Clinical Parkinsonism & Related Disorders 3 (2020) 100044

Contents lists available at ScienceDirect

Clinical Parkinsonism & Related Disorders

journal homepage: www.elsevier.com/locate/prdoa

Comorbid neuropsychiatric and autonomic features in REM sleep behavior disorder☆

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ARTICLE INFO

Article history:
Received 10 October 2019
Received in revised form 27 December 2019
Accepted 26 January 2020
Available online 22 February 2020

Keywords:
RBD
REM sleep
Alpha-synucleinopathy
Parkinson's disease

ABSTRACT

Objective: Our aim is to define the extent of comorbidities in order to improve clinical care of patients with idiopathic rapid eye movement sleep behavior disorder (iRBD) utilizing the REM Sleep Behavior Disorder Associations with Parkinson's Disease Study (RAPiDS) cohort.

Methods: Consecutive adult study participants with iRBD confirmed on polysomnogram (PSG) were prospectively recruited from the Weill Cornell Center for Sleep Medicine. Evaluations comprised multiple facets of sleep, neurological, autonomic, and psychiatric function.

Results: Participants evaluated included 30 individuals with iRBD, with mean 1.5 ± 2.3 years from PSG to neuropsychiatric evaluation. Mean age was 59.5 ± 16.0 years at time of PSG, and 6/30 were women. Urinary difficulties were reported in 14/30 (47%): slight 7 (23%), mild 4 (13%), moderate 2 (7%), and severe 1 (3.0%). Ten out of 29 (34%) had abnormal Montreal Cognitive Assessment (MoCA) scores and the mean was 26.5 ± 3.2. The distribution of MoCA scores was significantly associated with urinary problems insofar as the more severe urinary problems were, the lower the MoCA scores ($p = 0.04$).

Conclusions: In this RAPiDS cohort, we detected an unexpectedly high occurrence of non-motor dysfunction. Our results point to the need for screening patients with iRBD for complaints that are actionable, for example those affecting mood, cognition, urinary function, and bowel function. We propose the term RBD+ to be used to identify such individuals. For the quality of life in patients diagnosed with RBD, a closer look by the clinician should be enacted, with appropriate referrals and workup.

Introduction

Rapid eye movement (REM) sleep behavior disorder (RBD) is a condition consisting of abnormally increased muscle tone during REM sleep (noted during an overnight polysomnogram [PSG]) combined with a history of recurrent nocturnal dream enactment behavior [1]. The diagnosis of idiopathic RBD (iRBD) is made in the absence of conditions known to cause secondary RBD (i.e. autoimmune or inflammatory disorders), and when other causes of possible abnormal nocturnal behavior have been ruled out (i.e. nocturnal seizures).

Parkinson's disease (PD), multiple system atrophy (MSA), dementia with Lewy bodies (DLB), and pure autonomic failure (PAF), are termed alpha-synucleinopathies due to characteristic intracellular protein accumulation of alpha-synuclein [2]. iRBD has garnered attention as it can precede the onset of symptoms of these alpha-synucleinopathies by up to decades [2,3]. Research into iRBD is expected to advance understanding of the prodromal stages of the alpha-synucleinopathies, as well as provide a platform for the testing of possible neuroprotective agents for these neurodegenerative disorders [2]. However, how to predict prognosis and provide best care for an individual with iRBD remains an area of critical need.

We sought to evaluate the extent and nature of non-motor features that overlap with alpha-synucleinopathies, in a cross-sectional cohort of individuals with PSG-confirmed iRBD. Our short-term aim was to define the extent of comorbidities in order to improve clinical care of patients with iRBD. In the long term, this "REM Sleep Behavior Disorder Associations with Parkinson's Disease Study (RAPiDS)" cohort will be followed longitudinally to examine which features have potential predictive value for phenoconversion.

Methods

The institutional review board at Weill Cornell Medical College approved this protocol, and informed consent was provided by all

☆ Funding or sponsorship: Private grantAll authors have seen and approved the submission.
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http://dx.doi.org/10.1016/j.prdoa.2020.100044

participants. Each author completed a Conflict of Interest Disclosure form. This study was funded through a private grant.

Consecutive adult study participants with RBD confirmed on polysomnogram (PSG) according to American Academy of Sleep Medicine Criteria [4] were prospectively recruited from the Weill Cornell Center for Sleep Medicine. Individuals with an existing diagnosis of any neurodegenerative disorder were excluded. Those with other serious neurological disorders including stroke, epilepsy, and a history of brain tumor, hydrocephalus, encephalitis and other disorders were excluded. Additional exclusion criteria were existence of conditions that would confound autonomic and other neurological testing, such as cardiac disease, uncontrolled thyroid disease or diabetes, autoimmune conditions, and specific medications.

Evaluations comprised: PSG; the Epworth Sleepiness Scale [5]; RBD Screening Questionnaire (RBDSQ) [6]; medical history and medication review, as well as medical and neurological examination; and standardized rating scales and examination focused on neuropsychiatric (Montreal Cognitive Assessment (MoCA) [7]), neurologic (12-item University of Pennsylvania Smell Identification Test (UPSIT) [8]), psychiatric (Beck Depression Inventory II (BDI-II) [9], and Beck Anxiety Inventory (BAI) [10]), and autonomic function (Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part 1 [11] and orthostatic blood pressure evaluation).

Statistical analyses were performed to test the correlations between variables. In particular, for two continuous variables, One-Way ANOVA test was applied for they are normally distributed (judged by Q-Q plot) and otherwise we used non-parametric Kruskal-Wallis testing. Pearson Correlation was used to obtain correlation values of continuous variables. For one continuous variable and one categorical variable, we first group the values of the continuous variable into different groups as specified by the values of categorical variable, and then perform ANOVA/Kruskal-Wallis testing to check the significance of correlation among those multiple groups.

Results

Participants evaluated included 30 individuals with RBD, with mean 1.5 ± 2.3 years from the time of their PSG confirmed RBD diagnosis to the time of their evaluation in this study (Table 1.). Mean age was 59.5 ± 16.0 years at time of PSG, and 6/30 were women. The RBDSQ score was 9.0 ± 2.2, consistent with presence of RBD. The Epworth Sleepiness Scale score was 7.1 ± 3.4, consistent with borderline excessive daytime sleepiness. Borderline obstructive sleep apnea (OSA, apnea-hypopnea index [AHI]: 5.2 ± 5.6 events/h) was demonstrated, as well as borderline clinically significant periodic limb movements of sleep (PLMS, index: 16.8 ± 20.5 events/h) (Table 2). Sleep disorders other than RBD were common in this cohort: OSA/upper airway resistance syndrome (in 16: 3 of whom were female); restless legs syndrome/periodic limb movement disorder (in 4: all male); hypersomnia (in 4: all male); and sleepwalking (in 1: male).

Based upon responses to single questions in the MDS-UPDRS part 1 score (non-motor experiences of daily living), the composite score was 9.07 ± 5.02. This compares with a score of 6.0 ± 4.5 in a community-based study [12], but potential differences based upon age, gender, and other variables render direct comparison difficult. Urinary difficulties were reported in a total of 14/30 (47%), of whom 3 (10%) were women (Fig. 1). Constipation was reported in a total of 12/30 (40%), of whom 3 (10%) were women (Fig. 2). Eleven of 30 (37%) reported a history of psychiatric illness, including anxiety and depression for which severity, measured on validated rating scales, is indicated in Table 3. Current antidepressant use was reported by 8/30 (27%: just one of whom was female), and 2 of the remaining 22 (9%) reported taking antidepressant medication in the past. Current use of sertraline correlated with RBDSQ score ($p = 0.02$).

Ten out of 29 (34%) had abnormal (<26) Montreal Cognitive Assessment (MoCA) scores (mean 26.5 ± 3.2) (Table 3), and of the 10 just one was female. The distribution of MoCA scores was significantly associated with urinary problems, insofar as the more severe urinary problems were, the lower the MoCA scores ($p = 0.04$) (Fig. 3). UPSIT scores for the 24/30 participants who underwent testing were 39.3 ± 29.9% with 5/24 (one of whom was female) scoring below 15%, indicating hyposmia. None demonstrated orthostatic changes in blood pressure on examination.

Table 1
Demographic information.

Age - at time of polysomnogram (years)	59.5 ± 16.0
Time from diagnosis to evaluation (years)	1.5 ± 2.3
Sex (M/F)	24/6
Self-identified race	African American: 2 Asian/Asian American: 1 Latino/Hispanic: 2 White/Caucasian: 24 Mixed: 1
BMI (kg/m^2)	25.2 ± 3.6

BMI: body mass index.
All values are mean ± standard deviation.

Table 2
Polysomnogram data.

Polysomnogram data	
Total sleep time (minutes)	388.4 ± 83.1
Sleep efficiency (%)	81.2 ± 13.9
% TST stage REM	17.5 ± 9.0
AHI-TST (events/h)	5.2 ± 5.6
PLMS index (movements/h)	16.8 ± 20.5

AHI: apnea-hypopnea index; PLMS: periodic limb movement of sleep; TST: total sleep time.
All values are mean ± standard deviation.

Discussion

In this cohort of individuals with PSG-confirmed iRBD, despite excluding those with known neurodegenerative disorders, we detected an unexpectedly high occurrence of non-motor dysfunction, particularly in the domains of mood, cognition, autonomic function, and olfaction. The International RBD Study Group [13] recently reported a significantly increased rate of phenoconversion from RBD to conditions including PD and DLB, falling under the umbrella of alpha-synucleinopathy, in those with olfactory deficit (HR = 2.62), mild cognitive impairment (MCI) (HR = 1.91–2.37), color vision abnormalities (HR = 1.69), constipation (HR = 1.67), REM atonia loss (HR = 1.54), and erectile dysfunction (HR = 2.13), in addition to motor symptoms (HR = 2.11), abnormal quantitative motor testing [hazard ratio (HR) = 3.16], objective motor examination (HR = 3.03), and an abnormal DAT scan (HR = 1.98), and age (HR = 1.54) [13]. While our present findings do not include long-term follow-up, they are consistent

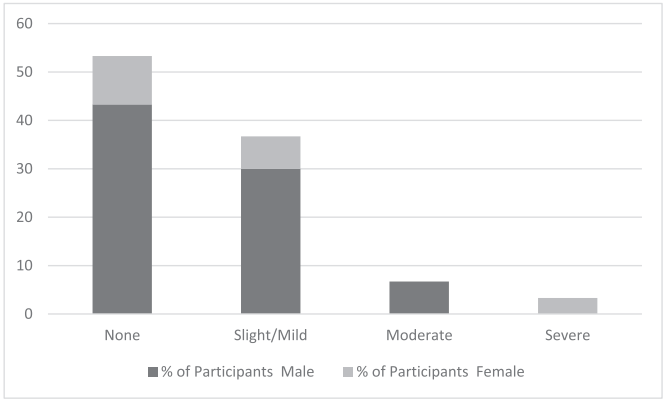

Fig. 1. Frequency of urinary problems. Urinary difficulties were reported in a total of 14/30 (46.7%): slight in 7 (23.3%), mild in 4 (13.3%), moderate in 2 (6.7%), and severe in 1 (3.3%).

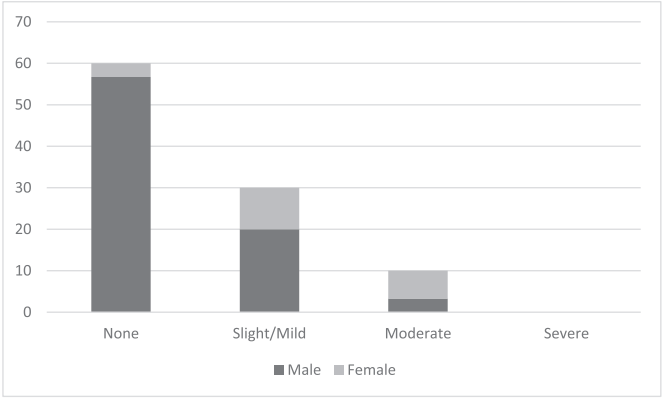

Fig. 2. Frequency of constipation. Constipation was reported in a total of 12/30 (40.0%): slight in 5 (16.7%), mild in 4 (13.3%), moderate in 3 (10.0%), and none were severe.

with increased risk for phenoconversion in a subset of our cohort, with younger age and presenting at an earlier stage of RBD compared to the International RBD Study Group cohort.

Autonomic features

Based on MDS-UPDRS part 1, urinary dysfunction and constipation were somewhat common in our cohort. Constipation has been previously reported in RBD, and its presence in our cohort is unsurprising [14,15]. In contrast, orthostatic hypotension, while similarly reported [14,15], was not seen in our cohort, and was not identified in a large multi-center study as a risk factor for phenoconversion [13]. In this same study, urinary dysfunction was not constipation significantly associated with development of alpha-synucleinopathy [13]. Urinary dysfunction has not been well-described in RBD patients, despite it being an important aspect of the nonmotor symptoms of PD [16]. In one cohort of early PD patients, a prevalence of urinary dysfunction of approximately 50% was demonstrated, suggesting that urinary dysfunction occurs very early in the course of PD [17]. Supporting this, slight dysfunction was found at 7–9 years prior to phenoconversion in one study [18]. Recently, Xu et al. demonstrated that frontal lobe executive impairment, severity of PD, and the presence of RBD accompanied a higher prevalence of overactive bladder in 100 Chinese PD patients [16]. We suggest that urinary dysfunction, especially as it relates to MCI (see below) is an important component of clinical care, quality of life, and further research utility in patients with RBD.

Table 3
Neuropsychiatric evaluation.

Beck Depression Inventory-II (BDI-II), N = 20		
	F = 4 (20.0%)	M = 16 (80.0%)
Minimal: 17 (85.0%)	3 (15.0%)	14 (70.0%)
Mild: 1 (5.0%)	0 (0.0%)	1 (5.0%)
Moderate: 1 (5.0%)	0 (0.0%)	1 (5.0%)
Severe: 1 (5.0%)	1 (5.0%)	0 (0.0%)
Beck Anxiety Inventory (BAI), N = 21		
	F = 4 (19.0%)	M = 17 (81.0%)
Minimal: 14 (66.7%)	2 (9.5%)	12 (57.2%)
Mild: 5 (23.8%)	1 (4.8%)	4 (19.0%)
Moderate: 2 (9.5%)	1 (4.8%)	1 (4.8%)
Severe: 0 (0.0%)	0 (0.0%)	0 (0.0%)
Montreal Cognitive Assessment (MoCA), N = 29		
	F (below score of 26)	M (below score of 26)
26.5 ± 3.1	1 (3.4%)	9 (31.0%)
10/29 (34.4%) scored <26		

F: female; M: male.
All values are mean ± standard deviation.

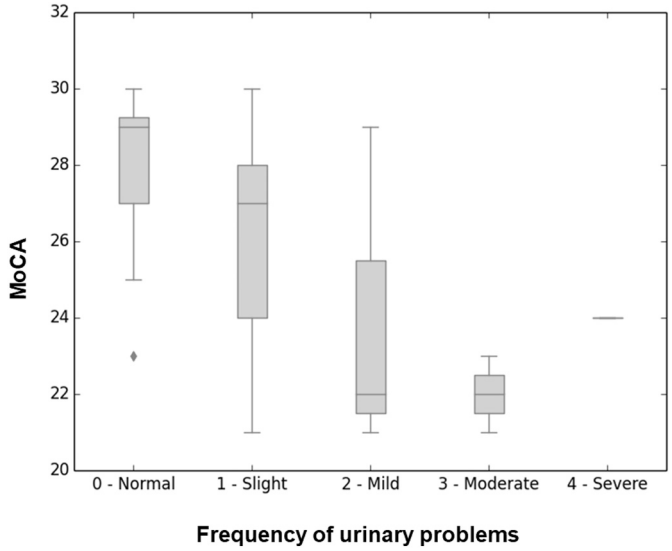

Fig. 3. Association between urinary problems and MoCA scores. The distribution of MoCA scores was significantly associated with urinary problems, insofar as the more severe urinary problems were, the lower the MoCA scores ($p = 0.04$). Ten of 29 subjects had abnormal MoCA scores (<26) and of these 1 subject was female.

Cognition

MCI has been previously described in patients with RBD [19,20], and cognitive dysfunction (based on abnormal MoCA scores) was common in our cohort, occurring in approximately one third. Urinary dysfunction was associated with MoCA score in our cohort, in that the worse the urinary complaints, the worse the MoCA score. Given that MCI is a significant risk factor in phenoconversion [13], the association with urinary dysfunction requires further investigation. It is unclear why this was the only association found with MoCA score, but perhaps this is a result of the younger age of our participants and/or an earlier stage of their RBD compared to the International RBD Study Group cohort; this would imply that the link between urinary dysfunction and MoCA score/MCI could be considered as symptoms that begin very early.

Psychiatric illness

A significant number within our cohort reported psychiatric illness, which is a consistent finding in those with RBD [21,22]. The relationship between RBD and depression and anxiety may be complex. According to the International RBD Study Group data [13], depression and anxiety do not seem to favor phenoconversion. However, in those with PD, depression is more common than in the general population, there is an increased prevalence of depression in PD patients before the clinical onset of PD, and it is a risk factor, independent of RBD, for development of PD. In a large Swedish study, depression was associated with a relative risk of 3.21 for PD [23], and in the NIH-AARP Diet and Health Study, the odds ratio for the development of PD was 2.7 for those diagnosed with depression [24]. While clinical anxiety has been demonstrated to be a part of RBD symptomatology [25], and is considered to be a potential prodromal marker [26] in alpha-synucleinopathy, the International RBD Study Group did not find this to be a significant risk factor regarding phenoconversion [13].

In our cohort, every participant who completed the BDI-II (n = 20) and BAI (n = 21) reported some form of anxiety and/or depression. These results did not correlate with any of the other measures reported in our cohort, but this may change in time on follow-up evaluations. Furthermore, the remaining participants who did not complete this aspect of their evaluation may have been more depressed or anxious, thus limiting their involvement and artificially removing an otherwise potential association.

Antidepressant use

A well-known association exists between use of antidepressants and RBD. In our study, use of sertraline correlated with RBDSQ score. While it is too early to determine if this means there is an increased risk for phenoconversion in those on sertraline, it is an intriguing prospect. It has been estimated that the odds ratio of developing RBD is 1.9 with antidepressant use [27], particularly with selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors (SNRIs). A few case reports have shown improvement of RBD upon discontinuation of fluoxetine [28,29], but RBD can persist for at least 19 months after discontinuation of SSRI medications [30].

Some have suggested that antidepressants may "unmask" RBD rather than cause it [31]. Markers of prodromal neurodegeneration may still be present in those with antidepressant-associated RBD, suggesting that antidepressants may be linked to early clinical presentation of an RBD that was nonetheless related to underlying neurodegeneration [32]. However, others have demonstrated that RBD patients taking antidepressants actually had less chance of developing neurodegenerative disease than those who were not [31]. Therefore, it is still unclear whether antidepressant-associated RBD is a side effect of the medication, or, in fact, a marker of prodromal neurodegenerative disease [2,31].

Olfaction

Hyposmia has been shown to be associated with an increased risk of phenoconversion in RBD patients [3], and despite the fact that 5/24 did demonstrate hyposmia, the UPSIT scores did not significantly correlate with any of the other non-motor markers of phenoconversion in our cohort. However, there was a correlation approaching significance for the past ($p = 0.06$) and current ($p = 0.07$) use of escitalopram (data not shown). Additionally, there is a known relationship between MCI and olfactory dysfunction in RBD [33], but again, this was not noted in our cohort. Perhaps further analysis on follow-up studies will provide more insight.

Sleep disorders

There was the presence of borderline OSA and borderline clinically significant PLMS in our cohort. Comorbid OSA in RBD patients is quite common, with 34%–60% of the RBD patients having sleep apnea [34]. The coexistence of OSA and RBD may arise from common risk factors, such as male preponderance and old age, and it is known that treatment of comorbid OSA may also improve the frequency and severity of RBD behaviors [35].

Similarly, PLMS in our cohort were present in frequency just above the clinical cutoff of >15/h. The clinical relevance of PLMS is controversial, as they can be a common incidental finding in healthy people without sleep complaints [36]. PLMS also occur in some sleep disorders such as RBD and other parasomnias [36,37], but their utility in predicting phenoconversion is not yet known. However, one study demonstrated that among older men without dementia, higher PLMS frequency was associated with greater decline in cognition [38]. How this relates to our cohort remains to be seen.

Management of RBD patients

The best practice guidelines [39], published in 2010, highlight the symptomatic treatment of RBD patients and the counseling that should take place regarding bedroom safety principles to prevent injury or other consequences. Others have suggested bed alarm systems that could reassure and alert the patient during RBD episodes [40].

However, our results and those of others suggest that there is an opportunity to improve work-up and facilitate appropriate referrals for multi-disciplinary care in RBD patients. Attention needs to be provided to identifying and treating depression, anxiety, cognitive deficits, urinary dysfunction or other features (Table 4). In patients diagnosed with RBD, we therefore suggest that a closer look by the clinician is warranted.

Given the strong associations between specific non-motor symptoms and the odds of development of PD and other neurodegenerative conditions; it has been suggested that screening programs may identify individuals at increased risk for such conditions. The non-motor features highlighted in this study often precede motor symptoms, and therefore their presence could provide an efficient method for early neurodegeneration identification. Indeed, our cohort demonstrated an association between MoCA scores with the presence urinary dysfunction. In the context of the other important findings listed above, there possibly exists the presence of a clinically relevant subtype of RBD, which we propose as "RBD-plus". However, it will be important, if and when such screening programs are undertaken, that treatment opportunities addressing for example mood or urinary dysfunction are not missed, as these may improve the patients' wellbeing. Seeking out of RBD-plus patients through the use of clinical history taking and examination, combined with screening tools such as those used in our study, could therefore dictate which additional specialist(s) should be involved in the care team of an individual with RBD. At this juncture, a Psychiatrist (for anxiety/depression), a Gastrointestinal or Genitourinary Specialist (for constipation and/or urinary dysfunction, respectively) and/or a Neuropsychologist for neuropsychiatric testing would be prudent considerations. Updated best practice guidelines could reflect this multi-disciplinary approach in the future.

Limitations

The low number of patients in our present report, despite being comparable to certain other studies [14,30,37,41], is a limitation. In particular, women were underrepresented in this cohort, limiting interpretation of sex-related differences. Our ability to identify associations between features reported is limited by participant number, and the cross-sectional design of the study does not permit testing of stability of the findings, nor their

Table 4
Available medical treatment options for non-motor symptoms identified in the RAPiDS cohort.

Symptom	Available medical treatments
Anxiety	Psychotherapy Anxiolytic medications such as buspirone; antidepressant medications including selective serotonin reuptake inhibitors (SSRI) and serotonin and norepinephrine reuptake inhibitors (SNRI); benzodiazepines; others
Constipation	Increase fluid intake Increase dietary fiber Medications such as laxatives; others
Depression	Psychotherapy Antidepressant medications such as selective serotonin reuptake inhibitors (SSRI); serotonin and norepinephrine reuptake inhibitors (SNRI); others Transcranial magnetic stimulation Electroconvulsive therapy
Hyposmia	No direct treatment; attention to appetite, food intake, and weight loss
Excessive daytime sleepiness	Address underlying cause if possible Stimulants, such as methylphenidate; modafinil; other Antidepressant medications
Obstructive sleep apnea	Positive airway pressure, such as continuous positive airway pressure devices Mouthpiece Surgical intervention such as uvulopalatopharyngoplasty; maxillomandibular advancement; upper airway stimulation; other
Restless legs syndrome	Identify and correct underlying causes such as iron deficiency Medications such as dopamine agonists; gabapentin and gabapentin enacarbil; pregabalin; opioids (in refractory cases); others
Urinary dysfunction	Bladder re-training Medications such as anticholinergic agents; miragebron; others Onabotulinum toxin injections

association with prognosis. The study enrolled patients from a single sleep center, presenting the possibility of referral bias, and the cohort is derived from an urban setting thus limiting its generalizability.

Conclusion

Our results point to the need for screening patients with iRBD in the clinic for complaints that are actionable, for example affecting mood, cognition, urinary function, and bowel function. For example, specifically screening for depression in iRBD might identify treatment opportunities to improve patient well-being. Moreover, screening would not only improve care for RBD patients in the short term, but identifying potential early indicators of alpha-synucleinopathy could eventually facilitate inclusion in trials focused on disease prevention or in slowing progression.

In summary, it is clear that RBD is a risk for impending alpha-synucleinopathy, but how and why this occurs is still a mystery. With our data, and those of other groups, it is hopeful that we will discover the answers to these questions. For now, it is noteworthy that urinary problems, and MCI needs to be closely watched clinically, as does abnormal smell testing and use of antidepressants; we propose the term RBD+ to be used to identify such individuals. For the quality of life in patients diagnosed with RBD, a closer look by the clinician should be enacted, with appropriate referrals and workup. And in time, perhaps a trial of a neuroprotective agent could be employed in these particular RBD patients.

Declaration of competing interests

Nothing to declare.

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