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Original Article

Protective effects of REM sleep without atonia against obstructive sleep apnea in patients with idiopathic REM sleep behavior disorder

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ABSTRACT

Background: This study investigated the protective effect of rapid eye movement (REM) sleep without atonia against obstructive sleep apnea (OSA) in patients with idiopathic REM sleep behavior disorder (RBD).
Methods: In this case–control study, patients with idiopathic RBD and OSA (RBD-OSA) were consecutively enrolled and OSA controls without RBD were matched for age, sex, and apnea–hypopnea index (AHI). Clinical and polysomnographic characteristics were compared between RBD-OSA patients and OSA controls. Additionally, differences in AHIs depending on sleep state and posture were analyzed.
Results: In total, 109 OSA patients (81 males and 28 females) with idiopathic RBD were included in the study. In OSA controls without RBD, AHI and respiratory distress index (RDI) were significantly higher during REM sleep than during non-rapid eye movement (NREM) sleep ($p < 0.01$). In RBD-OSA patients, however, AHI and RDI were slightly lower during REM sleep than during NREM sleep ($p < 0.05$). During REM sleep, AHI and RDI were significantly lower in RBD-OSA patients than in OSA controls ($p < 0.001$). Differences in apnea severity between RBD-OSA patients and OSA controls increased in supine REM sleep but disappeared or lessened in non-supine REM sleep. The prevalence of REM-related OSA was lower in RBD-OSA patients (9.2%) than in OSA controls (33.0%).
Conclusions: REM sleep without atonia has protective effects against OSA in patients with idiopathic RBD. These protective effects are much more potent in supine sleep than in non-supine sleep.

1. Introduction

Obstructive sleep apnea (OSA) is a common sleep disorder characterized by the repetitive obstruction of the upper airway during sleep. Untreated OSA is often associated with cardiovascular comorbidities and psychological distress [1–3]. Sleep apneas lead to intermittent hypoxia, episodic arousals, and sleep fragmentation; all of which are significantly affected by sleep state and posture. Rapid eye movement (REM) sleep causes the atonia of the upper airway muscles, including the genioglossus and other pharyngeal dilator muscles, causing OSA aggravation [4]. Simultaneously, upper airway muscles are prone to collapse by gravity in the supine position, which augments sleep apnea in OSA patients [5,6].

REM sleep behavior disorder (RBD) is a parasomnia characterized by abnormal behaviors emerging during REM sleep that may cause injury or sleep disruption [7]. Abnormal behaviors of RBD are associated with the loss of muscle atonia during REM sleep. Comorbid OSA in RBD patients is quite common, with 34%–60% of the RBD patients having sleep apnea [8,9]. The coexistence of OSA and RBD may arise from common risk factors, such as male preponderance and old age. Whether RBD comorbid with OSA is good or bad for sleep apnea is an intriguing idea. It has been hypothesized that the loss of muscle atonia during REM sleep in RBD patients exerts a protective effect against sleep apnea by preventing upper airway collapse [10]. However, previous studies evaluating this hypothesis remain limited, and their findings are contradictory [10–14]. Some studies [10–12] have reported data in favor of this hypothesis. In contrast, De Cock et al., [13] have demonstrated that the maintenance of chin muscle tone during REM sleep does not affect the frequency of apneic events in patients with Parkinson's disease (PD). Zhang et al., [14] have demonstrated that PD patients with RBD presented with even more severe OSA than did those without RBD. Such conflicting results among studies might have stemmed from methodological issues, such as small sample

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sizes, heterogeneous study populations, or inadequate control groups.

The aims of the present study were three-fold: (1) to document whether RBD has a protective effect against OSA; (2) to determine whether these protective effects vary depending on sleep posture and state; and (3) to determine the prevalence of REM-related OSA in RBD patients comorbid with OSA. In the present study, some methodological issues were taken into consideration. We recruited only patients with idiopathic RBD to eliminate the heterogeneity of study population. Sample sizes in most previous studies were small, with cohorts of less than 50 subjects [10,11,14]. In our study, we addressed this issue by including more patients with RBD. OSA controls were matched to patients with idiopathic RBD in terms of age, sex, and apnea severity.

2. Materials and methods

2.1. Patients

This was a case–control study including a consecutive series of patients with idiopathic RBD between 2009 and 2017. Criteria for inclusion were as follows: aged >45 years, newly diagnosed with RBD, and showing the apnea–hypopnea index (AHI) of ≥5/h (RBD-OSA), as determined by full-night polysomnography (PSG). RBD was defined according to the criteria of the International Classification of Sleep Disorder-3 [15]. Controls comprised OSA patients without RBD, as determined by full-night PSG. Controls were matched for age (difference <5 years), sex, and AHI (difference <5/h) from our sleep database. Patients were excluded if presented with any neurodegenerative disorders, such as PD, multiple system atrophy, and dementia; if they were using antidepressants or benzodiazepine; or if they had a total sleep time of <100 min or REM sleep of <10 min. When comparing the combined effects of sleep state and posture on sleep apnea, we excluded patients who had each supine or non-supine REM sleep lasting for <5 min and those who had each supine or non-supine non-rapid eye movement (NREM) sleep lasting for <10 min.

In addition to demographic information, medical comorbidities and medication information were obtained from a self-reported checklist for medical history and electronic medical records. Daytime sleepiness was evaluated using the 8-item Epworth Sleepiness Scale (ESS) [16]: higher scores indicate greater sleepiness during daily activities. Written informed consent was obtained from all participants, and the study was reviewed and approved by the Institutional Review Board of Asan Medical Center.

2.2. Polysomnography

PSG was performed using a digital polygraph system (RemLogic ver. 2.0, Embla Systems Inc., Broomfield, CO, USA). A position sensor is an integrated part of the system hardware and is located inside the Patient Unit. Sleep and respiratory events were scored according to the 2007 American Academy of Sleep Medicine guidelines [17]. Apnea was defined as ≥90% drop in the peak thermal sensor excursion from the baseline value for at least 10 s. Hypopnea was defined as ≥30% drop in the nasal pressure signal excursion from the baseline value for ≥10 s accompanied by ≥ 4% reduction in O_2 saturation from the pre-event baseline. Respiratory effort-related arousal (RERA) was defined as a sequence of breaths lasting at least 10 s characterized by the flattening of the nasal pressure waveform and leading to arousal from sleep when the sequence of breaths did not meet the criteria for apnea or hypopnea. AHI was defined as the average number of episodes of apnea and hypopnea per hour. Respiratory distress index (RDI) was calculated as the average number of episodes of apnea, hypopnea, or RERA per hour. Oxygen desaturation index (ODI) was defined as the number of times oxygen desaturation was ≥3% per hour of sleep.

According to a previous report, REM-related OSA was defined as follows: overall AHI ≥5/h, AHI during REM sleep (AHI_{REM}) to AHI during NREM sleep (AHI_{NREM}) ratio >2, and AHI_{NREM} <15/h [18].

2.3. Statistical analysis

Data were expressed as means and standard deviation (SD) for normally distributed data, median and interquartile range (IQR) for non-normally distributed data, or numbers and percentages for nominal variables. All statistical tests were two-tailed, and $p < 0.05$ was considered significant. Clinical and polysomnographic characteristics were compared between RBD-OSA patients and OSA controls using paired t-test, Wilcoxon signed-rank test, or McNemar test. AHIs depending on sleep state and posture were compared between the cases and controls using Wilcoxon signed-rank test. Data were analyzed using SPSS version 21.0 (SPSS Inc., Chicago, IL).

3. Results

3.1. Patients

Of the 126 RBD-OSA patients, 17 were excluded due to no matching OSA controls (n = 14) and REM sleep lasting <10 min (n = 3). The remaining 109 subjects (81 males and 28 females) were included in the study. Characteristics of RBD-OSA patients and OSA controls are summarized in Table 1. Compared with OSA controls, RBD-OSA patients had lower ESS scores ($p < 0.05$); slightly less severe sleep apnea, as measured by RDI, ODI, and minimum arterial oxygen saturation ($MinSaO_2$) ($p < 0.05$); and longer total and REM sleep durations, with a higher proportion of REM sleep ($p < 0.05$) (Table 1). In addition, RBD-OSA patients slept longer in a supine posture than did OSA controls ($p < 0.001$).

3.2. Comparisons of apnea severity between REM and NREM sleep

In OSA controls, AHI and RDI were significantly higher during REM sleep than during NREM sleep ($p < 0.01$) (Table 2). The mean differences in AHI and RDI between REM and NREM sleep were 6.6/h and 5.7/h, respectively. In RBD-OSA patients, however, AHI and RDI were slightly lower during REM sleep than during NREM sleep ($p < 0.05$) (Table 2).

3.3. Comparisons of apnea severity between RBD-OSA patients and OSA controls

AHI_{REM} and RDI_{REM} were significantly lower in RBD-OSA patients than in OSA controls ($p < 0.001$) (Table 3). The mean differences in AHI_{REM} and RDI_{REM} between RBD-OSA patients and OSA controls were −7.5/h and −8.7/h, respectively. These differences significantly varied depending on sleep posture (Table 4). Supine posture during REM sleep increased these differences, whereas non-supine posture during REM sleep reduced these differences between RBD-OSA patients and OSA controls.

In contrast to REM sleep, differences in AHI_{NREM} between RBD-OSA patients and OSA controls were dramatically reduced, becoming slightly reverse (Table 3). RDI_{NREM} did not show any differences between RBD-OSA patients and OSA controls. There were no postural effects on apnea severity during NREM sleep unlike during REM sleep (Table 4).

Table 1
Sample characteristics between RBD patients with OSA and OSA controls without RBD.

	OSA controls (n = 109)	RBD with OSA (n = 109)
Age, year, mean (SD)	63.5 (7.2)	64.1 (7.2)
Male, n (%)	81 (74.3)	81 (74.3)
Body mass index, Kg/m^2, mean (SD)	25.2 (3.0)	24.7 (3.0)
Hypertension, n (%)	45 (41.3)	40 (36.7)
Type 2 diabetes, n (%)	17 (15.6)	23 (21.1)
Epworth Sleepiness Scale, mean (SD)	9.1 (5.1)	7.2 (5.3)*
AHI,/h, median (IQR)	14.7 (9.5, 25.7)	14.8 (8.6, 26.7)
$5 \leq$ AHI < 15, n (%)	55 (50.5)	55 (50.5)
$15 \leq$ AHI < 30, n (%)	32 (29.4)	34 (31.2)
AHI ≥ 30, n (%)	22 (20.2)	20 (18.3)
Respiratory Distress Index, /h, median (IQR)	19.3 (14.4, 31.5)	18.5 (11.5, 29.8)**
Oxygen Desaturation Index, /h, median (IQR)	11.3 (6.8, 22.6)	9.9 (4.5, 23.8)*
Minimal SaO_2 saturation, %, median (IQR)	86.0 (82.0, 88.0)	88.0 (84.8, 90.0)***
Sleep architecture		
Total sleep time, min, mean (SD)	336.8 (44.3)	352.6 (52.7)*
N1 sleep, %, mean (SD)	28.4 (13.2)	29.3 (13.3)
N2 sleep, %, mean (SD)	48.2 (10.4)	44.8 (11.5)*
N3 sleep, %, median (IQR)	4.6 (0.2, 10.8)	2.7 (0.0, 9.8)
REM sleep, %, mean (SD)	17.1 (6.0)	19.5 (6.8)*
Sleep latency, min, median (IQR)	5.0 (2.6, 9.8)	7.0 (2.5, 12.5)
WASO, min, median (IQR)	44.0 (30.5, 72.5)	36.9 (19.5, 62.4)
Sleep efficiency, %, median (IQR)	86.0 (80.4, 90.6)	88.9 (80.9, 93.8)
Sleep time depending on sleep state and posture		
REM sleep time, min, mean (SD)	58.5 (23.9)	69.7 (29.5)**
NREM sleep time, min, mean (SD)	279.0 (35.6)	282.8 (43.8)
Supine sleep time, min, mean (SD)	189.7 (80.6)	238.2 (97.4)***
Non-supine sleep time, min, mean (SD)	147.0 (76.9)	114.1 (96.5)**

AHI apnea-hypopnea index, *IQR* interquartile range, *OSA* obstructive sleep apnea, *RBD* rapid eye movement sleep behavior disorder, *REM* rapid eye movement, *SD* standard deviation, *WASO* wake after sleep onset.
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

Table 2
Comparisons of apnea severity between REM and NREM sleep in RBD patients with OSA and OSA controls without RBD.

	OSA controls (n = 109)			RBD with OSA (n = 109)		
	REM sleep, median (IQR)	NREM sleep, median (IQR)	REM-NREM difference, mean (SD)	REM sleep, median (IQR)	NREM sleep, median (IQR)	REM-NREM difference, mean (SD)
AHI, /h	22.4 (11.3, 34.0)	13.3 (7.8, 25.8)	6.6 (17.2)***	12.1 (5.6, 25.1)	15.6 (7.9, 26.3)	−1.9 (14.9)*
RDI, /h	26.7 (16.1, 37.5)	18.3 (11.6, 30.3)	5.7 (17.9)**	12.7 (6.6, 27.8)	20.2 (11.1, 30.9)	−3.0 (15.1)**

AHI apnea-hypopnea index, *IQR* interquartile range, *NREM* non-rapid eye movement, *OSA* obstructive sleep apnea, *RBD* rapid eye movement sleep behavior disorder, *RDI* respiratory distress index, *REM* rapid eye movement, *SD* standard deviation.
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

3.4. Prevalence of REM-related OSA

In total, 10 (9.2%) of the 109 RBD-OSA patients had REM-related OSA (Fig. 1), whereas 36 (33.0%) of the 109 OSA controls had REM-related OSA. The prevalence of REM-related OSA was significantly lower in RBD-OSA patients than OSA controls ($p < 0.001$).

4. Discussion

We attempted to determine the protective effects of the loss of muscle atonia during REM sleep against OSA in idiopathic RBD patients. OSA controls were matched for age, sex, and AHI. As expected, we found that compared with OSA controls, RBD-OSA patients had significantly lower AHI and RDI during REM sleep but not during NREM sleep although RBD-OSA patients slept longer in the supine posture and in the REM sleep state. Such protective effects of REM sleep in RBD-OSA patients were more potent in the supine sleep rather than in the non-supine sleep. The prevalence of REM-related OSA was lower in RBD-OSA patients (9.2%) than in OSA controls (33.0%).

Thus, our study demonstrated that REM sleep without atonia has protective effects against OSA in patients with idiopathic RBD,

Table 3
Comparisons of apnea severity between RBD patients with OSA and OSA controls without RBD depending on sleep state.

	REM sleep			NREM sleep		
	RBD with OSA, median (IQR) (n = 109)	OSA controls, median (IQR) (n = 109)	RBD-Control difference, mean (SD)	RBD with OSA, median (IQR) (n = 109)	OSA controls, median (IQR) (n = 109)	RBD-Control difference, mean (SD)
AHI, /h	12.1 (5.6, 25.1)	22.4 (11.3, 34.0)	−7.5 (20.2)***	15.6 (7.9, 26.3)	13.3 (7.8, 25.8)	1.0 (6.2)*
RDI, /h	12.7 (6.6, 27.8)	26.7 (16.1, 37.5)	−8.7 (20.4)***	20.2 (11.1, 30.9)	18.3 (11.6, 30.3)	0.1 (7.7)

AHI apnea-hypopnea index, *IQR* interquartile range, *NREM* non-rapid eye movement, *OSA* obstructive sleep apnea, *RBD* rapid eye movement sleep behavior disorder, *RDI* respiratory distress index, *REM* rapid eye movement, *SD* standard deviation.
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

Table 4
Comparisons of the postural effects on apnea severity between RBD patients with OSA and OSA controls without RBD depending on sleep state.

	Supine			Non-supine		
	RBD with OSA, median (IQR)	OSA controls, median (IQR)	RBD-Control difference, mean (SD)	RBD with OSA, median (IQR)	OSA controls, median (IQR)	RBD-Control difference, mean (SD)
REM sleep	(n = 76)			(n = 65)		
AHI, /h	14.1 (6.4, 33.2)	39.6 (25.5, 52.7)	−20.3 (26.8)***	5.5 (0.0, 14.6)	6.0 (0.5, 22.5)	−3.3 (19.9)
RDI, /h	14.6 (7.7, 34.7)	45.6 (30.0, 57.0)	−21.3 (26.2)***	8.7 (2.1, 17.8)	12.0 (5.6, 27.7)	−4.87 (20.2)*
NREM sleep	(n = 109)			(n = 65)		
AHI, /h	19.8 (10.7, 38.5)	21.6 (12.5, 40.0)	−1.1 (15.9)	3.3 (1.2, 8.6)	3.0 (0.7, 9.0)	0.9 (9.8)
RDI, /h	25.8 (14.5, 38.8)	27.1 (17.9, 48.1)	−2.8 (17.6)	7.1 (2.8, 13.6)	6.1 (2.5, 11.1)	1.9 (9.4)

AHI apnea-hypopnea index, *IQR* interquartile range, *NREM* non-rapid eye movement, *OSA* obstructive sleep apnea, *RBD* rapid eye movement sleep behavior disorder, *RDI* respiratory distress index, *REM* rapid eye movement, *SD* standard deviation.
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

as reflected by the low prevalence of REM-related OSA subtype in RBD-OSA patients. These findings are consistent with reports of two previous studies [10,11], which demonstrated that excessive electromyography activity in RBD might protect patients against severe OSA. Their study design was similar to our study in terms of study sample (largely comprising patients with idiopathic RBD) and study controls (comprising OSA patients matched for age, sex, and AHI). In contrast to these studies in which protective effects against OSA were not shown in the parameter of AHI [10,11], the present study demonstrated protective effects against OSA through the parameters of AHI and RDI. This discrepancy might result from differences in study sample characteristics. Our study sample included younger patients, a higher proportion of female, and much milder apnea severity. The mean AHI of patients with RBD was 18.7/h (SD 13.2) in our study compared with the mean AHI of 32.6/h (SD 14.2) [11] and 34.2/h (SD 22.6) [10] in aforementioned studies. In addition, Bugalho et al., [11] found lower BMI values in RBD-OSA patients than in OSA controls, suggesting that obesity could be less important as a diagnostic marker of OSA in RBD patients. This finding was supported by one controlled study showing lack of association between OSA and obesity in patients with Parkinson's disease [19]. However, this finding was not reproduced in our study. Although unclear, this finding could be partly explained by that the impact of obesity on the severity of OSA differs between Asian and Western patients [20]. Asian patients have a lower incidence of obesity and are at a higher risk for more severe OSA than Western patient populations [21]. Furthermore, and craniofacial structures contribute more to OSA in Asian than in Western patients [20,21].

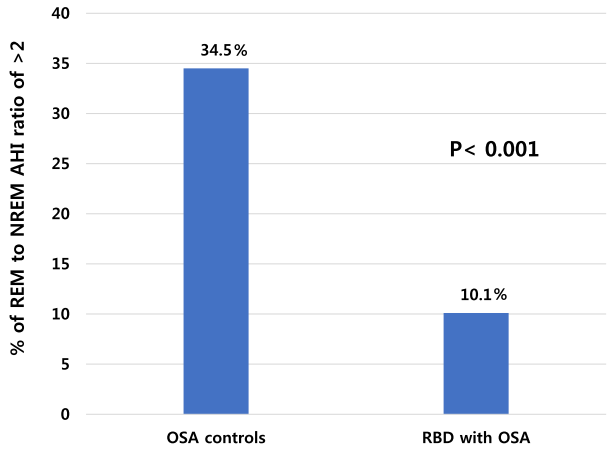

Fig. 1. Prevalence of REM-related OSA in RBD patients with OSA and controls with OSA. The REM/NREM AHI >2 shows predominance of sleep apnea during REM sleep. RBD with OSA group showed lower proportion of REM-related OSA compared to OSA controls.

In addition, studies performed in RBD patients with comorbid PD showed contradictory results [12–14]. Gong et al., [12] have reported that PD patients with RBD exhibited lower AHI and ODI and less time in arterial oxygen saturation <90% during REM sleep than those without RBD. Yet, De Cock et al., [13] have shown that the maintenance of muscle tone during REM sleep did not affect the frequency of apneic events in PD patients. Moreover, Zhang et al., [14] have shown that PD patients with RBD had even reduced mean SaO_2 and more severe sleep apnea-related parameters during total and NREM sleep than those without RBD. However, there were no differences in the apnea/hypopnea-related variables during REM sleep between PD patients with and without RBD [14]. The reasons for these discrepancies among the study results remain unclear, but possible explanations include methodological issues, such as a small sample size and an inadequate control sample. In addition, complex interactions between OSA and PD depending on the coexistence of RBD may have affected the results. In a recent clinical review of OSA in PD [22], five of the seven studies have reported similar or lower prevalence of OSA in patients compared with that in healthy age-matched controls. Two studies have reported less oxyhemoglobin desaturation during sleep among these patients [22]. These findings did not support the idea that PD patients are at an increased risk of OSA. Conversely, Zhang et al., [14] reported that OSA was more frequent in PD patients with RBD (51.4%) than in those without RBD (9.1%).

In general, the supine position aggravates OSA because upper airway muscles are prone to collapse by gravity in this position [5,6]. In the present study, differences in AHI_{REM} between RBD-OSA patients and OSA controls were larger in supine sleep than in non-supine sleep. Differences in AHI_{REM} between supine and non-supine postures were smaller in RBD-OSA patients than in OSA controls. These findings indicate that the protective effects of REM sleep without atonia against OSA were more potent in supine sleep. Therefore, OSA severity in RBD patients remained generally mild during supine REM sleep, thereby allowing RBD patients to sleep longer in the supine posture.

In the present study, RBD-OSA patients were less sleepy than OSA controls even though both groups were matched for AHI. This finding was contradictory to the finding reported by Huang et al., [10] that ESS scores were significantly higher in RBD-OSA patients than in OSA controls; although underlying reasons for this discrepancy remain unclear. Possible reasons include different study population characteristics. AHI was much milder in our study population. Based on the protective effects of REM sleep without atonia against OSA in RBD-OSA patients, it could be speculated that the aggravation of OSA during REM sleep resulting in the selective fragmentation or deprivation of REM sleep causes daytime sleepiness in patients with mild or moderate OSA. This assumption was

supported by a study of OSA patients with an AHI of <10 [23], in which AHI_{REM} correlated with daytime sleepiness, explaining 35% of the variance in sleep latency on the multiple sleep latency test (MSLT). The AHI_{REM} of >15/h on MSLT is predictive of reduced sleep latency [23]. In addition, REM-predominant OSA was independently associated with daytime sleepiness in another study [24]. However, the role of REM sleep and the impact of REM sleep deprivation on daytime sleepiness remain controversial [23–26]. A previous study has shown that OSA during NREM sleep but not during REM sleep is associated with an increased risk of daytime sleepiness [25]. A study of OSA patients with a mean AHI of 34.1/h (range, 5–126/h) showed no differences in ESS scores or mean sleep latency measured by the maintenance of wakefulness test between patients with AHI_{REM} to AHI_{NREM} ratio >2 and those with AHI_{REM} to AHI_{NREM} ratio ≤ 2 [27].

Certain limitations should be noted when interpreting the results of this study. First, even though OSA controls without RBD were matched for age, sex, and AHI, apnea severity measured by RDI, ODI, and $MinSaO_2$ was slightly milder in RBD-OSA patients than in OSA controls. Nevertheless, this was considered to not have any significant effects on our findings because protective effects against OSA were determined by AHI. Second, for determining whether protective effects on sleep apnea vary depending on sleep posture, we included patients with each supine or non-supine posture lasting for >5 min and >10 min during REM and NREM sleep, respectively. This sleep time according to sleep postures may not be long enough to evaluate postural effects on apnea severity in OSA patients. Third, high night-to-night AHI variability is well recognized in OSA patients [28]. Moreover, RBD patients show a night-to-night variability of muscle tone and movements during REM sleep [29,30]. Given that the data were collected from a single-night PSG, we cannot exclude the possibility that our findings are distorted by such a night-to-night variability. Finally, we did not collect data on insomnia symptoms, which would affect daytime sleepiness. Therefore, differences in the proportion of patients with insomnia symptoms between RBD-OSA patients and OSA controls may have resulted in different daytime sleepiness.

In conclusion, REM sleep without atonia has protective effects against OSA in patients with idiopathic RBD. Such protective effects are more potent in supine sleep than in non-supine sleep.

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Conflict of interest

The authors declare no conflicts of interest in relation to this study.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2018.10.032.

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