Sleep Medicine 12 (2011) 711–713

Contents lists available at ScienceDirect

Sleep Medicine

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

Brief Communication

Utility of the REM sleep behavior disorder screening questionnaire (RBDSQ) in Parkinson's disease patients

Takashi Nomura [a,*], Yuichi Inoue [b,c], Tatsuo Kagimura [b,c], Yusuke Uemura [a], Kenji Nakashima [a]

[a] Division of Neurology, Department of Brain and Neurosciences, Faculty of Medicine, Tottori University, Japan
[b] Japan Somnology Center, Neuropsychiatric Research Institute, Japan
[c] Department of Somnology, Tokyo Medical University, Japan

ARTICLE INFO

Article history:
Received 30 November 2010
Received in revised form 18 January 2011
Accepted 21 January 2011
Available online 22 June 2011

Keywords:
RBD
RBDSQ-J
Parkinson's disease
Screening
Cut-off value
ROC

ABSTRACT

Objective: We evaluated the usefulness of the REM sleep behavior disorder (RBD) screening questionnaire (RBDSQ) among patients with Parkinson's disease (PD).
Methods: Forty-five patients with PD were evaluated (22 male and 23 female, 72.9 ± 9.1 years old). After patients completed the RBDSQ, we conducted interviews regarding RBD symptoms and performed polysomnographic examinations on the subjects. We then compared RBDSQ scores among the following groups: PD with RBD (n = 19), PD without RBD (n = 26), and idiopathic RBD (n = 31, 22 male and 9 female, 67.8 ± 6.5 years old), and estimated the cut-off score for an RBD diagnosis.
Results: RBDSQ scores in PD with RBD and idiopathic RBD groups were similar and higher than those in the PD without RBD group (PD with RBD: 7.2 ± 1.9, idiopathic RBD: 7.9 ± 2.8, PD without RBD: 2.9 ± 1.6). Cronbach's α for RBDSQ sub-scores was 0.73, suggesting a fair internal consistency. A receiver-operator characteristics curve revealed that a total score of 6 points on the RBDSQ represented the best cut-off value for detecting RBD (sensitivity = 0.842, specificity = 0.962).
Conclusion: RBDSQ could be a useful tool for the screening of RBD in PD patients.

1. Introduction

REM sleep behavior disorder (RBD) is characterized by vigorous and injurious behaviors related to vivid, action-filled, and violent dreams during nocturnal REM sleep [1]. Many patients with neurological disorders are reported to have RBD symptoms (secondary RBD). In particular, RBD has been widely accepted as one of the preclinical symptoms of Parkinson's disease (PD) [2]. In the second edition of the International Classification of Sleep Disorders (ICSD second), the existence of REM sleep without atonia (RWA) on polysomnogram (PSG) is essential for the diagnosis of RBD [3]. However, it is impossible to perform PSG on all the patients with suspicion of RBD because the examination is time- and labor-consuming. Hence, an appropriate questionnaire for RBD screening in clinical settings is warranted.

Stiasny-Kolster et al. created the RBD screening questionnaire (RBDSQ) as a diagnostic instrument and have already validated its diagnostic accuracy [4]. The Japanese version of RBDSQ was also validated (RBDSQ-J), targeting idiopathic RBD [5]. These two studies agreed that a total score of 5 points on the RBDSQ represented a cut-off value for the screening of idiopathic RBD with the highest sensitivity and specificity. However, the usefulness of the RBDSQ for screening secondary RBD in PD patients, in whom non-violent dream enactment behaviors based on the existence of RWA (non-violent RBD symptoms) are relatively common [6], has not been evaluated. Therefore, in this study we explored the effectiveness of RBDSQ as a screening tool for secondary RBD among PD patients.

2. Subjects and methods

The ethics committees of Tottori University approved this study. Forty-five consecutive PD patients hospitalized at the University Hospital of Tottori University, Division of Neurology gave informed consent to participate in the study (mean age: 72.9 ± 9.1 years old, 22 male and 23 female, length of PD morbidity: 8.6 ± 7.2 years, Hohen and Yahr grade: 2.8 ± 0.9). For comparison, 31 age- and gender-matched idiopathic RBD patients who had received the diagnosis based on both PSG findings and the results of clinical interviews at the Japan Somnology Center were included in the study (mean age: 67.8 ± 6.5 years old, 22 male and 9 female). Overnight PSG recordings were performed by standardized methods [7], and RWA was defined according to the scoring manual of the American Sleep Disorders Association [8].

* Corresponding author. Address: Division of Neurology, Department of Brain and Neurological Sciences, Tottori University Faculty of Medicine, 36-1 Nishicho, Yonago 683-8504, Japan. Tel.: +81 859 38 6757; fax: +81 859 38 6759.
E-mail address: ntnomura@med.tottori-u.ac.jp (T. Nomura).

1389-9457/$ - see front matter
doi:10.1016/j.sleep.2011.01.015

All the patients and their bed partners were asked to complete the RBDSQ-J and were then systematically interviewed regarding sleep problems (with an emphasis on dream enactment behavior or vocalization while dreaming) by sleep disorder expert physicians who were blind to the RBDSQ-J results. The diagnosis of RBD was made according to criteria from the ICSD second [3]. Next, we categorized the PD patients into PD groups with RBD and those without RBD (including the patients with normal REM sleep and those with RWA but clearly not having RBD symptoms). We compared the scores of RBDSQ-J sub-items between PD patients with violent RBD versus those with non-violent RBD. In addition, we compared the positivity rate of RBDSQ-J sub-item scores between all PD patients having RBD symptoms and iRBD patients to determine differences in the distribution of positive scores on each sub-item between these two groups.

Internal consistency of the RBDSQ-J was estimated using Cronbach's α coefficient. The criterion value was $\geqslant 0.70$ for item homogeneity. Moreover, sensitivity and specificity for different cut-off points for total RBDSQ-J score for the screening of RBD among the PD patients were both calculated and presented by means of a receiver-operator characteristics curve (ROC) function. The diagnostic value of the RBDSQ-J was calculated by using the area under the curve (AUC), which was independent of an arbitrary choice of a cut-off point, and statistical significance was tested using the Mann–Whitney U test.

3. Results

According to the above-indicated criteria, the PD patients were divided into 19 patients with RBD (42%, violent RBD: $n = 13$, non-violent RBD: $n = 6$) and 26 patients without RBD (58%). But all the iRBD patients had clear violent RBD symptoms. The mean total RBDSQ-J scores were 7.2 ± 1.9 in the PD group with RBD (range: 3–11), 2.9 ± 1.6 in the group without RBD (range: 1–7), and 7.9 ± 2.8 in the iRBD group (range: 2–12). There was a significant difference in the total RBDSQ-J scores among the three groups as revealed by an analysis of variance [$F_2 = 37.28$, $p < 0.001$], and a *post hoc* Bonferroni correction determined that the PD group with RBD and the iRBD group had significantly higher values compared to the PD group without RBD. However, there were no significant differences in the total RBDSQ-J scores between the former two groups (Fig. 1).

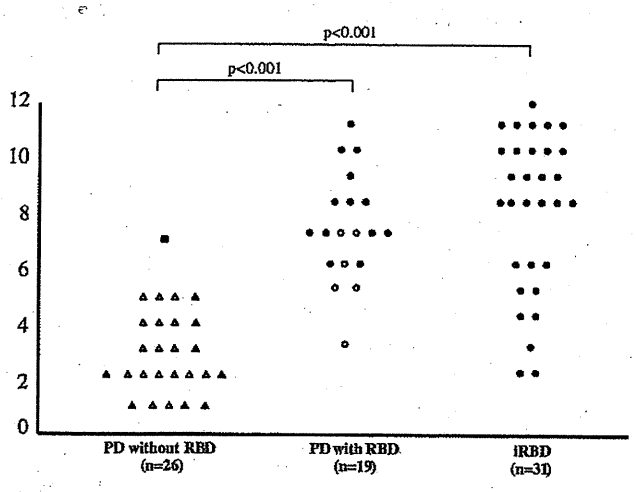

Fig. 1. Comparison of RBDSQ-J scores among the three groups. symbols indicate individual RBDSQ-J scores for each patient among the subject groups (PD without RBD, PD with RBD, iRBD). ●, Violent RBD symptoms; ○, non-violent RBD symptoms; ■, non-violent symptoms without RWA; ▲, RWA with no RBD symptoms; △, neither RWA nor RBD symptoms.

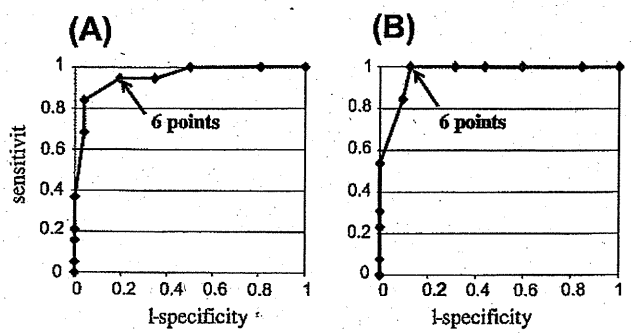

Fig. 2. Receiver-operator characteristics (ROC) curves of PD patients. Curves show distributions of sensitivity and specificity for the existence of any RBD symptom (A) and violent RBD symptoms only (B). The cut-off value of RBDSQ-J scores for the existence of any RBD symptoms in PD patients was 6 points, with a sensitivity of 0.842 and a specificity of 0.962. The AUC was 0.953. The likelihood ratios of positive and negative results were 21.872 and 0.164, respectively (A). When the target was restricted to cases with violent RBD symptoms, the cut-off value was again 6 points with a sensitivity of 1.000 and a specificity of 0.875. The AUC was 0.969 in this case, and the likelihood ratios of positive and negative results were 8.000 and 0.875, respectively (B).

The thirteen items of the RBDSQ-J had an overall reliability coefficient (Cronbach's α) of 0.73, indicating a high degree of internal consistency. Each of the thirteen items of RBDSQ-J was judged to measure a particular aspect of the same overall construct.

We compared the positivity rate of each RBDSQ-J item score between PD patients with RBD and iRBD patients using a χ^2-test. iRBD patients had significantly higher positivity rates for item 5 (they hurt their bed partner or themselves; PD with RBD: 1/19, iRBD: 15/31, $p = 0.006$) and lower positivity rates for item 10 (they have/had a disease of the nervous system; PD with RBD: 19/19, iRBD: 5/31, $p < 0.001$) versus PD patients with RBD. However, there were no significant differences in the rates of positivity for the other items between the two groups. After item 10 was removed, there was also a significant difference in the total RBDSQ-J score between the two groups (PD with RBD: 6.2 ± 1.9, iRBD: 7.7 ± 2.7, $p = 0.025$).

The mean total RBDSQ-J scores in 13 PD patients with violent RBD were significantly higher than that in 6 PD patients with non-violent RBD symptoms (8.0 ± 1.6 vs. 5.5 ± 1.5, Mann–Whitney U test $p = 0.007$). Moreover, there were significant differences in the positivity rates between these two groups for items 6.2 (they have/had sudden limb movements, "fights" during their dreams; violent RBD: 9/13, non-violent RBD: 0/6, $p = 0.005$), 6.3 (they have/had displayed gestures and complex movements during their dreams; violent RBD: 9/13, non-violent RBD: 1/6, $p = 0.033$), 6.4 (they fell down somewhere around the bed during their dreams; violent RBD: 6/13, non-violent RBD: 0/6, $p = 0.044$), and 7 (their movements awaken themselves; violent RBD: 10/13, non-violent RBD: 0/6, $p = 0.002$).

ROC curve analyses revealed that a total score of 6 points on the RBDSQ represented the best cut-off value for detecting any RBD symptoms (sensitivity of 0.842 and specificity of 0.962) and for detecting violent RBD symptoms (sensitivity of 1.000 and specificity of 0.875) (Fig. 2). Three PD cases with non-violent RBD symptoms showed a false negativity as judged from this cut-off value. However, all of them had a positive score on item 6.1 (they have or had symptoms of speaking, shouting, swearing, or laughing loudly during dreams).

4. Discussion

From our results, the mean total RBDSQ score in the iRBD group was 7.9 ± 2.8 points, which is similar to the values reported by

Miyamoto et al. (7.5 ± 2.8 points) [5], indicating a good score reproducibility between two different cohorts of Japanese iRBD patients.

The present study also showed that RBDSQ had a fair internal consistency even in PD patients, suggesting a proper validity for the screening of RBD in this population. Of note, 6 points was revealed to be the best cut-off value for the screening of RBD in this population. This cut-off value for RBD secondary to PD was approximately 1 point higher than that reported for iRBD in previous studies [4,5]. However, the cut-off value of RBDSQ in this patient population would become equal to the above-indicated value of iRBD patients if item 10 were removed.

Our results demonstrated that PD patients with violent RBD symptoms had higher total RBDSQ scores compared to those with non-violent RBD symptoms. The difference in the positivity rate in some items between total PD patients having RBD and iRBD patients could reflect the phenomenon that approximately 30% of the former group had only non-violent RBD symptoms. In addition, patients with iRBD had higher RBDSQ scores compared to PD patients with RBD after item 10 was removed. These findings suggest that PD patients had milder RBD symptoms compared with iRBD patients. However, the cut-off value for RBD positivity was the same between the analyses after including or not including the patients with non-violent symptoms. Considering that the sensitivity and specificity of RBDSQ-J for the screening of RBD in our PD patients was similar to the results obtained by Miyamoto et al., RBDSQ may be useful for detecting RBD among PD populations regardless of the RBD symptom content. In addition, positivity on item 6.1 might represent a key criterion for analyzing populations with non-violent RBD.

In our study, the main limitation was that we could not investigate the test–retest reliability of RBDSQ-J among the study population.

In conclusion, the RBDSQ could be useful for the screening of RBD among PD populations. Reportedly, the existence of RBD in PD patients is associated with the development of dementia and/or autonomic failure [9,10]. We want to emphasize that the use of RBDSQ should be promoted in PD clinics for detecting RBD symptoms and could thereby facilitate the prediction of clinical courses of PD patients.

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: doi:10.1016/j.sleep.2011.01.015.

References

[1] Schenck CH, Bundlie SR, Ettinger MG, Mahowald MW. Chronic behavioral disorders of human REM sleep: a new category of parasomnia. Sleep 1986;9:293–308.
[2] Chaudhuri KR, Naidu Y. Early Parkinson's disease and non-motor issues. J Neurol 2008;255:S33–8.
[3] American Academy of Sleep Medicine. International classification of sleep disorders: diagnostic and coding manual, 2nd ed. Westchester; 2005. p. 148–52.
[4] Stiasny-Kolster K, Mayer G, Schafer S, Moller JC, Heinzel-Gutenbrunner M, Oertel WH. The REM sleep behavior disorder screening questionnaire – A new diagnostic instrument. Mov Disord 2007;22:2386–93.
[5] Miyamoto T, Miyamoto M, Iwanami M, Kobayashi M, Nakamura M, Inoue Y, et al. The REM sleep behavior disorder screening questionnaire: validation study of a Japanese version. Sleep Med 2009;10:1151–4.
[6] Oudiette M, de Cock VC, Lavault S, Leu S, Vidaihet M, Arnulf I. Nonviolent elaborate behavior may also occur in REM sleep behavior disorder. Neurology 2009;72:551–7.
[7] Uemura Y, Nomura T, Inoue Y, Yamawaki M, Yasui K, Nakashima K. Validation of the Parkinson's disease sleep scale in Japanese patients: a comparison study using the Pittsburgh sleep quality index, the epworth sleepiness scale and polysomnography. J Neurol Sci 2009;287:36–40.
[8] American Sleep Disorders Association. Manuals of the scoring of sleep and associated events. Rules, technology, and technical specifications 2007. p. 42–3.
[9] Gagnon JF, Vendette M, Postuma RB, Desjardins C, Massicotte-Marquez J, Panisset M, et al. Mild cognitive impairment in rapid eye movement sleep behavior disorder and Parkinson's disease. Ann Neurol 2009;66:39–47.
[10] Postuma RB, Gagnon JF, Vendette M, Charland K, Montplaisir J. Manifestations of Parkinson's disease differ in association with REM sleep behavior disorder. Mov Disord 2008;23:1665–72.

Psychiatry and Clinical Neurosciences 2011; 65: 264–271 doi:10.1111/j.1440-1819.2011.02201.x

Regular Article

Comparison of the clinical features of rapid eye movement sleep behavior disorder in patients with Parkinson's disease and multiple system atrophy

Takashi Nomura, MD, PhD,[1]* Yuichi Inoue, MD, PhD,[2,3,4] Birgit Högl, MD,[5] Yusuke Uemura, MD,[1] Kenichi Yasui, MD, PhD,[1] Taeko Sasai, PhD,[4] Kazuyoshi Namba, PhD[4] and Kenji Nakashima, MD, PhD[1]

[1]*Division of Neurology, Department of Brain and Neurosciences, Faculty of Medicine, Tottori University, Yonago, Departments of* [2]*Psychiatry and* [3]*Somnology, Tokyo Medical University, and* [4]*Japan Somnology Center, Neuropsychiatric Research Institute, Tokyo, Japan, and* [5]*Department of Neurology, Innsbruck Medical University, Innsbruck, Austria*

Aims: The aim of this study was to evaluate differences in the clinical presentation and polysomnographic characteristics of rapid eye movement sleep behavior disorder (RBD) between patients with Parkinson's disease (PD) and those with multiple system atrophy (MSA).

Methods: We conducted clinical interviews examining RBD symptoms, including violent and non-violent behaviors, in 49 patients with PD and 16 patients with MSA (as well as their bed partners) and performed polysomnography on all subject patients.

Results: Twenty-seven patients with PD (55.1%) and 11 patients with MSA (68.8%) had rapid eye movement sleep without atonia (RWA) on polysomnogram. The relative amounts of RWA were quite similar between the two groups. For most of the RWA-positive patients in both groups, RBD symptoms remained non-violent or silent. RBD symptoms in PD patients seemed to increase with the course of PD, while most of the RBD symptoms in the MSA patients occurred just prior to or at the onset of MSA and then disappeared within a short period.

Conclusion: Although PD and MSA frequently accompany RWA, RBD symptoms often remain non-violent or silent. Differences in the course of RBD symptoms in patients with PD and MSA may reflect the difference in the degeneration process of the two disorders.

Key words: multiple system atrophy, Parkinson's disease, polysomnography, rapid eye movement sleep behavior disorder, retrospective study.

RAPID EYE MOVEMENT (REM) sleep behavior disorder (RBD) is characterized by vigorous and injurious behaviors related to vivid, action-filled, and violent dreams during nocturnal REM sleep and REM sleep without atonia (RWA).[1] Diagnosis and treatment of this disorder is one of the most important issues in the field of sleep psychiatry. According to the second edition of the International Classification of Sleep Disorders (ICSD), a clinical diagnosis of RBD can only be made when a patient displays violent, potentially violent or sleep-disruptive dream-enactment behavior along with RWA, as determined by a polysomnogram (PSG).[2]

RBD has been reported to occur in alpha-synucleinopathies, including Parkinson's disease (PD)[3] and multiple system atrophy (MSA).[4] The brainstem regions responsible for the occurrence of RBD are also known to be involved in the primary pathology of both PD and MSA.[5] Longitudinal

*Correspondence: Takashi Nomura, MD, PhD, Division of Neurology, Department of Brain and Neurosciences, Faculty of Medicine, Tottori University, 36-1 Nishicho, Yonago 683-8504, Japan.
Email: ntnomura@med.tottori-u.ac.jp
Received 11 August 2010; revised 15 December 2010; accepted 21 January 2011.

studies have shown that 17.7–65% of patients with RBD develop PD over a period of 5–20 years.[6–9] For MSA, 69–100% of patients have also been reported to have RBD symptoms, which especially occur before onset of the disorder.[4,10–12] These data strongly suggest that RBD symptoms may precede PD and MSA.[8,9] Moreover, both PD and MSA frequently complicate RBD symptoms after the onset of these disorders.[11,12] However, courses and symptomatic characteristics of RBD in patients with PD and MSA have not been elucidated, although such information could provide important clues for understanding the correlations between RBD and alpha-synucleinopathies. Such knowledge could also be helpful for physicians in preparing a treatment plan for RBD symptoms in patients with PD and MSA. In order to help clarify these issues, we investigated the clinical features, PSG findings, and courses of RBD symptoms in patients with PD and MSA.

METHODS

This study was approved by the ethics committees of Tottori University, and informed consent was obtained from all of the subjects taking part in the study. Consecutive patients with PD and MSA who were hospitalized at the Department of Neurology of Tottori University from July 2004 to May 2008 were targeted. Patients taking sedative drugs and/or antidepressants, or those with no bed partners were excluded. Forty-nine patients with PD (mean age 70.3 ± 11.2 years, 21 male and 28 female) and 16 patients with MSA (60.2 ± 6.9 years, eight male and eight female) were examined. PD patients were diagnosed according to the standard criteria for the diagnosis of PD.[13] The PD patients had all been receiving oral dopaminergic agents for 6.8 ± 6.4 years, and their levodopa dose equivalent[14] was 347 ± 203 mg/day. The mean Hoehn and Yahr stage for the patients was 2.7 ± 0.9. Fifteen of the 49 PD patients reported having visual hallucinations that occurred mainly during the nocturnal period. MSA patients were diagnosed according to the standard criteria for the diagnosis of MSA.[15] The 16 MSA subjects consisted of 12 patients with MSA-C which was defined as predominant cerebellar symptoms and four with MSA-P which was defined as predominant parkinsonism symptoms.[16] The mean duration of MSA morbidity was 4.7 ± 2.4 years. Twelve of the MSA patients were treated with thyrotropin-releasing hormone (TRH) analogues, and six were taking 85.6 ± 140.0 mg/day levodopa dose equivalent of dopaminergic agents. None of the patients with MSA reported having hallucinations.

Overnight PSG recordings were performed on all the patients and included the following: electroencephalography (EEG) with four-channel scalp EEG montages (C3, C4, O1, and O2 referred to the contralateral ear), electrooculography, electromyography (EMG) (submental, left lower limb and right lower limb), oronasal airflow monitoring using thermistors, measurements of thoracic and abdominal respiratory movements with a strain gauge, transcutaneous oxygen saturation, and electrocardiography. Sleep stages were scored according to the established criteria of Rechtschaffen and Kales.[17] During REM sleep, the presence of submental phasic EMG activity (3-s mini-epochs containing phasic twitches exceeding 4 times the background EMG activity) or submental tonic EMG activity (more than half of a 30-s epoch of duration) was used to determine the stage of RWA.[18] Periodic limb movements in sleep (PLMS) were scored following the new standards for recording and scoring periodic limb movement,[19] and the PLMS index (PLMI) was calculated. Abnormal breathing events during sleep were defined as apnea or hypopnea,[20] and the apnea–hypopnea index (AHI) was estimated.[21] Arousals were scored visually according to standard criteria.[22]

Within 1 month prior to the PSG recordings, patients and their bed partners were retrospectively interviewed by a physician specializing in sleep disorders. The interviews focused especially on dream enactment behavior or vocalization while dreaming. Patients were diagnosed as having violent RBD if they exhibited RWA on PSG and reports of dream enactment-related problematic behaviors from interviews according to criteria from the second edition of the ICSD.[2] If patients had RWA and talked aloud in their sleep while dreaming but did not display violent behavior, they were defined as having non-violent RBD according to the criteria created by Oudiette *et al.*[23] Four patients with PD (PD4, 6, 11 and 18) and one patient with MSA (MSA9) took clonazepam at the time of investigation without aiming to treat RBD, except for PD6, who suffered from severe RBD symptoms. However, none of these patients reported that their RBD symptoms improved after starting clonazepam treatment.

We compared the PSG findings and the history of violent and non-violent RBD between patients with PD and MSA. Thereafter, we calculated both the

cross-sectional prevalence and the lifetime prevalence of RBD (including both violent and non-violent RBD symptoms) at the time of investigation in the PD and MSA groups. Regarding lifetime prevalence, the number of patients with experiences related to each RBD symptom category (regardless of presence/absence of symptoms at the time of investigation) was calculated as a percentage of total patients in both groups.

A χ^2-test followed by rest error test was used to compare categorical variables. Comparisons of continuous variables between the two groups were made using the Mann–Whitney *U*-test. A comparison of the amount of RWA in patients with violent RBD, non-violent RBD, and no RBD symptoms between the two patient groups was examined using the Kruskal–Wallis test. Data are presented as the mean ± SD unless otherwise indicated. Statistical significance was defined as $P < 0.05$ (SPSS, ver. 11.5J, SPSS Japan, 2002).

RESULTS

PSG findings

Twenty-seven patients (55.1%) in the PD group and 11 patients (68.8%) in the MSA group had RWA on PSG at the time of the investigation. The rate of RWA was not different between the two patient groups. However, the amount of RWA relative to total sleep time in the MSA group was greater than that observed in the PD group. PLMI scores in the MSA group were also significantly higher than those from the PD group. The proportion of MSA patients with a PLMI of 15 or more was also higher compared to PD patients. There were no significant differences in the other parameters between the two groups (Table 1).

Proportion of patients with RBD symptoms and course of symptoms in PD and MSA patients

PD

In 27 PD patients with RWA, seven patients (25.9%) had violent RBD symptoms, 10 patients (37.0%) had non-violent RBD symptoms, and 10 patients (37.0%) reported no RBD symptoms at the time of the investigation. From these findings, we estimated the frequency of patients with violent RBD as 14.3% (7/49) for the PD patients. When non-violent RBD symptoms were included, the prevalence of RBD symptoms increased to 34.7% (17/49). In 22 PD patients without RWA, a false positivity of RBD was recognized in two patients who had experienced non-violent RBD-like symptoms once before the onset of PD.

Regarding sex distribution, PD patients with violent RBD symptoms included three men and four women, while patients with non-violent RBD symptoms included three men and seven women. Thus, there was no difference in sex distribution between the patients with violent RBD symptoms and those with non-violent RBD symptoms (χ^2-test *t*, $P = 0.642$).

There was no difference in the proportion of RWA to total sleep time among the PD patients with violent RBD (1.39 ± 1.20%), non-violent RBD (1.08 ± 1.08%), or those without RBD symptoms

Table 1. Comparison of polysomnography findings between PD and MSA

	PD ($n = 49$)	MSA ($n = 16$)	Significance
Total sleep time (min)	296 ± 86	252 ± 89	0.163
REM sleep/total sleep time (%)	8.5 ± 6.4	8.1 ± 4.2	0.629
RWA/total sleep time (%)	0.6 ± 1.0	1.1 ± 2.9	0.042
Proportion of patients with RWA (%)	55.1	68.8	0.319
AHI (/h)	13.1 ± 14.4	22.5 ± 24.8	0.378
PLMI (/h)	10.0 ± 25.9	68.2 ± 105.4	0.005
Proportion of patients with 15/h or more PLMS (%)	16.3	39.1	0.001

Values are expressed as mean ± SD or percentage.
PD, Parkinson's disease; MSA, multiple system atrophy; REM, rapid eye movement; RWA, rapid eye movement sleep without atonia; AHI, apnea–hypopnea index; PLMI, periodic leg movements index; PLMS, periodic limb movements in sleep.

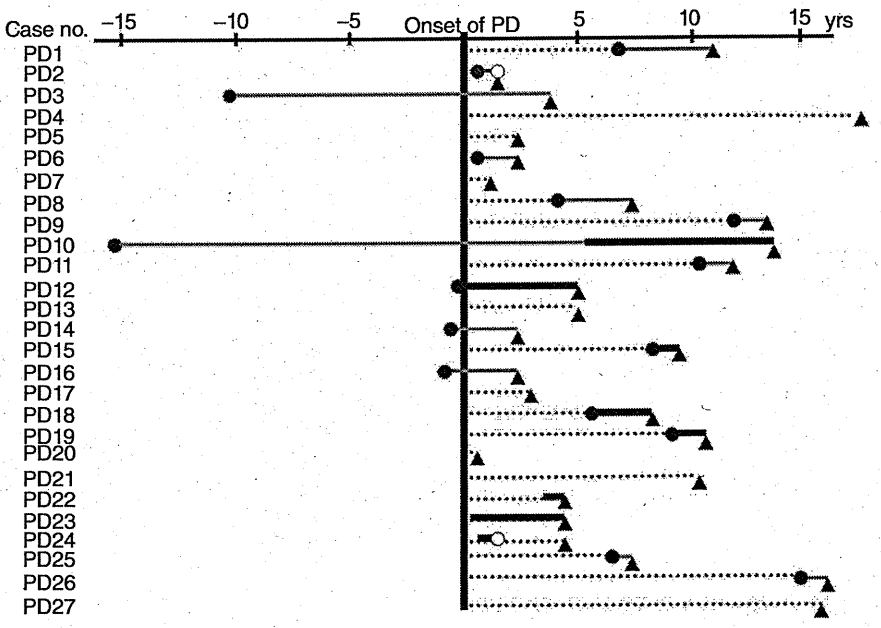

Figure 1. Self-reported onset and course of rapid eye movement (REM) sleep behavior disorder (RBD) symptoms in Parkinson's disease (PD) patients with REM sleep without atonia on polysomnogram ($n = 27$). Dotted lines (·····) indicate symptom-free periods for RBD. Thick black lines (▬) indicate periods of violent RBD symptoms. Grey lines (——) indicate periods of non-violent RBD symptoms. Filled circles (●) indicate onset of RBD symptoms, and open circles (○) indicate disappearance of symptoms. Black triangles (▲) indicate the time period of investigation, including interviews and polysomnography.

(1.26 ± 1.21%) ($P = 0.932$), despite the ratio of RWA to total sleep time being higher in the patients with violent RBD than in those with non-violent RBD.

Five of the 27 PD patients with RWA (18.5%) reported having RBD symptoms before the onset of motor symptoms (PD3, 10, 12, 14, 16) (Fig. 1). In one case (PD10), symptoms of possible non-violent RBD began occurring 15 years prior to the onset of motor symptoms, and the patient developed violent RBD about 5 years after the onset. However, all other patients with non-violent symptoms did not experience a progression to more violent symptoms.

As shown in Figure 1, the number of patients with RBD symptoms seemed to increase along with prolongation of PD morbidity. Natural disappearance of symptoms was not reported for this group except for the two patients (PD2, 24) whose violent RBD symptoms disappeared within 1 year after the onset of PD. Thus, the lifetime prevalence of violent RBD was estimated at 18.4% (9/49), that of non-violent RBD at 20.4% (10/49), and that of total RBD symptoms at 38.8% (19/49) in this patient population.

There was a significant difference in the number of patients experiencing visual hallucinations between the groups with and without RBD symptoms (10/17 vs 5/32, $P = 0.002$). Ten out of 15 PD patients who were having hallucinations (66.7%) developed clear symptoms after the appearance of RBD symptoms. In addition, in the two cases mentioned above (PD2, 24), nocturnal visual hallucinations disappeared almost simultaneously with the disappearance of RBD symptoms.

MSA

Among 11 MSA patients with RWA, one patient (9.1%) had violent RBD symptoms and three patients (27.3%) had non-violent RBD symptoms at the time of the investigation. Thus, the cross-sectional prevalence of patients with violent RBD in the MSA patients at the time of the investigation was 6.3% (1/16). When non-violent RBD symptoms were included, the prevalence of RBD symptoms increased to 25.0% (4/16). Among five patients without RWA, a false positivity of RBD was recognized in three patients (two cases reported having violent RBD-like symptoms and one reported having non-violent RBD-like symptoms).

Among the MSA patients with RWA there was no difference in the proportion of RWA to total sleep for those with violent RBD (0.4%), non-violent RBD (4.0 ± 5.0%), and no RBD symptoms (4.5 ± 3.92%) ($P = 0.231$).

Seven out of 11 MSA patients with RWA (MSA2, 4, 5, 6, 7, 8, 10) clearly reported the development of RBD symptoms before the onset of MSA, but only one patient (MSA9) experienced symptoms after the onset of the disorder (Fig. 2). In four of the eight

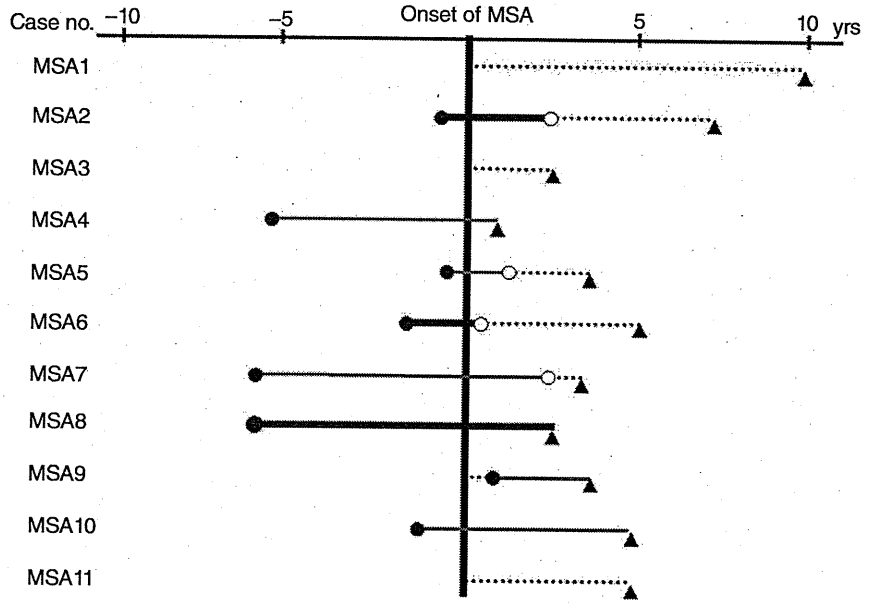

Figure 2. Self-reported onset and course of rapid eye movement (REM) sleep behavior disorder (RBD) symptoms in multiple system atrophy (MSA) patients with REM sleep without atonia on polysomnogram ($n = 11$). Dotted lines (.....) indicate symptom-free periods for RBD. Thick black lines (▬) indicate periods of violent RBD symptoms. Grey lines (——) indicate periods of non-violent RBD symptoms. Filled circles (●) indicate onset of RBD symptoms, and open circles (○) indicate disappearance of symptoms. Black triangles (▲) indicate the time period of investigation, including interviews and polysomnography.

patients with experiences of RBD symptoms (MSA2, 5, 6, 7), the symptoms disappeared within 3 years after the onset of MSA, while symptoms were still present in the other four patients (MSA4, 8, 9, 10) at the time of the investigation. The lifetime prevalence for violent RBD symptoms was estimated at 18.8% (3/16), that of non-violent RBD at 31.3% (5/16), and that of total RBD symptoms at 50.0% (8/16) in this MSA patient population.

Regarding sex, the one MSA patient who had violent RBD symptoms at the time of the survey was male, while the three MSA patients having non-violent RBD symptoms were female. Regarding the lifetime prevalence of RBD symptoms, MSA patients with a history of violent symptoms included two men and one woman, and MSA patients with non-violent RBD symptoms also included two men and three women.

Comparison between PD and MSA (Table 2)

Five PD patients (10.2%) and seven MSA patients (43.8%) with RWA experienced RBD symptoms before the onset of motor symptoms. On the other hand, 14 PD patients (28.6%) and only one MSA patient (6.3%) reported having RBD symptoms after the onset of motor symptoms. Eight patients with PD (16.3%) and three patients with MSA (18.7%) reported no experience of RBD symptoms in their clinical histories despite the clear existence of RWA on PSG. Twenty-two patients with PD (44.9%) and five patients with MSA (31.3%) had no RWA. The distribution of patients divided by both the existence of RWA and the period of appearance of RBD symptoms for these two groups were significantly different ($P = 0.014$). The rest error test revealed that the MSA group had a larger number of patients with RBD symptoms that appeared before the onset of motor symptoms compared with the PD group.

Table 2. Correlations between occurrence of RBD-related symptoms and motor symptoms, and existence of RWA

	PD ($n = 49$)	MSA ($n = 16$)
Patients with RWA who showed RBD-related symptoms before the onset of motor symptoms	5 (10.2)	7 (43.8)*
Patients with RWA who showed RBD-related symptoms after the onset of motor symptoms	14 (28.6)	1 (6.3)
Patients with clinically silent RWA	8 (16.3)	3 (18.7)
Patients without RWA	22 (44.9)	5 (31.3)

Parentheses indicate percentage. Fisher's exact test, $P = 0.014$.
*Significant difference by the residual error test.
PD, Parkinson's disease; MSA, multiple system atrophy; RBD, rapid eye movement sleep behavior disorder; RWA, rapid eye movement sleep without atonia.

DISCUSSION

Our results showed that both PD and MSA patients frequently show RWA on PSG, which is consistent with results from previous studies.[10,24,25] However, in this study, the calculated lifetime prevalence of violent RBD symptoms was 18.4% in the PD group and 18.8% in the MSA group, both of which were remarkably lower than rates previously reported.[4,7,10,11] The reason for this phenomenon is unclear. However, considering that the higher prevalence of RBD reported in previous studies (especially in PD patients) was diagnosed after relatively long periods of the disorder, the short PD morbidity length in our subject population might contribute to the observed lower prevalence rate of RBD. In addition, an unexpectedly high number of patients with PD and MSA reported experiencing non-violent RBD symptoms. After combining patients with violent RBD and those with non-violent RBD, the prevalence of RBD seems to not be so low relative to previous reports.

A study by Iranzo *et al.* showed that subjects with MSA or PD had a lower severity of RBD than those with idiopathic RBD.[24] Frauscher *et al.* also reported that RBD patients with parkinsonian symptoms show few motor events and violent episodes on PSG.[26] Taking these reports and our present results together, it is possible that RBD symptoms in a significant number of PD and MSA patients remain mild. However, a future follow-up study will determine whether non-violent RBD symptoms in our subject patients progress to violent RBD symptoms.

Interestingly, in our study there was no difference in the rate of RWA among patients with violent RBD, patients with non-violent RBD, and those without RBD symptoms in either MSA or PD patients. This result might indicate that RBD pathology remains mild or clinically silent in MSA and PD regardless of the amount of RWA. Thus, it could be possible that the existence of RWA is necessary, but hardly sufficient, for the appearance of clinical RBD.

Generally, patients with idiopathic RBD are predominantly male.[1,2] However, the patients with MSA and PD having RBD in this study did not show a male predominance. This finding is consistent with previous reports on PD patients with RBD.[27,28] Taking this into account, there may exist differential gender distribution characteristics between idiopathic RBD and secondary RBD complicated with α-synucleinopathies.

Some studies have indicated that many patients with idiopathic RBD develop α-synucleinopathies.[8] This concept corroborates the proposed staging for the neuropathological process of PD outlined by Braak *et al.*[29] However, a majority of our PD patients reported having RBD symptoms after the onset of motor symptoms, and only less than 20% of them reported that their RBD symptoms occurred prior to the onset of motor symptoms. The reason for this phenomenon is unclear. However, it might be possible that PD patients who develop from 'idiopathic RBD' constitute only a small percentage of the total PD population.

In the PD group, the number of patients with nocturnal visual hallucinations was significantly larger in those with RBD symptoms than in those without. Interestingly, some cases showed the disappearance of violent RBD symptoms in conjunction with the disappearance of visual hallucinations. Although a causal correlation between RBD and hallucinations remains controversial,[27] these findings corroborate our previous report[30] as well as reports by Arnulf *et al.*[31] and Sinforiani *et al.*[28] suggesting that there is a pathophysiological correlation between visual hallucination and RBD in PD patients.

Patients with MSA had a significantly higher rate of RWA as well as higher PLMI scores than those with PD. This finding is consistent with the result reported by Iranzo *et al.*[24] However, it is noteworthy that RBD symptoms in this patient group displayed a limited appearance in the period shortly before the onset of other neurological symptoms, but mostly disappeared within a few years after the onset of neurological symptoms. The neurodegeneration of MSA is known to spread more rapidly and widely compared with PD.[5] Considering this characteristic, it is possible that RBD symptoms in MSA patients could disappear upon worsening of their neurological condition due to progressive degeneration of the neuronal structures in the brain stem responsible for the occurrence of RBD. In addition, severe motor symptoms in patients with advanced MSA might mask RBD symptoms. We found that the number of MSA patients with RBD symptoms did not increase with the course of the disease. This finding could be in line with a previous report in which RBD episodes of MSA patients diminished along with the occurrence of status dissociatus over the course of the disease.[32] Thus, we speculate that RBD symptoms in patients with MSA are likely to disappear with aggravation of MSA.

With respect to PD, Lavault *et al.* reported the fluctuation and disappearance of RBD symptoms in some patients with the disorder.[27] However, considering the report by Gjerstadt *et al.* in which the frequency of RBD in PD increased over 8 years of follow-up investigation,[33] a longer-term follow up might be necessary to evaluate changes in RBD status throughout the disease course of PD.

The present study has several limitations. First, especially with regard to MSA, our study was conducted on only a small number of patients, which might have led to a sampling bias. Second, we could not use video PSG and this methodological inadequacy might have led to some misidentification of RBD symptoms.

Our study could not yield compelling evidence that the synuclein pathology described in Braak Stage 2 provides a neural substrate for RBD.[34] However, patients with both MSA and PD frequently have RWA on PSG even though RBD symptoms remain mild or silent in a majority of these patients. The course of RBD symptoms can differ between PD and MSA, possibly reflecting neuropathological differences and severity of motor symptoms. Future studies, including interviews and polysomnographic evaluations of patients with MSA and PD, will be necessary to draw better conclusions regarding these issues.

ACKNOWLEDGMENTS

This work was supported in part by the Research Committee for Ataxic Diseases, the Ministry of Health and Welfare, Japan.

REFERENCES

1. Schenck CH, Bundlie SR, Patterson AL, Mahowald MW. Rapid eye movement sleep behavior disorder. A treatable parasomnia affecting older adults. *JAMA* 1987; **257**: 1786–1789.
2. American Academy of Sleep Medicine. REM sleep behavior disorder. In: *International Classification of Sleep Disorders: Diagnostic and Coding Manual*, 2nd edn. American Academy of Sleep Medicine, Westchester, 2005; 148–152.
3. Comella CL, Nardine TM, Diederich NJ, Stebbins GT. Sleep-related violence, injury, and REM sleep behavior disorder in Parkinson's disease. *Neurology*. 1998; **51**: 526–529.
4. Plazzi G, Corsini R, Provini F *et al.* REM sleep behavior disorders in multiple system atrophy. *Neurology* 1997; **48**: 1094–1097.
5. Benarroch EE. Brainstem in multiple system atrophy: Clinicopathological correlations. *Cell Mol. Neurobiol.* 2003; **23**: 519–526.
6. Schenck CH, Bundlie SR, Mahowald MW. Delayed emergence of a parkinsonian disorder in 38% of 29 older men initially diagnosed with idiopathic rapid eye movement sleep behaviour disorder. *Neurology* 1996; **46**: 388–393.
7. Schenck C, Bundlie SR, Mahowald MW. REM behavior disorder (RBD): Delayed emergence of parkinsonism and/or dementia in 65% of older men initially diagnosed with idiopathic RBD, and an analysis of the minimum & maximum tonic and/or phasic electromyographic abnormalities found during REM sleep. *Sleep* 2003; **26**: A316.
8. Postuma RB, Gagnon JF, Vendette MV *et al.* Qualifying the risk of neurodegenerative disease in idiopathic REM sleep behavior disorder. *Neurology* 2009; **72**: 1296–1300.
9. Iranzo A, Molinuevo JL, Santamaria J *et al.* Rapid-eye-movement sleep behaviour disorder as an early marker for a neurodegenerative disorder: A descriptive study. *Lancet Neurol.* 2006; **5**: 572–577.
10. Tachibana N, Kimura K, Kitajima K *et al.* REM sleep motor dysfunction in multiple system atrophy: With special emphasis on sleep talk as its early clinical manifestation. *J. Neurol. Neurosurg. Psychiatry* 1997; **63**: 678–681.
11. Vetrugno R, Provini F, Cortelli P *et al.* Sleep disorders in multiple system atrophy: A correlative video-polysomnographic study. *Sleep Med.* 2004; **5**: 21–30.
12. Iranzo A, Santamaria J, Tolosa E. The clinical and pathological relevance of REM sleep behavior disorder in neurodegenerative disease. *Sleep Med. Rev.* 2009; **13**: 385–401.
13. Daniel SE, Lees AJ. Parkinson's Disease Society Brain Bank, London: Overview and research. *J. Neural. Transm.* 1993; **39** (Suppl.): S165–S172.
14. Hobson DE, Lang AE, Martin WR *et al.* Excessive daytime sleepiness and sudden-onset sleep in Parkinson disease: A survey by the Canadian Movement Disorders Group. *JAMA* 2002; **287**: 455–463.
15. Gilman S, Low P, Quinn N *et al.* Consensus statement on the diagnosis of multiple system atrophy. American Autonomic Society and American Academy of Neurology. *Clin. Auton. Res.* 1998; **8**: 359–362.
16. Wenning GK, Ben Shlomo Y, Magalhaes M, Daniel SE, Quinn NP. Clinical features and natural history of multiple system atrophy. An analysis of 100 cases. *Brain* 1994; **117**: 835–845.
17. Rechtschaffen A, Kales A. *A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages in Human Subjects*. U.S. Government Printing Office, National Institute of Health Publication, Washington DC, 1968.
18. American Sleep Disorders Association. Manuals of the scoring of sleep and associated events. Rules, technology, and technical specifications, 2007; 42–43.

19. Zucconi M, Ferri R, Allen R *et al.* The official World Association of Sleep Medicine (WASM) standards for recording and scoring periodic leg movements in sleep (PLMS) and wakefulness (PLMW) developed in collaboration with a task force from the International Restless Legs Syndrome Study Group (IRLSSG). *Sleep Med.* 2006; **7**: 175–183.
20. Kryger MH. Monitoring respiratory and cardiac function. In: Kryger M, Roth T, Dement W (eds). *Principles and Practice of Sleep Medicine*, 3rd edn. W.B. Saunders, Philadelphia, 2000; 1217–1230.
21. The Report of an American Academy of Sleep Medicine Task Force. Sleep-related breathing disorders in adults: Recommendations for syndrome definition and measurement techniques in clinical research. *Sleep* 1999; **22**: 667–689.
22. American Sleep Disorders Association. EEG arousals: Scoring rules and examples: A preliminary report from the Sleep Disorders Atlas Task Force of the American Sleep Disorders Association. *Sleep* 1992; **15**: 173–184.
23. Oudiette D, De Cock VC, Lavault S *et al.* Nonviolent elaborate behavior may also occur in REM sleep behavior disorder. *Neurology* 2009; **72**: 551–557.
24. Iranzo A, Santamaria J, Rye DB *et al.* Characteristics of idiopathic REM sleep behavior disorder and that associated with MSA and PD. *Neurology* 2005; **65**: 247–252.
25. Gagnon JF, Bedard MA, Fantini ML *et al.* REM sleep behavior disorder and REM sleep without atonia in Parkinson's disease. *Neurology* 2002; **59**: 585–589.
26. Frauscher B, Gschliesser V, Brandauer E *et al.* Video analysis of motor events in REM sleep behavior disorder. *Mov. Disord.* 2007; **22**: 1464–1470.
27. Lavault S, Leu-Semenescu S, Tezenas du Montcel S *et al.* Does clinical rapid eye movement behavior disorder predict worse outcomes in Parkinson's disease? *J. Neurol.* 2010; **257**: 1154–1159.
28. Sinforiani E, Zangaglia R, Manni R *et al.* REM sleep behavior disorder, hallucinations, and cognitive impairment in Parkinson's disease. *Mov. Disord.* 2006; **21**: 462–466.
29. Braak H, Del Tredici K, Rüb U *et al.* Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol. Aging* 2003; **24**: 197–211.
30. Nomura T, Inoue Y, Mitani H *et al.* Visual hallucinations as REM sleep behavior disorders in patients with Parkinson's disease. *Mov. Disord.* 2003; **18**: 812–817.
31. Arnulf I, Bonnet AM, Damier P *et al.* Hallucinations, REM sleep, and Parkinson's disease: A medical hypothesis. *Neurology.* 2000; **55**: 281–288.
32. Vetrugno R, Alessandria M, D'Algelo R *et al.* Status dissociatus evolving from REM sleep behavior disorder in multiple system atrophy. *Sleep Med.* 2009; **10**: 247–252.
33. Gjerstadt MD, Boeve B, Wentzel-Larsen T, Aaraland D, Larsen JP. Occurrence and clinical correlates of REM sleep behavior disorder in patients with Parkinson's disease over time. *J. Neurol. Neurosurg. Psychiatry.* 2008; **79**: 387–391.
34. Burke RE, Dauer WT, Vonsattel JP. A critical evaluation of the Braak staging scheme for Parkinson's disease. *Ann. Neurol.* 2008; **64**: 485–491.