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Changes in the symptom frequency of rapid eye movement sleep behavior disorder according to disease duration

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Abstract

Background: This descriptive study was conducted to examine the changes in the symptom frequency in patients with rapid eye movement (REM) sleep behavior disorder (RBD) without medical intervention, in order to determine the association of RBD symptom frequency with disease duration.

Methods: Data were collected from 70 consecutive RBD patients who visited the Sleep Clinic in Shiga University of Medical Science. RBD symptom frequencies at the first visit to the clinic were quantified based on the reports by the patients and their family members. For quality assurance, patients living alone or those with cognitive decline were excluded. Finally, 50 patients with family-confirmed symptom history were enrolled. The symptom frequencies were converted to a unit that reflects the estimated number of nights in a year affected by RBD (NAR). Using NAR, we observed the relation between RBD symptom frequency and the disease duration.

Results: Of the 50 patients, 41 were male and 9 were female, consistent with the male-dominant nature of this disease. The mean age at RBD onset was 62.2 ± 9.1 years, and the mean disease duration at the time of visit was 6.0 ± 4.9 years. The median symptom frequency was 50 NAR, with a 1st quantile value of 24 NAR and a 3rd quantile value of 115 NAR. When RBD symptom frequency was plotted against disease duration, we found that the frequency was lowest in the first 2 years of RBD (median, 18; range, 2–29 NAR), and higher frequencies were found in 2-year bin groups from 2 to 8 years after RBD onset (median, 60; range, 50–150 NAR). Intriguingly, after 8 years of RBD, the frequency returned to a level comparable to that in the first 2 years of RBD (median, 50; range, 12–100 NAR).

Conclusions: There was no association between RBD symptom frequency and disease duration. RBD clinical symptoms could be less prominent when neural damage becomes severe. Therefore, a natural decrease in RBD symptom frequency may be indicative of progression of neurodegeneration.

Keywords: REM Sleep Behavior Disorder, Symptom frequency, Disease duration

Background

Rapid eye movement (REM) sleep behavior disorder (RBD) is a sleep-related disorder characterized by vocalization and violent enactment during REM sleep. Recently, this type of parasomnia has drawn attention because RBD is believed to share a common neuropathology with alpha-synucleinopathies, including Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple-system atrophy (MSA) (Boeve 2010; Gilman et al. 2008). Intriguingly, RBD symptoms typically appear before the onset of PD, DLB and MSA. Although the occurrence rates vary among reports, a recent study found that PD or DLB occurred in about 81% of RBD patients at a mean of 14.2 years after RBD onset (Schenck et al. 2013a).

Based on these findings, much effort has been put into assessing whether RBD could be used as a predictor of severe symptoms, such as deteriorated motor function and cognitive decline (Fujishiro et al. 2013). Recently, detection of preclinical phase of Alzheimer's disease is

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thought to be pivotal in reducing the disease-related burden. For example, an early intervention that extends well-being by 5 years is estimated to reduce the cost related to the disease by 50% (Sperling et al. 2011). Likewise, identifying the preclinical phase of PD/DLB/MSA may lead to significant reduction of the medical cost. Thus, an appropriate approach to assess precursor symptoms is essential to reduce social burden and improve patient quality of life.

Although RBD has been shown to be a prodromal symptom of PD/DLB/MSA (Mahowald & Schenck 2013), the method to quantify or assess RBD symptom severity has not been well studied. This is typically problematic in PD/DLB/MSA because the time relationship between RBD onset and PD/DLB/MSA onset varies considerably (Schenck et al. 2013a; Fujishiro et al. 2013). It is often clinically experienced that RBD symptoms disappear over the course of PD/DLB/MSA progression. In a study targeting early PD patients, it was reported that 15% of the subjects without concurrent RBD symptoms reported cessation of RBD symptoms prior to the study (Bugalho et al. 2011). Similar findings were reported for MSA, where 50% of the MSA patients with RBD symptoms reported disappearance of these symptoms (Nomura et al. 2011).

In order to determine the association of RBD symptom frequency with RBD duration, we semi-quantitatively examined RBD symptoms based on the frequency of dream-related enactments or vocalizations, and, using this method, we retrospectively examined the RBD symptom frequency at the time of clinic visit when no medical action was taken.

Materials and Methods

Participants

We retrospectively collected the medical records of RBD patients who visited Shiga University of Medical Science between June 1, 2008 and December 31, 2015. Patients who satisfied following inclusion criteria were included in this study: (a) having a diagnosis of RBD based on the 2nd edition of the International Classification of Sleep Disorders (ICSD-2) criteria, and (b) being able to report the onset time as well as frequency of RBD symptoms, which were consistent with those reported by their families. Because reporting of RBD symptom frequency was pivotal in this study, patients meeting the criteria for dementia, as defined in DSM-IV-TR, were excluded. Also, subjects were investigated for whether they satisfied the diagnostic criteria for PD (Hughes et al. 1992), DLB (McKeith et al. 2005), and MSA (Gilman et al. 2008). Patients who fulfilled all criteria for RBD were diagnosed as having definite RBD, and those who were not confirmed with RBD on video-polysomnography examination were diagnosed as having probable RBD (Boeve et al. 2007). All diagnoses were independently reviewed and confirmed by two trained physicians (YS and MM). RBD symptoms were confirmed using video recordings and concurrent respiratory monitor recordings to differentiate them from activities related to sleep apnea that has been reported to have symptoms resembling RBD symptoms (Iranzo & Santamaria 2005). All subjects were inquired about the current intake of antidepressants as they are known to cause RBD.

Symptom frequency

Patients were asked about the approximate year and month of RBD onset. Symptom frequencies were quantified as the approximate number of nights per year in which RBD symptoms were estimated to have occurred. Conventionally, we defined this frequency unit as Nights affected by RBD (NAR). For example, when a patient reported that symptoms appeared every night, the frequency was quantified as 365 NAR. If a patient reported a range, such as 2–3 nights per week, the estimation was based on the greater number in the report, and thus, the frequency was quantified as 150 NAR (calculated as follows: $3/7 \times 365 \fallingdotseq 150$). Although all symptom frequencies were reported by patients and confirmed by their family members, onset time was rated as unknown when both family members and the patient reported that the time of RBD onset was unclear.

Statistical analysis

Data are presented as mean ± standard deviation, unless otherwise stated. The Student's *t*-test was used to statistically compare the 2 groups. For statistical comparisons of symptom frequencies at different time points, the Kruskal-Wallis test was used, followed by Dunn's multiple comparison test. The differences in the occurrence of definite RBD and probable RBD between females and males were examined using χ^2 test.

Multivariate logistic regression analysis was performed to estimate the association between disease features and RBD symptom frequency. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated after controlling simultaneously for potential confounders. The explanatory variables included sex, BMI, RBD onset age, and duration of RBD. Statistical analyses were performed using IBM SPSS Statistics for Macintosh, Version 22.0(IBM Corp. Armonk, NY).

Ethical consideration

The study protocol was approved by the ethics committee of Shiga University of Medical Science (27–229). Informed consent was obtained by the use of an opt-out methodology, owing to the low risk nature of this study.

Results

We collected RBD data between June 1, 2008 and December 31, 2015. During this period, 70 patients had

either definite or probable RBD, according to criteria defined elsewhere (Boeve et al. 2007). Among these patients, 1 was excluded because of comorbid Alzheimer's dementia. Additionally, 17 patients were excluded because of inadequate validity of information on symptom frequency, and 2 were excluded because RBD onset was unclear. All subjects did not meet the diagnostic criteria for PD, DLB, or MSA. Therefore, 50 patients were finally included in this study (Table 1). The patients were predominantly male, reflecting the male-dominant nature of this disease (Postuma et al. 2016). The mean age at RBD onset was 62.2 ± 9.1 years, and there was no significant difference in the age at onset between female and male patients (57.5 ± 15.1 vs. 63.2 ± 6.7, respectively, two-tailed t-test $p > 0.05$). Also, there were no sex-related differences in BMI and disease durations (two-tailed t-test, $p > 0.05$) in our study sample. There was no significant difference in the proportions of definite or probable RBD between females and males (χ^2 test, $p > 0.05$). Nineteen subjects had sleep apnea syndrome as their apnea–hypopnea index (AHI) value was greater than 5, which was confirmed by video PSG.

Of the 50 study patients, 31 were diagnosed with definite RBD and 19 with probable RBD. There were no significant differences in the RBD onset age or duration of symptoms between the 2 groups of patients (data not shown).

On assessing the distribution of symptom frequencies at the first visit to our sleep clinic, we noted a skewed distribution. Many patients reported rare occurrences of symptoms, and the numbers of patients decreased as the RBD symptom frequency increased (Fig. 1). In this analysis, 60% of the patients reported that symptoms appeared no more than once per a week (50 NAR). In contrast, 4 patients reported that RBD symptoms appeared every day, and this group represented a small peak at 365 NAR. The median symptom frequency was 50 NAR, with a 1st quantile value of 24 NAR and a 3rd quantile value of 115 NAR.

In addition to the symptom frequency profile, we examined the changes in the symptom frequency during the time course after RBD onset. We found that the RBD symptom frequency did not continuously increase as a function of the disease duration and that RBD symptoms appeared most frequently in the second 5-year period of the disease (Fig. 2). To confirm the differential symptom frequency after disease onset, we performed statistical analysis by binning every 2 years of disease duration. We combined patients with a disease history of more than 8 years into one group, because of the small number of patients in this group. The analysis showed that RBD symptoms appeared approximately 1–2 times a month in the first 2 years of RBD (median, 18 NAR; range, 2–29 NAR; Table 2 and Additional file 1: Figure S1). The symptom

Table 1 Demographic data of the participants

	All	Male	Female	p
N	50	41	9	
BMI	22.4 ± 3.20	22.7 ± 3.09	21.0 ± 3.33	0.608
Age at RBD onset	62.2 ± 9.13	63.2 ± 6.67	57.5 ± 15.1	0.320
RBD duration	6.0 ± 4.9	6.5 ± 5.0	3.9 ± 3.7	0.587
Definite/Probable RBD	31/19	24/17	7/2	0.282

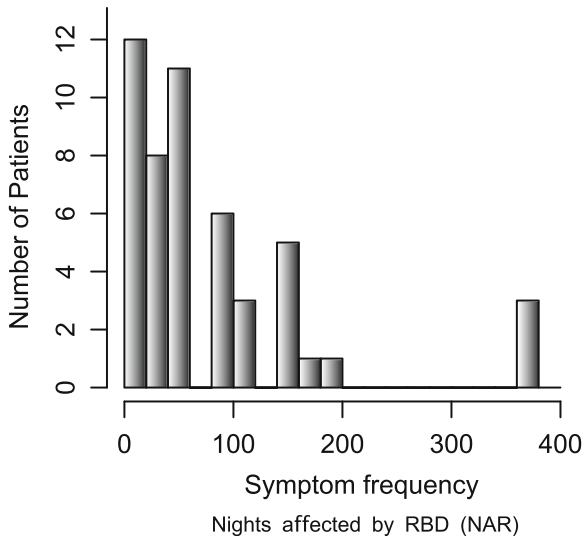

Fig. 1 RBD symptom frequency at sleep clinic visit. A histogram representation of the RBD symptom frequency distribution. The x-axis shows the RBD symptom frequency in NAR units. The y-axis shows the number of patients in every 20 NAR bin group

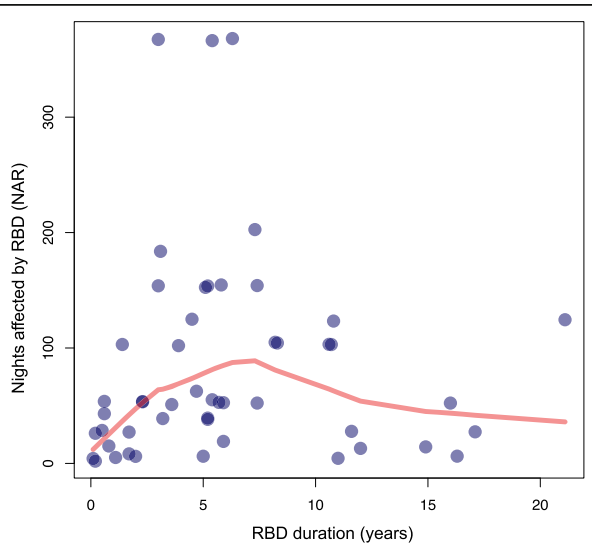

Fig. 2 RBD frequencies and the relation with the RBD duration. A scatter plot of RBD frequencies is shown. The x-axis denotes the duration of RBD in years. The y-axis denotes the frequency of RBD symptoms in NAR units. The blue spots represent RBD duration and RBD symptom frequency at the first visit to our sleep clinic. For better understanding of the RBD symptom frequency changes, trend is indicated with a red line, which was generated using the locally weighted scatterplot smoothing method

Table 2 RBD symptom frequencies in every 2-year bin of RBD duration

Symptom frequency (NAR)				
Duration (years)	*n*	Median	Interquartile range	*p*
0–2	12	18	2–29	Reference
2–4	8	75	50–158	0.006
4–6	13	50	36–150	0.016
6–8	4	175	125–241	0.003
>8	13	50	12–100	0.280
All	50	50	24–115	

NAR: Nights affected by RBD
The median RBD frequencies are calculated within each disease duration group

frequencies were significantly higher in the following 6 years, with median frequencies of 75 NAR for 2–4 years, 50 NAR for 4–6 years, and 175 NAR for 6–8 years. Interestingly, 8 years after RBD onset, the frequency was comparable to that in the first 2 years (median, 50 NAR; range, 12–100 NAR). On the other hand, multiple comparison test showed no significant differences among groups of 2–4 years, 4–6 years, 6–8 years, and over 8 years. Although a report showed that patients with severe sleep apnea (AHI around 60) can mimic RBD symptoms (Iranzo & Santamaria 2005), NARs for 2–4 years and 4–6 year groups remained significantly higher even after limiting study subjects to patients with normal or mild apnea (AHI less than 15, Additional file 2: Table S1). Also, the main findings remained the same after excluding the patients with antidepressant medication (Additional file 3: Table S2).

As the disease duration did not appear to be associated with RBD symptom frequency, we assessed the possible associations between symptom frequency and other features of the patients. For this assessment, we conducted multivariate analysis after controlling for possible cofounders, including sex, BMI, and age at RBD onset. We found that symptom frequency was not associated with sex, BMI, age at RBD onset, or RBD duration (Table 3).

Discussion

Although RBD is known to be a prodromal symptom of PD/DLB/MSA (Mahowald & Schenck 2013), the time-dependent changes in RBD symptoms before PD/DLB/MSA have not been well studied. In the present study, we did not find any association between RBD symptom frequency and disease duration.

Our finding that RBD symptoms were most frequent in the 2–8 years of disease duration was unexpected. This trend was statistically confirmed as NARs during 2–8 years of disease were comparable and remained constantly higher than those during first 2 years, despite apparent fluctuation in their median values. This trend could not be explained by possible effects of antidepressants because the findings remained the same even after excluding three subjects who were taking antidepressants. Also, SAS was not likely the explanation for the current findings, because NAR was significantly higher for groups with 2–4 and 4–6 years of disease history than for those with 0–2 years history after excluding moderate and severe SAS patients. Poor statistical power could explain the reason why we could not find significantly higher NAR in 6–8 years bin, as exclusion of those SAS patients reduced the number of study patients within this group.

Recent studies have shown that RBD is one of the manifestations of alpha-synucleinopathies (Boeve 2013), which irreversibly damage the neural system (Boeve et al. 2007). Consistent with this irreversible neural damage model, previous reports showed that the severity of REM atonia loss is enhanced as the disease duration increases (Iranzo et al. 2009; Postuma et al. 2010). One explanation for the discrepancy is that RBD symptom frequency could be discordant with the severity of REM atonia loss. To conclude this assumption, a future prospective study with follow-up PSG will be required. However, current findings could be advantageous for clinicians, as we focused on clinically observable RBD symptom frequencies instead of muscle atonia, which can only be observed with polysomnography examination.

Notably, some studies have reported a possibility that rate of development of neurodegenerative disease is slower in Asian RBD patients (Inoue 2016; Postuma 2013) than in Caucasians. Along with the known heterogeneity of alpha-synucleinopathies (Thenganatt & Jankovic 2014) and reported ethnic differences in RBD rate, genetic background of the patients could interfere with the progression rate and frequency of appearance of RBD symptoms. Thus, current findings could only reflect the characteristics limited to Asian patients.

The present study has several limitations. First, our study depended on the reports of patients and their family members, and thus, there might have been recall bias. The recall bias may apply to the accuracy of disease duration, as patients were often unsure of the exact month of disease onset. Even with time resolution of this level, current conclusion will not be affected enormously because we conducted disease-duration–related analysis on a 2-year bin basis. Another limitation to our study is the exclusion of dementia patients. This exclusion could result in a selection bias, in which we observed the RBD population who does not proceed to dementia. However, based on the reported high rates and several years required to convert to dementia from RBD, we believe the effect of this selection bias to be minimal. Instead, the reliability of disease durations was ensured by excluding dementia patients as well as by confirmation from the family members. There may have been another selection bias because only patients visiting our sleep clinic were enrolled.

Table 3 Association between patient features and RBD symptom frequencies

	Unadjusted			Multivariable Adjusted (b)		
	OR	(95% CI)	*p*-value	OR	(95% CI)	*p*-value
Sex	−3.144	(−70.43 to 64.14)	0.926	−7.894	(−86.81 to 71.022)	0.841
BMI	−0.913	(−8.990 to 7.163)	0.821	−1.113	(−9.663 to 7.436)	0.794
Onset age (years)	−0.254	(−3.100 to 2.592)	0.858	−0.406	(−4.070 to 3.258)	0.824
Duration (years)	0.215	(−5.040 to 5.470)	0.935	−0.231	(−6.904 to 6.441)	0.945

Summary of the multivariate analysis results is presented. Odd ratios (ORs) and 95% confidence intervals (CIs) are shown for each explanatory variable

One limitation that needs attention is the retrospective nature of our study. This design was selected to better follow the naturalistic evolution of RBD. One factor that could hamper the observation of the naturalistic evolution of RBD symptoms is the fact that the symptoms could be resolved with medication (Schenck et al. 2013b; Li et al. 2016). Because of this favorable action of medication, it is often difficult to observe the natural progression of symptom change. Because of the same reason, the setting of placebo cohort for comparison is not ethically allowable. Another factor is the long-lasting nature of RBD symptoms, which require a long observation duration. Indeed, Schenck et al. reported that RBD onset occurs long before the onset of PD or DLB, with a mean interval of 14.2 years and a wide range of 5–29 years (Schenck et al. 2013a). This long and varying duration is problematic for long-term observation and the eventual estimation of PD and DLB occurrence. The current study circumvented these obstructions by employing a retrospective review of RBD symptom frequencies before medical intervention. Using this strategy, we could observe the naturalistic evolution of RBD symptoms, which were not quantitatively reported in the previous studies. This observation shed new light on understanding the nature of RBD progression and the possible link to alpha-synucleinopathy occurrence.

Future studies will be required to develop precise techniques that can assess RBD symptom progression not only quantitatively but also qualitatively. Additionally, longitudinal follow-up studies are required to assess the relationship of RBD progression with PD, DLB or MSA onset.

Conclusion

There was no association between RBD symptom frequency and disease duration. RBD clinical symptoms could be less prominent when neural damage becomes severe. Therefore, decrease in RBD symptom frequency may be indicative of progression of neurodegeneration.

Additional files

Additional file 1: Figure S1. Distributions of RBD frequencies within each disease history bin. Distributions of RBD symptom frequency are shown for every disease duration bin. The x-axis denotes the RBD duration bin. The y-axis denotes the frequency of RBD symptoms in NAR units. Median and interquartile range are shown. (PDF 339 kb)

Additional file 2: Table S1. RBD symptom frequencies in every 2-year bin of RBD duration after excluding moderate and severe SAS patients. (PDF 118 kb)

Additional file 3: Table S2. RBD symptom frequencies in every 2-year bin of RBD duration after excluding patients on antidepressant medication. (PDF 192 kb)

Abbreviations

AHI: Apnea-hypopnea index; BMI: Body mass index; DLB: Dementia with Lewy bodies; NAR: Nights affected by RBD; PD: Parkinson's disease; MSA: Multiple-system atrophy; RBD: REM behavior disorder; REM: Rapid eye movement; SAS: Sleep apnea syndrome

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Availability of data and materials

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Authors' contributions

YS and MM conceived and designed the study. TN, FM, and M Takahashi recruited participants, under management by KK and NY. TK scored PSG data, and M Takami and HK conducted the statistical analysis. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study protocol was approved by the ethics committee of the Shiga University of Medical Science (27–229). Informed consent was obtained by the use of an opt-out methodology based on the low risk to the patient.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Publisher's Note

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