idiopathic RBD-then disease’ would have only answered the relatively trivial question of whether motor findings are present before PD diagnosis; however, assessing progression at annual follow-up allowed a direct examination of prodromal disease evolution. Similarly, a study assessing dopaminergic functional imaging found that patients with RBD had more rapid decline than age-matched controls (15–19% vs. 10%).\textsuperscript{20} This suggests that dopaminergic function progressively declines in RBD (as expected) but also provides baseline and expected progression values that can be used if dopaminergic imaging becomes a surrogate marker in neuroprotective trials. Prospective studies of olfaction and color vision have also demonstrated relatively slow progression in at least the last 4 years of prodromal disease, suggesting that these functions may become abnormal many years before full clinical disease develops.\textsuperscript{21}

Another angle afforded by thinking of RBD patients as prodromal PD patients rather than ‘at-risk’ patients comes from recent studies performed by members of the RBD study group. A large case-control study (347 patients, 347 controls) found that similar to PD and dementia, pesticide use, head injury, farming, and low years of education were risk factors for RBD.\textsuperscript{31} However, the differences between RBD and PD were of special interest. Every large epidemiologic study has found that caffeine non-use and non-smoking are risk factors for PD. However, caffeine was not associated with RBD, and smoking was associated with higher risk. This raises the intriguing possibility that caffeine and nicotine ‘prevent’ PD by specifically targeting basal ganglia motor structures rather than preventing synucleinopathy in general. That is, synucleinopathy proceeds unimpeded, but clinical expression in motor structures is prevented or delayed. Analyses of family history, co-morbidities, medications, and autonomic dysfunction are underway in this cohort. Prospective follow-up studies will allow the assessment of environmental risk factors as predictors of disease outcome – for example, could smoking and caffeine non-use indicate a higher risk of dementia rather than primary motor parkinsonism?

Neuroprotection

One of the most important factors hampering neuroprotective therapy development for neurodegenerative disease is that the disease process is well established by the time a patient presents to their physician with clinical symptoms. This severely limits the ability to intervene in early stages, when protective treatments might be most effective. In this regard, RBD patients provide an important opportunity – they are the ideal group to include in clinical trials of neuroprotective therapies for ‘preventing’ synuclein-mediated neurodegeneration. RBD patients have two essential characteristics required for such a trial. First, they have a very high ‘risk’ of disease conversion, and second, the latency is long enough that the intervention can be provided early enough to affect change.

Can a neuroprotective trial for RBD be developed? Such a trial would have numerous challenges to overcome. First, the long latency to development of defined disease, although a major advantage in terms of opportunity to intervene early, does imply that trials would need to be of sufficiently long duration. It is unlikely that a pharmaceutical company with a patent-protected product would be interested in funding such long-term trials because the patent would expire soon after publication. Selecting patients who already have ancillary evidence of neurodegeneration, such as dopaminergic denervation on SPECT or olfactory loss, may mitigate this (although at the cost of intervening later in the disease process). For example, addition of olfaction as a selection criterion would produce up to a 65% ‘conversion’ rate in a 3-year trial, and if even this is not sufficiently high to plan adequately powered trials of reasonable size, further stratification with dopaminergic imaging would likely produce even higher conversion rates. Second, just like in established disease, symptomatic confounds may also confound outcome interpretation if the definition of the endpoint (i.e., disease diagnosis) is altered by symptomatic motor or cognitive effects. For example, if development of defined parkinsonism on examination is an outcome of the trial, and patients are given an agent that improves parkinsonism symptoms, the diagnosis would be delayed, resulting in an apparent ‘protective’ effect. Third, given that RBD patients develop both motor impairment and dementia, agents that target synucleinopathy in general rather than just the substantia nigra are more likely to be useful. Regardless of these challenges, there is probably no other clinical group that can provide the combination of specificity for prodromal PD and adequate lead time that is so essential to a successful neuroprotective trial.

Finally, any consideration of future research points us towards the most important direction that RBD research must take, that is, to collaborate. Because RBD patients rarely present in large numbers to any single center, the most essential future studies, including trials of symptomatic therapy, neuroprotective studies, and large-scale evaluations of prodromal disease, can only be answered through open and intensive collaborations among centers. As our networks of collaboration improve, opportunity for real advance continues to expand.

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