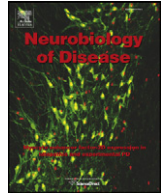




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Review

REM sleep behavior disorder: From dreams to neurodegeneration

Ronald B. Postuma^{a,b,*}, Jean-Francois Gagnon^{b,c}, Jacques Y. Montplaisir^{b,d}^a Department of Neurology, McGill University, Montreal General Hospital, Montreal, Quebec, Canada^b Centre d'Études Avancées en Médecine du Sommeil, Hopital du Sacre-Coeur, Montreal, Canada^c Department of Psychology, Université du Québec à Montréal, Québec, Canada^d Department of Psychiatry, Université de Montréal, Canada

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ABSTRACT

REM sleep behavior disorder is a unique parasomnia characterized by dream enactment behavior during REM sleep. Unless triggered by pharmacologic agents such as antidepressants, it is generally related to damage of pontomedullary brainstem structures. Idiopathic REM sleep behavior disorder (RBD) is a well-established risk factor for neurodegenerative disease. Prospective studies have estimated that at least 40–65% of patients with idiopathic RBD will eventually develop a defined neurodegenerative phenotype, almost always a 'synucleinopathy' (Parkinson's disease, Lewy Body dementia or multiple system atrophy). In most cases, patients appear to develop a syndrome with overlapping features of both Parkinson's disease and Lewy body dementia. The interval between RBD onset and disease onset averages 10–15 years, suggesting a promisingly large window for intervention into preclinical disease stages. The ability of RBD to predict disease has major implications for design and development of neuroprotective therapy, and testing of other predictive markers of synuclein-mediated neurodegeneration. Recent studies in idiopathic RBD patients have demonstrated that olfaction, color vision, severity of REM atonia loss, transcranial ultrasound of the substantia nigra, and dopaminergic neuroimaging can predict development of neurodegenerative disease.

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* Corresponding author at: Department of Neurology, L7-312 Montreal General Hospital, 1650 Cedar Ave., Montreal, Quebec, Canada H3G 1A4. Fax: +1 514 934 8265.

E-mail address: ronald.postuma@mcgill.ca (R.B. Postuma).Available online on ScienceDirect (www.sciencedirect.com).

RBD—an introduction

REM sleep behavior disorder is characterized by loss of the normal atonia of REM sleep (Schenck and Mahowald, 2002; Schenck et al., 1986). Patients often present with dream enactment behavior, apparently moving in response to content of their dreams. Movements may occur even without recall of dream content, so failure to recognize a connection between dream content and movements does not rule out RBD (Iranzo et al., 2009). Spouses are usually the main initiator of medical consultation, as their sleep is often disturbed, and injury can occur. There have been suggestions that dream content may become more violent in RBD (Fantini et al., 2005), although apparent changes in dream content could also be an artefact of presentation to sleep clinics (patients with aggressive dream enactment may be more likely to present to a clinic) or of dream recall (violent dreams are selectively recalled because the aggressive movements accompanying these dreams wake the patient).

Risk factors and prevalence of RBD have been incompletely defined. There is a clear male predominance of the disorder; again, whether this is a result of selection bias or a true biological effect is unclear (Boeve et al., 2007; Iranzo et al., 2009) (e.g., men may have more violent dreams and aggressive sleep behaviors than women (Bodkin and Schenck, 2009), women are more likely to sleep alone due to lifespan differences, etc). When in its idiopathic form, RBD typically has onset in the ages of 50–70, although many patients with long-duration disease have been described. Often dream enactment can be triggered by antidepressant medications, in which case, demographics include more younger patients and women (Bonakis et al., 2009; Ju et al., 2011; Teman et al., 2009). No clear prevalence studies have been reported; studies which first screened for sleep injury, and then estimated the prevalence of RBD among screen positives (thereby identifying a more severe subtype of RBD) find prevalence estimates of 0.38–0.5% (Chiu et al., 2000; Ohayon et al., 1997) (note that this estimate would include all forms of RBD, not only idiopathic). Given that sleep injury was the screen, inclusion of cases who did not have injury (i.e. a substantial proportion of cases (Oudiette et al., 2009; Sixel-Doring et al., 2011)) would likely result in a higher estimate.

Diagnosis depends on polysomnogram, mainly because there are mimics of RBD. The most prominent of these are obstructive sleep apnea with confusional arousals, non-REM parasomnias, and nocturnal frontal lobe epilepsy (Iranzo and Santamaria, 2005). The main diagnostic feature on polysomnography is loss of REM atonia, which when combined with clinical history and absence of confounds, establishes the diagnosis (American Academy of Sleep Disorders, 2005) (witnessing dream enactment on polysomnography can substitute for clinical history). The exact definition of REM atonia loss has not been established, but standardization studies are being published (Montplaisir et al., 2010). Treatment is primarily with clonazepam 0.5–2.0 mg or melatonin 3–12 mg at bedtime. Recently, the effectiveness of melatonin in mild RBD was confirmed in a small-scale randomized trial (Kunz and Mahlberg, 2010).

Pathophysiology of RBD

In 1964, Jouvet described apparent dream enactment behaviors during REM sleep after brainstem lesions in the peri-locus ceruleus area (Jouvet and Delorme, 1965). Subsequent animal studies have focused on pontine and medullary areas such as the sublateral dorsal nucleus (a REM tone flip-flop switch), and their glutaminergic projections to medullary (ventral gigantocellular reticular nucleus or magnocellular reticular formation (Luppi et al., 2011)) and/or spinal interneurons as being the crucial structures for generation of RBD (for review, see (Boeve et al., 2007; Luppi et al., 2011)). Disruption of these systems allows uninhibited control of motor cortex to limbs, likely bypassing basal ganglia or other modulatory structures (De

Cock et al., 2007, 2011; Luppi et al., 2011). These models have been supported by several human cases of stroke causing RBD, all of which were localized to pontomedullary areas (Boeve et al., 2007). Therefore, it is clear that the anatomical lesions that cause RBD are generally in the lower brainstem.

RBD has been associated with non-neurodegenerative syndromes such as narcolepsy, limbic encephalitis and Guillain–Barre syndrome (Gagnon et al., 2006a). Pharmacologic agents, including tricyclic antidepressants, newer serotonergic antidepressants (fluoxetine, paroxetine, citalopram, sertraline, and venlafaxine), alcohol, and beta blockers have been linked to RBD (Gagnon et al., 2006b). However, the commonest disease association, by far, is with neurodegenerative diseases that affect brainstem structures. RBD has been less commonly associated with many neurodegenerative diseases, including progressive supranuclear palsy, corticobasal syndrome, frontotemporal dementia, and Huntington's disease. However, idiopathic RBD is most often caused by one of the synuclein-mediated neurodegenerative diseases (i.e. Parkinson's disease (PD), Lewy body dementia (LBD), and multiple system atrophy (MSA)). Therefore, RBD is a common 'non-motor' (or, a 'sleep-related motor') manifestation of early PD. Whereas RBD itself is often relatively benign and can generally be successfully treated, the other aspects of these synucleinopathies are devastating to patients and their families. Therefore, the most important clinical implications of RBD stem from its relationship with synuclein-mediated neurodegenerative disease. In particular, the ability of RBD to predict future disease years, or even decades in advance of their clinical presentation has the potential to lead to breakthroughs in disease treatment, and it is on this aspect that this review will focus.

What is the risk of neurodegenerative disease in idiopathic RBD?

Based on prospective studies, many (if not most) patients who present to sleep clinics with idiopathic RBD will eventually develop a neurodegenerative syndrome. In the large majority of cases, this will be either PD, LBD, or MSA. Information as to the outcome of RBD has come mainly from three studies:

In 1996 Schenck et al. reported that after a median 5-year follow-up from diagnosis, 11 of their original 29 (38%) patients with idiopathic RBD had developed a parkinsonian disorder (Schenck et al., 1996). The diagnosis was 'definite PD' in 8 and 'probable PD' in the remaining 3. Two patients with PD later developed PD dementia. A 12th patient developed dementia and was given a diagnosis of Alzheimer's disease. Neurodegenerative disease developed on average 4 years after diagnosis of RBD, but more than 12 years after the first RBD symptoms. Subsequent follow-up of this cohort (reported in abstract form) has found that disease risk continues to increase; at 10 years follow-up, 65% developed a defined neurodegenerative disease (Schenck and Mahowald, 2003).

In 2006, Iranzo and colleagues reported outcome of a series of 44 idiopathic RBD patients (Iranzo et al., 2006). This follow-up included neuropsychological evaluation, increasing sensitivity to identify dementia. 16/44 (36%) patients developed a defined neurodegenerative disorder, and an additional 4 patients developed mild cognitive impairment. The latency between diagnosis of RBD and development of degenerative disease was 5.1 years, with 13.4 years between symptom onset and disease. Of the 16 patients with defined disease, 9 developed PD (2 with PD dementia), 1 developed MSA, and 6 developed LBD. Subsequent follow-up of this cohort (reported in abstract form) found that 64% of patients developed a neurodegenerative disease (including MCI) by 7 years (Iranzo et al., 2008).

In 2009, our group examined risk of disease in a cohort of 93 patients with idiopathic RBD (Postuma et al., 2009a). Using a Kaplan–Meier analysis, we estimated a disease risk of 17.7% at 5 years (from diagnosis) in patients with idiopathic RBD, which increased to 40.6% at 10 years, and 52.4% at 12 years. These estimates are somewhat

lower than the previous two studies, but are not as divergent as they initially appear—calculating our proportions using the same method as previous studies provides a conversion rate of 28% over a 5.2-year follow-up. At the time of disease onset, the primary diagnosis was parkinsonism in 15 (14 PD, 1 MSA) and dementia in 11; however, there was substantial overlap between conditions (Postuma et al., 2009b), which suggests that boundaries between disease states are not clear.

On review of these studies, two key findings emerge that suggest potential for RBD as a clinically-important predictor for PD:

- 1) The risk of neurodegeneration is high—one of the biggest limitations of clinical markers of disease is their lack of specificity. For example, in the Honolulu Asia Aging Study, over 25% of subjects had olfactory loss, but well under 1% developed PD (Ross et al., 2008). Similarly, constipation and depression are experienced by 20–40% of the population, only a small minority of which will eventually develop PD (Garrigues et al., 2004; Ishihara and Brayne, 2006). In contrast, with risk estimates as high as 65% at 10 years, RBD is by far the strongest clinical predictor of neurodegenerative disease available (Postuma et al., 2010a). That is, the specificity of diagnosed idiopathic RBD in identifying a presymptomatic phase of neurodegeneration is at least 50–65%. The high disease risk implies that if a neuroprotective agent was developed, idiopathic RBD patients might be possible candidates for therapy (although for each patient, this would require balancing of potential risks of therapy vs uncertain outcome of RBD).
- 2) Latency to clinical disease is long. In the three major series, mean interval between RBD symptom onset and neurodegenerative disease averaged 13 years from RBD symptom onset to disease definition. This is in contrast to PET studies of the substantia nigra, which have estimated premotor PD phases of 4–7 years before clinical symptoms (Hilker et al., 2005; Morrish et al., 1998; Vingerhoets et al., 1994). A recent report has suggested that some cases of RBD have extremely long latency of 550 patients with clinical RBD and neurodegenerative disease, 27 had latencies of more than 15 years between symptom onset and disease (mean interval = 25 years) (Claassen et al., 2010) (note that interpretation of extremely long latencies depends critically upon understanding the prevalence of RBD).

These key points imply RBD may be an ideal marker for use in neuroprotective trials. RBD satisfies two of the key criteria for such a trial; specificity is high enough so that the size of a trial is not excessively large, and latency is long enough that there is a sufficient window of opportunity to intervene.

Caveats and limitations

No marker is the ideal agent, and several caveats must be noted in the considering the utility of RBD in PD prediction and in development of neuroprotective therapy.

Prevalence of diagnosed idiopathic RBD

So far, epidemiologic studies of RBD are limited, and the prevalence of RBD is unclear. As of 2011, the largest cohort of idiopathic RBD patients ever reported is 93 patients (Postuma et al., 2009a). This implies that the large majority of RBD patients do not present to physicians a major challenge to those who would wish to identify RBD patients for neuroprotective therapy.

RBD diagnosis is not simple

Although RBD is readily recognized clinically, diagnosis currently requires confirmation with polysomnogram (American Academy of Sleep Disorders, 2005). Although not a major practical barrier for

neuroprotective trials, it would be a barrier for eventual screening of RBD in an age of neuroprotective therapy. Recently, several RBD screening questionnaires have been designed. The first, the 14-item Stiasny-Kolster RBD Screening Questionnaire obtained 96% sensitivity but only 56% specificity when using sleep center patients as controls (specificity was 92% when using normal volunteers as a control group) (Stiasny-Kolster et al., 2007). Its utility for PD prediction is made somewhat problematic by its inclusion of a diagnosis of a neurodegenerative disease as an additional point in the scale. A single question of dream enactment from the Mayo Sleep Questionnaire was able to detect RBD with 98% sensitivity and 74% specificity (Boeve et al., 2011), suggesting a simple screen that could be used in large-scale population studies. Finally, the 13-item RBD-HK scale has demonstrated 82% sensitivity and 87% specificity using predominantly sleep-center controls—this scale has the advantage of grading severity of dream enactment, so has potential application (with minimal modification) as a severity scale in clinical trials. It should be noted that positive predictive value in uncommon conditions can cause difficulty even in tests with optimal specificity—in a condition with 1% prevalence, using a test with 95% specificity would translate to a positive predictive value of only 18%.

What is the true risk of disease?

The three studies on which RBD risk estimates are based were all performed on patients in sleep clinics presenting with clinical RBD—this implies they were on the severe end of the disease spectrum. Population screening is likely to identify milder cases than what is routinely seen in sleep disorders clinics (which may include a higher proportion of women (Bodkin and Schenck, 2009)), and disease risk may not be the same in these populations. There are preliminary suggestions that 'milder' RBD may have a lower risk of developing PD (see discussion below) (Postuma et al., 2010b). Similarly, the risk of neurodegenerative disease in the context of medication-triggered RBD is unclear; if antidepressants unmask a latent synucleinopathy, disease risk may be still substantial, but if antidepressants cause RBD in the absence of preclinical degeneration, risk may be low.

How well does RBD generalize to PD?

Although RBD is strongly associated with PD, only a minority of patients with PD begin with RBD. There is evidence that the presence of RBD in PD may indicate a unique disease subtype. In a recent prospective follow-up study that included a comprehensive annual examination, 16/21 patients who developed neurodegeneration had evidence of both parkinsonism and cognitive impairment at disease onset (Postuma et al., 2009b, 2011a). The majority of those with a primary diagnosis of dementia developed defined parkinsonism within a year of onset, and vice versa. This is a pattern unlike typical PD, in which dementia occurs late. PD patients with associated RBD also tend to have an akinetic-rigid form (i.e. with less tremor) (Kumru et al., 2007; Lee et al., 2010; Postuma et al., 2008a). PD-RBD patients also have increased autonomic dysfunction, as characterized by orthostatic blood pressure changes (Postuma et al., 2008b, 2009c), cardiac beat-to-beat-variability (Postuma et al., 2011b), and MIBG scintigraphy (Nomura et al., 2010) and increased cognitive impairment, on quantification by neuropsychologic testing (Gagnon et al., 2009; Marion et al., 2008; Naismith et al., 2011; Sinforiani et al., 2006; Vendette et al., 2007). All of these findings suggest that studies in idiopathic RBD may not perfectly generalize the entire PD population.

Practical challenges in trial design

There are considerable challenges in designing neuroprotective trials, and these challenges apply equally to RBD. For example, the

long latency to disease, although an important advantage, also implies practical challenges in the design of such neuroprotective trials including funding difficulties (especially given short timelines of pharmacologic patents) and potential loss of follow-up over long duration studies. Additional challenges include considerable uncertainty as to appropriate molecular targets, absence of reliable biomarkers in patients with 'premotor' disease, and difficulty in defining a positive outcome with the potential confounding of symptomatic effects on disease (for review, see (Lang, 2010; Meissner et al., 2011; Olanow and Kiebertz, 2010; Sommer and Stacy, 2008)).

Predicting outcomes—markers for disease outcome

As noted above, idiopathic RBD patients are relatively uncommon in even subspecialty sleep centers (Postuma et al., 2009a), and it is unlikely that the majority of preclinical PD patients would be identifiable by screening for RBD. However, studying idiopathic RBD can also help evaluate other potential predictive markers. One major difficulty currently confounding the evaluation of potential predictive markers is that PD is uncommon—for a study to have sufficient power to test a potential predictor, long-term studies of thousands of participants would be required, even to find the most basic differences in mean values between diseased and not diseased (precision of sensitivity and specificity for prediction would require many more). In this regard, idiopathic RBD patients are the ideal 'high-risk' group to test predictors. By examining RBD patients before defined neurodegenerative disease, the utility of other prospective markers can be directly assessed.

Potential markers of neurodegeneration in idiopathic RBD are very diverse. Generally, potential markers have been proposed based on either of two principles: redundancy (the ability of the organism to compensate for mild losses of neuronal function) or the presence of non-motor manifestations of PD early in disease (which may indicate that they precede disease). Some potential predictors that have been assessed in RBD include.

Markers of substantia nigra dysfunction

One potential marker of subtle dopaminergic denervation is dopaminergic PET and SPECT imaging, which use radiolabelled ligands to label either pre- or post-synaptic dopaminergic terminals (Ravina et al., 2005) and therefore directly measure innervation from the SNpc. Dopaminergic PET and SPECT have very high sensitivity and specificity for parkinsonism (they will also detect MSA and LBD) (Ravina et al., 2005). Abnormalities on dopaminergic imaging have been described in patients with idiopathic RBD (Albin et al., 2000; Eisensehr et al., 2000). A second potential SNpc marker of preclinical PD is transcranial ultrasound (TCS). Approximately 80–90% of PD patients have abnormal hyperechogenicity of the SNpc (Gaenslen et al., 2008), which is found early in disease course. Studies have suggested that approximately 40% of patients with idiopathic RBD have abnormalities on TCS (Stockner et al., 2009; Unger et al., 2008).

Recently, a prospective study has suggested that TCS and dopaminergic PET/SPECT may predict neurodegenerative outcome in RBD (Iranzo et al., 2010). In a cohort of 43 idiopathic RBD patients, 40% had abnormal B-CIT SPECT, and 36% had abnormal TCS at baseline (63% had abnormalities on either modality). Over a 2.5-year prospective follow-up, 8 (19%) patients developed disease. 6/8 patients with disease had had abnormal SPECT at baseline, and 5/8 had had abnormal TCS; all patients had an abnormality of at least one modality. This study provides strong evidence that these modalities may predict disease. However, neither imaging procedure on its own was capable of predicting disease—it required both examinations with either/or determination. In fact, SPECT and TCS were discordant in most patients, which is difficult to reconcile with markers that assess the same anatomical area. Also, interval between procedure and development of disease was 21 months; since the utility of a predictive

marker depends entirely upon the lead time that can be gained by its use; future studies will need to assess utility at longer intervals. Finally PET/SPECT are relatively expensive (and require injection of radiotracer), and transcranial ultrasound requires specialized training. This implies that these modalities may serve a role as follow-up studies in already-identified high-risk populations (e.g. idiopathic RBD patients, screen-positives on other modalities, etc).

Olfaction

The large majority of PD patients have severe olfactory loss at disease onset (Hawkes, 2003). Olfactory loss may also be an important preclinical marker of Lewy body dementia (LBD) (Olichney et al., 2005). Based upon large-scale prospective studies, there have been strong suggestions that olfaction can predict PD (Ross et al., 2008). Recently, in a 5-year prospective follow-up study of 62 patients with idiopathic RBD, those with impaired olfaction at baseline had a 65% 5-year risk of developing a defined neurodegenerative disease, compared to a 14% risk in those with normal olfaction (Postuma et al., 2011a). Olfactory abnormalities appeared to be present up to 5 years before diagnosis, suggesting that lead time may be relatively long. However, this was not universal—a subset of tremor-predominant PD patients developed olfactory abnormalities only proximate to disease diagnosis.

Visual changes

Visual changes such as loss of color vision and contrast sensitivity commonly occur in PD, often early in the course of the disease (Price et al., 1992). In a recent prospective 5-year prospective study, patients with impaired color vision at baseline, as estimated by the Farnsworth–Munsell 100-Hue test, had an estimated 74% risk of developing a defined neurodegenerative disease at 5 years follow-up, compared to a 26% risk among those with normal vision. As with olfaction, abnormalities were present as much as 5 years before diagnosis and predicted both parkinsonism and dementia. It is unclear whether these results were due to retinal changes, or to visuoperceptive cortical changes, since those with normal cognition demonstrated relatively preserved color vision even at disease onset.

Autonomic dysfunction

Staging systems of PD have described synuclein deposition of unmyelinated projection neurons of the dorsal motor nucleus of the vagus (Braak et al., 2003), and postganglionic sympathetic denervation at earliest stages of the degeneration of PD (Braak et al., 2007; Orimo et al., 2007). These abnormalities are also often seen in LBD, and cardiac denervation may even be more severe in LBD than PD (Oka et al., 2007a; Yoshita et al., 2006). Numerous studies document autonomic dysfunction in RBD, as measured by orthostatic blood pressure drop (Postuma et al., 2006, 2009c), symptoms of constipation (Postuma et al., 2009c), decreased beat-to-beat variability in cardiac rhythm (Postuma et al., 2010c), and decreased MIBG tracer uptake on scintigraphy (a marker of cardiac sympathetic innervation (Miyamoto et al., 2006; Oka et al., 2007b)). Interestingly, however, in the only prospective follow-up that examined autonomic dysfunction as a predictor of disease, cardiac denervation on EKG tracing could not distinguish between idiopathic RBD patients destined to develop neurodegenerative disease and those who remained disease-free (despite ability to distinguish patients from controls (Postuma et al., 2011c)). This could be consistent with a concept that essentially all RBD patients are in 'Stage 2' Braak PD and have near-complete cardiac denervation by the time they present to a sleep clinic. If so, autonomic dysfunction may be the ideal predictor of disease. On the other hand, other explanations are possible (e.g. autonomic dysfunction contributes to generation or clinical presentation of RBD, perhaps due to

alteration of dream content). Of note there are cases of RBD occurring with Guillain–Barre syndrome, a peripheral nervous system disorder unrelated to synucleinopathy, exclusively in the subset with autonomic dysfunction (Cochen et al., 2005) and studies have suggested that autonomic dysfunction in PD is more linked to the presence of RBD than to PD itself (Postuma et al., 2009c, 2011b). Long-term prospective follow-up studies using sensitive measures will be essential to clarify the true predictive value of autonomic dysfunction as a predictor of disease.

Sleep measures

RBD varies considerably between patients in terms of severity, presentation, and underlying etiology. In a recent clinical follow-up study, baseline sleep variables in idiopathic RBD patients were compared between those who eventually developed a defined neurodegenerative disease and those who remained disease-free. There were no differences in sleep stages between groups, except for a slight increase in Stage 1 sleep in those who developed disease, and a slight reduction in slow-wave sleep in those destined to develop dementia (consistent with known abnormalities in patients with early-stage neurodegeneration) (Postuma et al., 2010b). The most prominent abnormality was that patients who eventually developed disease had more severe loss of REM atonia at baseline ($63 \pm 6\%$ tonic REM) than those who remained disease-free ($42 \pm 6\%$). This change was most prominent in those destined to develop PD ($73 \pm 6\%$). This suggests that there may be a 'milder' subtype of idiopathic RBD who could have a lower progression risk.

Other potential predictors in Idiopathic RBD

Numerous studies have described other potential markers of disease in patients with idiopathic RBD, including subtle motor dysfunction on clinical examination (Postuma et al., 2009c), motor slowing on quantitative tests of movement speed (Postuma et al., 2006, 2009c), anxiety and depression symptoms, personality changes (similar to the proposed 'Parkinson personality') (Postuma et al., 2009c), subtle cognitive dysfunction (Ferini-Strambi et al., 2004; Massicotte-Marquez et al., 2008), waking EEG slowing (Fantini et al., 2003), volumetric MRI changes (Scherfler et al., 2011), cerebral blood flow changes (Mazza et al., 2006), and diffusion tensor imaging (Scherfler et al., 2011; Unger et al., 2010). These markers are abnormal in clinical synucleinopathies, often early in the disease course, suggesting that they will be able to identify patients in preclinical stages of disease. However, confirmation of their predictive value will require prospective studies which correlate abnormalities at baseline with eventual disease risk.

Conclusion

RBD is a unique parasomnia related to degeneration of critical REM tonic areas in the lower brainstem. Patients with idiopathic RBD are at a high risk of developing neurodegenerative disease, a risk that continues for many years after the first symptoms develop. This has profound implications for the future development and use of neuroprotective therapy. RBD patients may be ideal candidates for neuroprotective trials in preclinical disease, and for testing other potential predictive markers of neurodegeneration for future application to the general population once neuroprotective therapy is developed.

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