(LDEs) [6] PD: 371 ± 214 mg/day]. We excluded patients from this study who were taking selegiline or antidepressants and those having suffered from heart failure and/or diabetes mellitus since these factors might have affected the MIBG scintigraphic findings.

Overnight PSG recordings were performed by standardized methods [6]. During REM stage sleep, submental phasic EMG activity (defined as 3-s mini-epochs containing phasic twitches which are at least four times higher than the background EMG activity) or submental tonic EMG activity with durations of more than half of a 30-s epoch was scored as RWA [7].

All the PD patients and their bed partners were also systematically interviewed regarding their sleep problems by a physician specializing in sleep disorders. Interviews especially focused on dream enactment behavior or vocalization while dreaming within one month before the PSG. In line with criteria from the second edition of the International Classification of Sleep Disorders [1], we diagnosed clinical RBD when a patient had both RWA on PSG and the experience of dream enactment behaviors associated with uncomfortable dream content during the preceding year, and included not only violent cases but also non-violent cases. This last criterion was included according to the suggestion by Oudiette et al. [8] that non-violent symptoms might represent the first step in the neurodegenerative process of the disorder. We also defined patients with RWA but without RBD symptoms as subclinical RBD. Finally, we categorized the patients into three groups: PD group with clinical RBD, PD group with subclinical RBD, and PD group with normal REM sleep.

Patients received an intravenous injection of 111-mBq of ^{123}I-MIBG (Daiichi Radioisotope Laboratories, Tokyo, Japan). A single photon emission computed tomography (SPECT) image was obtained in an anterior view after 30 min for the early image and after 3.5 h for the delayed one. Average counts per pixel in the heart and mediastinum were used to calculate the heart-to-mediastinum (H/M) ratio. In this study, the H/M ratio of the delayed images, which display the neuronal uptake of MIBG scintigrams more explicitly than those of the early image [9], were used for the analysis.

We compared the continuous variables, including MIBG scintigraphic findings, among the above three groups by using an analysis of variance (ANOVA) followed by *post hoc* testing with Bonferroni correlation. A χ^2-test was also used to compare the categorical variables. Finally, multiple linear regression analysis was performed to explore the risk model of reduced MIBG uptake among the PD patients. The independent variables included age, gender, PD symptom-related variables (duration of morbidity, Hoehn & Yahr stages, and LDEs), and RBD measures (RBD symptoms and RWA on PSGs). Statistical significance was defined as $p < 0.05$ (SPSS, ver. 15.0J, SPSS Japan, 2006).

3. Results

Twenty-six of the 49 PD patients without dementia had RWA on PSG (53.1%); 18 patients were classified as having clinical RBD (36.7%), including 8 with violent behavior and 10 with non-violent behavior. Eight patients were classified as displaying subclinical RBD (16.3%). The other 23 patients had normal REM sleep (46.9%). There were no significant differences in any of the above descriptive parameters among the three PD groups (Table 1).

There was a significant difference in H/M ratios on the MIBG scintigrams among the three groups [$F_{3,54} = 6.33$, $p = 0.001$]. *Post hoc* tests revealed that the PD group with clinical RBD had significantly lower values compared to both the group with subclinical RBD ($p < 0.01$) and the group with normal REM sleep ($p < 0.01$). However, there were no significant differences in H/M ratios between the PD group with subclinical RBD and the group with normal REM sleep (Fig. 1). Within the PD group exhibiting clinical RBD, there was no significant difference in the ratio between patients with violent behavior and those with non-violent behavior (patients with violent behavior: 1.18 ± 0.24, those with non-violent behavior: 1.16 ± 0.09).

Multiple linear regression analysis revealed that the existence of RBD ($\beta = -0.511$, $p = 0.002$) appeared to be the only significantly associated factor among the studied independent variables for reduced MIBG uptake in the final model ($R^2 = 0.314$, $p = 0.006$; Table 2).

4. Discussion

Our results confirmed that MIBG uptake is decreased in non-dementia PD patients with clinical RBD. Moreover, among the studied variables, the existence of RBD symptoms alone was associated with reduced MIBG uptake among PD patients. Interestingly, our results indicate that patients with subclinical RBD do not show significantly reduced MIBG uptake. This finding raises the possibility that neuronal loss and inclusion of Lewy bodies in the sympathetic ganglia as reflected by the reduced MIBG uptake is marked, especially in PD patients having clinical RBD symptoms. PD patients experiencing hallucinations are likely to have more reduced MIBG uptake compared to those that do not [10]. Therefore, our results may corroborate the idea that the existence of RBD symptoms in PD is one of the risk factors for developing hallucinations [2].

As mentioned above, patients with idiopathic RBD have reduced MIBG uptake [5]. Moreover, they have been characterized as likely to have autonomic symptoms including orthostatic hypotension [3] and cardiac dysfunction during both wakefulness and sleep [11,12]. As for PD patients, orthostatic abnormalities have been reported to be more frequent in patients with RBD [3]. Taking this finding and the present MIBG results together, it is possible that the existence of RBD symptoms accelerates autonomic dysfunction in PD patients. Considering that patients with non-violent behaviors showed MIBG findings similar to those with violent behaviors in the present study, it appears that the existence (but not the severity) of RBD symptoms might be related with reduced MIBG uptake. From this finding, we speculate that patients with α-synuclein pathology expanding into the limbic system, resulting in the occurrence of uncomfortable dreams associated with RBD symptoms, might simultaneously have lesions of cardiac sympathetic ganglia.

Our study has several limitations. First, our study did not include normal age-matched control subjects or patients with idiopathic RBD. Although our results show a clear difference in MIBG uptake between PD patients with and without clinical RBD, further study including these two control groups is necessary for drawing definitive conclusions. Second, the existence of RBD symptoms was investigated by retrospective interviews of the subjects and their bed partners. For this reason, we may have been unable to detect the existence of mild RBD symptoms in our subjects.

In conclusion, reduced MIBG uptake on scintigrams could be observed in PD patients with RBD symptoms. Although definitive

Table 1
Comparison of descriptive variables among the three subject groups.

	Groups with clinical RBD ($n = 18$)	Groups with subclinical RBD ($n = 8$)	Groups with Normal REM sleep ($n = 23$)	Significance
Age	71.3 ± 8.3	65.4 ± 8.6	71.5 ± 7.2	n.s.
Gender (Male/Female)	5/13	3/5	10/13	n.s.
Length of PD morbidity	9.0 ± 4.7	3.6 ± 2.6	5.3 ± 4.8	n.s.
Hoehn &Yahr Stages	3.0 ± 0.9	2.5 ± 0.5	2.7 ± 0.9	n.s.
Levodopa dose Equivalents (mg/day)	408 ± 214	283 ± 193	347 ± 199	n.s.
MMSE	25.6 ± 3.9	26.8 ± 2.3	26.3 ± 3.2	n.s.

RBD: REM sleep behavior disorders; MMSE: Mini Mental State Examination.
The values are expressed as mean ± SD. n.s.: not significant.

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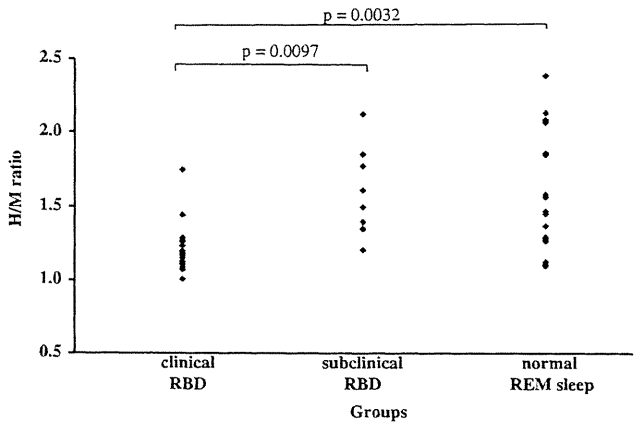

Fig. 1. Comparison of delayed image on MIBG scintigraphic findings among the three groups. ◆ symbols indicate the H/M ratios on MIBG scintigrams for each patient among the three groups (clinical RBD, subclinical RBD, and normal REM sleep).

Table 2
Multiple regression analysis on factors associated with H/M ratio on MIBG scintigrams among the total PD patients.

Model	β	t	p
Age	−0.243	−1.831	0.074
Duration of PD morbidity	0.75	0.488	0.628
Hoehn & Yahr stages	−0.104	−0.721	0.475
The existence of RBD symptoms	−0.511	−3.267	0.002
The existence of RWA on PSG	0.61	0.410	0.684

H/M: heart-to-mediastinum, MIBG: meta-iodobenzylguanidine.
RBD: REM sleep behavior disorders, RWA: REM sleep without atonia.

conclusions cannot be obtained from the results of this study, RBD symptoms might be associated with wider α-synuclein pathology as reflected by cardiac autonomic dysfunction.

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Mild parkinsonian signs in a community-dwelling elderly population sample in Japan

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ABSTRACT

Mild parkinsonian signs (MPS) may represent the mild end of a disease spectrum that spans from normal aging to neurodegenerative diseases. We conducted a population-based study in a rural island town in western Japan, Ama-cho. Participants included 1129 subjects, aged 60 years and older, residing in the town. Participants were classified according to a modified Unified Parkinson's Disease Rating Scale (mUPDRS) score. MPS was determined to be present if any of the following conditions were met: (1) two or more mUPDRS ratings = 1 [MPS-mild]; (2) one mUPDRS rating ≥ 2; or (3) mUPDRS rest tremor rating ≥ 1; [(2) and (3): MPS-severe]. Subjects wore a uniaxial accelerometer (Actiwatch), resulting in the measurement of actigraphic activity counts (AC).

Of the 804 participants with complete data, 178 subjects (22.1%) were classified as demonstrating MPS. AC was significantly lower in the MPS-severe group compared with both the CTL and the MPS-mild groups. Diagnostic sensitivity for MPS-severe became 100% when we adopted a cutoff point of low physical activity, as measured by actigraphy, combined with the presence of subjective depression.

We established the prevalence of MPS in a community-dwelling elderly population sample in Japan. Actigraphy may be a useful objective tool for screening MPS-severe.

1. Introduction

Mild parkinsonian signs (MPS), including bradykinesia, rigidity, gait disturbance and resting tremor, may represent the mild end of a disease spectrum that spans from normal aging [1] to neurodegenerative diseases [2], including Parkinson's disease (PD). MPS has also been reported to be the result of nigrostriatal Alzheimer's disease (AD)-type pathology [3], associated with increased risk of dementia [4], associated with vascular lesions of basal ganglia and white matter [5,6], and a significant predictor of mortality [7]. However, the clinical significance of MPS is not yet fully understood. The prevalence of MPS in sample populations in East Boston, England [8], New York, USA [9] and Jiangsu, China [7] has been reported, but inconsistencies exist across reports because of differences in MPS definition, study methodology, age structure, and cognitive status [10]. The prevalence of MPS in Japan has hitherto not been reported.

We have conducted the first epidemiological study to suggest the prevalence of MPS in Japan. Furthermore, we examined the usefulness of actigraphy as an objective indicator for MPS through a population-based study in order to establish screening methods for MPS in association with questionnaires about motor and nonmotor symptoms of Parkinson's disease (PD).

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2. Methods

2.1. Subjects

This study was conducted in the municipality of Ama-cho, a rural island town located 70 km from Yonago city, in the northwestern part of Japan [11]. To be included in the study, subjects were required to be living and to be legally residing in the town on March 31, 2008. The total population of Ama-cho on this day was 2402 (1124 men). The number of elderly people aged 60 years and older was 1129 (479 men, mean age ± SD 74.6 ± 9.1 years old). Board certified neurologists of the Japanese Society of Neurology (neurologists) belonging to our department have visited this town twice a year since 1980, and diagnosed patients having neurological disorders. Before this study, 11 patients with PD were recognized through these visits.

The study was approved by the committee for medical research ethics at Tottori University following the principles outlined in the "Declaration of Helsinki", and all participants provided written informed consent to participate in the study.

2.2. Questionnaire survey

We administered a questionnaire survey in May 2008. First, we mailed the questionnaires to residents aged 60 years or older. To assess motor symptoms, we included the Tanner questionnaire, [12], which is validated as a PD patient screening form. To evaluate depressive symptoms, we included the Japanese version of the

Geriatric Depression Scale with 15 questions (GDS-15). [13]. It has been validated for the diagnosis of depression, and the recommended cutoff points are ≥6 as mild depression and ≥10 as severe depression [13,14]. We included the Pittsburgh Sleep Quality Index (PSQI) [15] and the REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ) [16] to assess sleep disturbances. The cutoff value of the PSQI for a poor sleeper was 5/6 points, [15], and the RBDSQ to detect REM sleep behavior disorder (RBD) was 5/6 points. [17]. Demographic data, including age, gender, duration of education, and present smoking and drinking habits, were collected using the questionnaire. In order to evaluate nonmotor symptoms, we assessed the presence of constipation, hallucinations, hyposmia, and orthostatic hypotension with the questionnaire.

2.3. Neurological examination

Each participant underwent a structured medical interview including a past history of hypertension, diabetes mellitus, and hyperlipidemia. A standardized neurological examination was conducted by one of four neurologists, including an abbreviated (10-item) version of the motor portion of the Unified PD Rating Scale (UPDRS) in 2008–2009. The 10 items screened for speech, facial expression, tremor at rest, rigidity (rated separately in the neck, right arm, left arm, right leg, and left leg), posture, and body (axial) bradykinesia, with each item rated from 0 to 4. A rating of 1 indicated a mild abnormality and a rating of ≥2 indicated an abnormality of moderate or greater severity [9]. Subjects with a total UPDRS score of 0 were classified as being normal controls (CTL). We assigned a diagnosis of PD based on research criteria [18] and participants were considered to have PD if (1) they had previously received a diagnosis of PD by neurologists and responded to L-dopa or (2) their symptoms fulfilled the UK PD brain bank criteria, [19], or both. Those who had two or more cardinal signs (UPDRS rating≥2) on the standardized neurologic examination were classified as having parkinsonism. These cardinal signs include bradykinesia, rigidity, postural instability, and resting tremor.

MPS were defined as present when any one of the following conditions was met: (1) two or more UPDRS ratings=1; (2) one UPDRS rating≥2; or (3) a UPDRS resting tremor rating≥1 [10]. MPS was further stratified into subtypes according to symptom types and severity as shown in Table 1 [4, 20, 21].

2.4. Measurement of physical activity using actigraphy

In order to obtain participants for the actigraphy study, we gathered subjects in five districts, randomly selected from the fourteen districts in the town (participation rate: 65.0%).

Physical activity was quantified using wrist-worn uniaxial accelerometers (Actiwatch-16, Mini Mitter-Philips Respironics, Bend, OR) [22]. Physical activity was monitored in the participant's own homes, and participants were instructed to continue their normal daily routine. Participants wore Actiwatches on their nondominant wrist for 1 week collecting data in 1-minute epochs. Those subjects with unilateral PD wore monitors on their least affected side. This placement has been shown to better represent whole-body movement [25] and was intended to reduce artifacts such as low level constant activity when writing with the dominant hand or dyskinesias in the most affected arm. At the same time, all participants completed a sleep log for 7 days. All actigraphic data were validated in accordance with entries in sleep logs. Automatic activity analysis using dedicated software (Actiware, Mini Mitter-Philips Respironics) was conducted. The measures analyzed were Total AC (the sum of all valid physical activity counts for all awake epochs), Avg AC (the average of all valid physical activity counts for all awake epochs divided by the epoch length in minutes), and Max AC (the largest of any valid physical activity count for all awake epochs).

Table 1
Classification of mild parkinsonian signs.

Classification according to symptoms	
Axial dysfunction	(1) UPDRS ratings=1 in two or more of the four items of axial function (changes in speech, facial expression, posture, and axial bradykinesia), or (2) one UPDRS rating≥2 in one of the four items
Abnormality in rigidity	Either (1) UPDRS ratings=1 in two or more of the five items of rigidity, or (2) one UPDRS rating≥2 in one of the five items
Tremor	A UPDRS resting tremor rating≥1
Unclassified	Could not be classified into any of the above-mentioned categories
Classification according to severity of UPDRS score	
MPS-mild	A UPDRS rating of 1
MPS-severe	A UPDRS rating of 2 or higher, or presence of resting tremor

MPS: mild parkinsonian signs, UPDRS: Unified PD Rating Scale.

2.5. Statistical analyses

The adjusted prevalence was calculated for all types of MPS and PD using the Japanese population on March 1, 2008. Paired *t* tests and analysis of variance (ANOVA) were used for comparison of medians for continuous variables, and categorical variables were analyzed using a chi-square test. Pearson's test was used for correlation analyses. Differences in the total physical activities between groups were evaluated with an analysis of covariance (ANCOVA), adjusting for age. Analyses of the relationship between the background of the nonmotor symptoms and MPS-severe were performed by multivariate logistic regression analysis. Significance was defined as $p<0.05$, and all analyses were conducted using the Statistical Package for the Social Sciences version 17.0 software (SPSS17.0, 2008, Tokyo, Japan).

3. Results

3.1. Questionnaire survey

Nine hundred sixty-eight (85.7%) of 1129 residents returned their questionnaire. As compared to survey nonrespondents, respondents were similar in age (mean=74.7 years vs. 75.1 years) and gender (47.1% male vs. 43.5% male).

3.2. Prevalence of PD and MPS in a community-dwelling elderly population sample

Eight hundred four of 1129 subjects received a neurological examination (71.2%). We diagnosed 69 subjects as having parkinsonism (24 men, 82.9±7.1 years). Of the parkinsonism patients, 14 were diagnosed as having PD (4 men, 79.6±7.6 years). The crude prevalence of PD and the age-adjusted prevalence when calculated using the Japanese population in 2008 were 1.5% and 1.3% for PD in those over the age of 65.

Of the examined subjects, 178 were diagnosed as having MPS (62 men, 78.1±8.1 years). The crude prevalence of MPS was 22.1% (95% CI: 19.3–25.0) in participants over 60 years of age, and 23.7% (95% CI: 20.6–26.9) in participants over 65 years of age. The age-adjusted prevalence of MPS was 13.8% in the over 60 population, and 16.8% in the over 65 population. We showed the classification of MPS according to its type and severity in Table 2.

3.3. Physical activity measured by actigraphy

Using actigraphy, we evaluated 265 subjects (121 men; age: 74.2±7.9 years), including 174 control (CTL) subjects (75 men; 72.2±7.2 years), 53 subjects with MPS-mild (22 men; 78.3±7.2 years), 19 subjects with MPS-severe (5 men; 78.4±6.6 years), and 19 subjects with parkinsonism (7 men; 81.0±7.5 years) including 7 PD patients

Table 2
Age- and sex-specific prevalence of MPS.

Age (years)	Residents	Population at risk	MPS																Parkinsonism	
			Total		Type										Severity					
					Axial dysfunction		Rigidity		Mixed		Tremor		Unclassified		MPS-mild		MPS-severe			
			Cases	Prevalence	Cases	Prevalence	Cases	Prevalence	Cases	Prevalence	Cases	Prevalence	Cases	Prevalence	Cases	Prevalence	Cases	Prevalence	Cases	Prevalence
Both sexes																				
60–64	183	88	8	9.1%	1	1.1%	7	8.0%	–	–	–	–	–	–	7	8.0%	1	1.1%	–	–
65–69	180	135	18	13.3%	2	1.5%	12	8.9%	2	1.5%	2	1.5%	–	–	15	11.1%	3	2.2%	1	0.7%
70–74	198	164	28	17.1%	5	3.0%	18	11.0%	3	1.8%	2	1.2%	–	–	23	14.0%	5	3.0%	9	5.5%
75–79	227	183	49	26.8%	12	6.6%	25	13.7%	11	6.0%	1	0.5%	–	–	34	18.6%	15	8.2%	13	7.1%
80–84	158	121	43	35.5%	14	11.6%	16	13.2%	7	5.8%	2	1.7%	4	3.3%	26	21.5%	17	14.0%	11	9.1%
85–	183	113	32	28.3%	9	8.0%	18	15.9%	4	3.5%	–	–	1	0.9%	23	20.4%	9	8.0%	35	31.0%
Total	1129	804	178	22.1%	43	5.3%	96	11.9%	27	3.4%	7	0.9%	5	0.6%	128	15.9%	50	6.2%	69	8.6%
Men																			–	–
60–64	94	38	3	7.9%	1	2.6%	2	5.3%	–	–	–	–	–	–	2	5.3%	1	2.6%	–	–
65–69	84	63	8	12.7%	1	1.6%	5	7.9%	1	1.6%	1	1.6%	–	–	8	12.7%	–	–	1	1.6%
70–74	89	67	11	16.4%	1	1.5%	7	10.4%	2	3.0%	1	1.5%	–	–	9	13.4%	2	3.0%	5	7.5%
75–79	97	72	17	23.6%	4	5.6%	7	9.7%	6	8.3%	–	–	–	–	11	15.3%	6	8.3%	3	4.2%
80–84	53	38	10	26.3%	2	5.3%	3	7.9%	2	5.3%	1	2.6%	2	5.3%	6	15.8%	4	10.5%	2	5.3%
85–	62	44	13	29.5%	2	4.5%	10	22.7%	–	–	–	–	1	2.3%	11	25.0%	2	4.5%	13	29.5%
Total	479	322	62	19.3%	11	3.4%	34	10.6%	11	3.4%	3	0.9%	3	0.9%	47	14.6%	15	4.7%	24	7.5%
Women																			–	–
60–64	89	50	5	10.0%	–	–	5	10.0%	–	–	–	–	–	–	5	10.0%	–	–	–	–
65–69	96	72	10	13.9%	1	1.4%	7	9.7%	1	1.4%	1	1.4%	–	–	7	9.7%	3	4.2%	–	–
70–74	109	97	17	17.5%	4	4.1%	11	11.3%	1	1.0%	1	1.0%	–	–	14	14.4%	3	3.1%	4	4.1%
75–79	130	111	32	28.8%	8	7.2%	18	16.2%	5	4.5%	1	0.9%	–	–	23	20.7%	9	8.1%	10	9.0%
80–84	105	83	33	39.8%	12	14.5%	13	15.7%	5	6.0%	1	1.2%	2	2.4%	20	24.1%	13	15.7%	9	10.8%
85–	121	69	19	27.5%	7	10.1%	8	11.6%	4	5.8%	–	–	–	–	12	17.4%	7	10.1%	22	31.9%
Total	650	482	116	24.1%	32	6.6%	62	12.9%	16	3.3%	4	0.8%	2	0.4%	81	16.8%	35	7.3%	45	9.3%

(2 men; 77.8 ± 7.2 years). Ruling out a selection bias, there were no significant differences between activity measurement participants and non-participants with regard to age (74.3 ± 8.0 vs. 75.0 ± 9.4 years, respectively, p = 0.253), gender (43.3% male vs. 42.1% male, respectively, p = 0.390), or UPDRS score (1.4 ± 2.3 vs. 1.2 ± 2.4, respectively, p = 0.239).

While there was no significant difference in Total AC between the CTL and MPS-mild groups, Total AC in the MPS-severe group was significantly lower than that in the CTL and MPS-mild groups (Fig. 1). Our measure of Avg AC showed the same tendency as Total AC. However, our measure of Max AC was not significantly different among the groups. These three indices of physical activity were significantly associated with age (Total AC: $r = -0.358$, $p<0.001$, Avg AC: $r = -0.330$, $p<0.001$, Max AC: $r = -0.258$, $p<0.001$). ANCOVA analysis, adjusted for the age of subjects, revealed that Total AC in the MPS-severe group was significantly lower than that in the CTL group.

We divided the MPS group according to axial dysfunction scores into three subgroups: non-axial dysfunction (axial dysfunction score = 0, n = 34), mild axial dysfunction (axial dysfunction score = 1 or 2, n = 28), and moderate/severe axial dysfunction (axial dysfunction score = 3 or more, n = 10). Total AC, Avg AC and Max AC in the non-axial dysfunction group were 323,834.6 ± 21,927.8, 383.9 ± 25.0, and 2507.9 ± 151.5, those in the mild axial dysfunction group were 240,077.7 ± 22,175.5, 300.8 ± 25.9, and 2149.2 ± 124.9, and those in the moderate/severe axial dysfunction group were 193,873.6 ± 20,551.1, 245.7 ± 25.6, and 1755.9 ± 174.4, respectively. Total AC and Avg AC of the moderate/severe axial dysfunction group were significantly lower than those of the non-axial dysfunction group. In addition, Total AC, Avg AC, and Max AC of the mild axial dysfunction group were significantly lower than those of the non-axial dysfunction group. However, there were no significant differences in the three activity parameters between the mild axial dysfunction group and the moderate/severe axial dysfunction group.

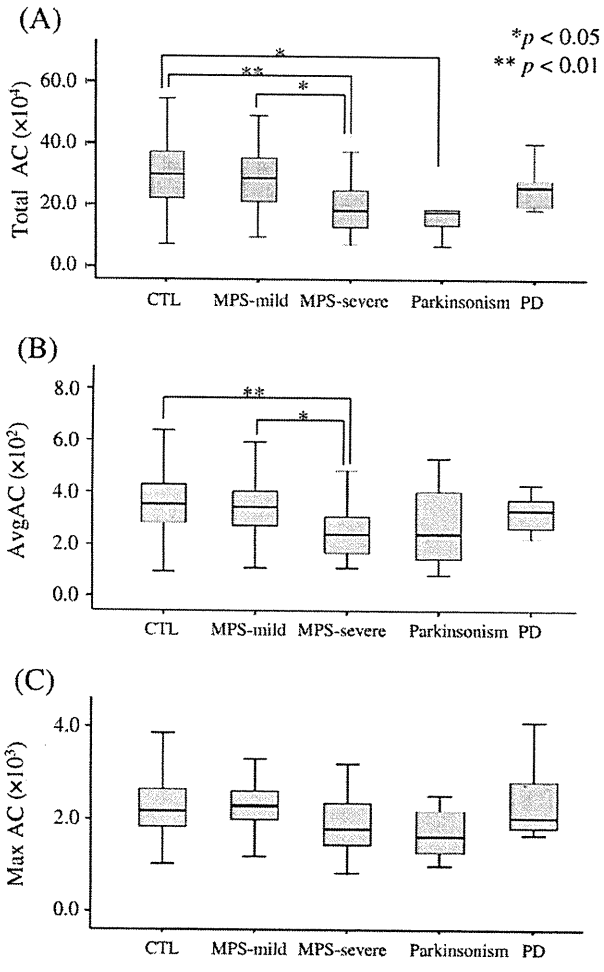

Fig. 1. Comparison of physical activity. The box plots show the median values (thick lines), 25th percentile (lower line of box), and 75th percentile (upper line of box). T bars indicate the 10th and 90th percentiles. Statistical differences were calculated using an ANOVA followed by Tukey tests. CTL: normal controls, MPS: mild parkinsonian signs. PD: Parkinson's disease. (A) Total AC: the sum of all valid physical activity counts for all epochs from the start time to the end time of the given awake interval, (B) Avg AC: the average of all valid physical activity counts for all awake epochs divided by the epoch length in minutes, (C) Max AC: the largest of any valid physical activity count for all awake epochs. *$p<0.05$, **$p<0.01$.

We also divided the MPS group according to rigidity scores into three subgroups: non-rigidity (maximum rigidity score = 0, n = 17), mild rigidity (maximum rigidity score = 1, n = 53), and moderate/severe rigidity (maximum rigidity score = 2, n = 2). There were no significant differences in the three activity parameters among these groups.

Finally, we also divided the MPS group according to tremor scores into three subgroups: non-tremor (tremor score = 0, n = 67), mild tremor (tremor score = 1, n = 5), and moderate/severe tremor (tremor score = 2, n = 0). There were no significant differences in activity between these groups.

3.4. Association of nonmotor PD symptoms with MPS

There were no significant differences between the CTL group and both the MPS-mild and MPS-severe groups for habitual history, past history, nonmotor PD symptoms, or RBDSQ scores (Table 3). There was a significantly lower proportion of 'sleep disturbance' on the PSQI in the MPS-mild group, but not in the MPS-severe group, as compared with the CTL group.

The GDS scores of the MPS group were significantly higher than those of the CTL group (4.3 ± 3.4 vs. 3.2 ± 3.1, $p = 0.01$) and there was a significantly higher proportion of subjects with 'mild depression' on the GDS in the MPS group as compared with the CTL group (41.3% vs. 27.0%, $p<0.001$), indicating a strong association of subjective depression with MPS.

The proportion of subjects with 'mild depression' on the GDS was significantly higher in the MPS-mild group than in the CTL group. The proportion of subjects with 'severe depression' was significantly higher in the MPS-severe group than in the CTL group.

3.5. Screening for MPS

In the present study, when one point was assumed to be a cutoff in the Tanner questionnaire, the sensitivity for detecting PD was 100%. However, it was only 71.9% for detecting MPS (both MPS-mild and MPS-severe) and 73.3% for detecting MPS-severe. When predictors of MPS-severe were examined by multivariate logistic analysis, GDS and

Table 3
Demographic characteristics of participants stratified by MPS.

	CTL	MPS-mild	MPS-severe
Present smoking, n (%)	33 (7.5%)	4 (3.9%)	3 (7.1%)
Present drinking, n (%)	116 (26.6%)	19 (18.4%)	4 (9.3%)
Constipation, n (%)	97 (22.9%)	37 (37.0%)	15 (38.5%)
Hallucination, n (%)	30 (7.0%)	8 (8.3%)	7 (17.1%)
Hyposmia, n (%)	49 (11.4%)	17 (17.0%)	7 (17.1%)
Orthostatic hypertension, n (%)	79 (18.3%)	24 (24.2%)	14 (32.6%)
GDS ≥ 6, n (%)	123 (27.4%)	42 (40.4%)**	17 (39.5%)
GDS ≥ 10, n (%)	23 (5.1%)	7 (6.7%)	7 (17.1%)**
RBDSQ ≥ 5, n (%)	37 (8.2%)	17 (16.3%)	5 (11.6%)
PSQI ≥ 6, n (%)	107 (23.8%)	18 (17.3%)*	8 (18.6%)

GDS: Geriatric Depression Scale, PSQI: Pittsburgh Sleep Quality Index, RBDSQ: REM Sleep Behavior Disorder Screening Questionnaire. *$p<0.05$, **$p<0.01$ vs. CTL.

Table 4
Predictors of MPS-severe status by multivariate logistic regression analysis.

Variable	Pearson's rank correlation	Univariate logistic regression analysis	Multivariate logistic regression analysis
		Odds ratio (95% CI)	Odds ratio (95% CI)
Age	0.231**	1.129** (1.081–1.181)	–
Education	−0.114*	0.793* (0.665–0.946)	–
Tanner	0.261**	1.435** (1.274–1.616)	–
GDS	0.155**	1.172** (1.074–1.279)	1.4* (1.1–1.8)
PSQI	−0.021	–	–
RBDSQ	−0.010	–	–
Total AC	−0.267**	0.694** (0.553–0.870)	0.5** (0.3–0.8)

Education: duration of education, GDS: Geriatric Depression Scale, PSQI: Pittsburgh Sleep Quality Index, RBDSQ: REM Sleep Behavior Disorder Screening Questionnaire. *$p<0.05$, **$p<0.01$.

Total AC were shown to be independent predictive factors (Table 4). Based on this finding, diagnostic sensitivities, specificity, and positive predictive value (PPV) became 100%, 83.5%, and 62.2% (respectively) for MPS-severe when we adopted a cutoff point of more than 6 points for GDS or less than 40×10^4 for Total AC. When we used the same screening method, diagnostic sensitivities, specificity, and PPV became 85.7%, 83.5%, and 68.2% for the entire MPS group, 94.4%, 83.5%, and 37.8% for the parkinsonism group including PD, and 87.5%, 83.5%, and 73.3% for a combination of all the groups (MPS and parkinsonism including PD), respectively.

4. Discussion

Only a few reports have documented the prevalence of MPS, indicating a prevalence of 15.8% in retired military officers aged 75 years or older in Nanjing [7]; 14.9% (age 65–74), 29.5% (age 75–84), and 52.5% (age 85 and older) in East Boston [8]; and 40.1% in residents aged 65 years or older in New York [9]. Our study revealed that the crude prevalence of MPS was 22.1% in the population over 60 years of age, and 23.7% in the population over 65 years of age. These data are in agreement with earlier cohort studies reporting similar findings.

One of the difficulties in studying the prevalence of MPS is the definition of MPS. Several studies have defined MPS liberally (any one UPDRS rating of 1 or higher [9,21]), while others have defined it more rigorously (two or more such signs or one sign of moderate severity (UPDRS rating≥2) [10]). One motivation for using more rigorous criteria is to try to separate MPS from the signs of normal aging. The more rigorous criteria are also considered to avoid the influence of other chronic illnesses and the aging process, and thus more likely to reflect pathological brain changes resulting in MPS [10]. However, a clear distinction between MPS and normal aging has not been established.

In the present study, we classified MPS into two subgroups according to the severity of the UPDRS rating. In order to investigate differences in physical activity between these two subgroups, we measured physical activity using actigraphy. Previous studies have reported the usefulness of standard actigraphy to assess fluctuation of akinesia [23], tremor, motor fluctuation [24], and sleep in PD patients [25,26]. In the present study, measured activity counts in the PD group were higher compared to the MPS-severe group. We noted that the PD patients who showed higher activity counts on actigraphy measures tended to receive higher Levodopa equivalent doses, had a shorter PD duration, and/or displayed a resting tremor (data not shown). These factors might account for higher activity counts in the PD group compared to the MPS group or parkinsonism group. In particular, the PD patient who generated the highest activity counts in the PD group displayed excessive overactivity due to the side effects of anti-parkinsonian drugs when he wore the Actiwatch. When we excluded this patient from the analysis, the activity counts of the PD group were significantly lower than those of both the CTL group ($p=0.036$) and the MPS-mild group ($p=0.044$). Unfortunately, the number of PD patients present in this study might be too small to confidently analyze their activity counts.

On the other hand, our measure of Total AC in the MPS-severe group was significantly lower than that measured in both the CTL and MPS-mild groups. Levels of physical activity were significantly associated with age, as participants with MPS were significantly older than those in the CTL group. However, an ANCOVA analysis revealed that the Total AC of subjects in the MPS-severe group, even after adjusting for age, was significantly lower compared to the CTL group.

To further clarify the clinical meaning of our actigraphic data, we divided the MPS group according to axial dysfunction scores, rigidity scores, and tremor scores. There were no significant differences between the mild axial dysfunction group and the moderate/severe axial dysfunction group. However, there was a significant difference between the non-axial dysfunction group and the moderate/severe axial dysfunction group in both Total AC and Avg AC, and between the non-axial dysfunction group and the mild axial dysfunction group in Total AC, Avg AC, and Max AC. Among the rigidity groups, there were no significant differences, although the activity counts of the mild tremor group were higher compared to the non-tremor group.

Therefore, we believe that our actigraphic data primarily relates to axial dysfunction.

These data suggest that a UPDRS rating of 2 may be more appropriate than a rating of 1 for distinguishing between MPS and normal aging. Future longitudinal studies evaluating the condition of MPS subjects after several years should be conducted in order to assess the suitability of the distinction between MPS-mild and MPS-severe classifications.

While the sensitivity of the Tanner questionnaire for detecting PD was 100%, its sensitivity for detecting MPS-severe was only 73.3% in our sample, indicating that the Tanner questionnaire is not suitable for screening MPS. Moreover, nonmotor symptoms such as constipation, hallucination, hyposmia, and orthostatic hypotension, which have been considered to be suggestive diagnostic markers for PD, were also not suitable for screening MPS in our sample. Sleep disturbance was also inadequate as a screening marker for MPS. We had a large number of subjects with sleep disturbance in our CTL group. In contrast, GDS scores and our measure of Total AC were independent predictive factors for MPS-severe status when we entered age, duration of education, Tanner questionnaire, GDS, PSQI, and RBDSQ scores, and Total AC as predictors of MPS-severe. Interestingly, when we adopted a cutoff point of more than 6 points on the GDS or less than 40×10^4 of Total AC, diagnostic sensitivities became 100%.

Finally, although depression was associated with the presence of MPS, the presence of depression is not unique to MPS. Depression is a common and disabling disorder in later life [13,27], and while subjects with depression have been reported to have significantly lower scores for activity of daily living (ADL) and quality of life (QOL) than those without depression [28], depression in the elderly has also been reported to be associated with poor cognitive function [29], dementia [30], developing AD [31], premotor symptoms in PD [32], and cerebrovascular disease [33]. Viewing these findings together with the organic pathological changes of the brain, leads us to believe that such brain changes may influence both the mood as well as motor function of the elderly who only have mild symptoms of neurodegenerative disease.

This study has several strengths, including the assessment of a well-characterized cohort of community-dwelling elderly subjects. In addition, our findings are based on validated actigraphy. Limitations include the use of a volunteer cohort and the cross-sectional nature of our study design. An accurate evaluation of sleep disturbances and RBD was not made because we screened subjects based on subjective symptoms without polysomnography. Future longitudinal studies are necessary to clarify the prognosis of MPS and the use of UPDRS rating of 2 to distinguish between MPS and normal aging.

5. Conclusions

Here we report the prevalence of MPS in Japan for the first time. Measuring physical activity using actigraphy and evaluating depression using GDS enabled us to detect MPS, which may lead to the early intervention of neurodegenerative disorders in aging populations.

Authors' roles

Yusuke Uemura: Research project Conception, Organization, Execution, Statistical Analysis Design, Execution, Review and Critique, Manuscript Writing of the first draft, Review and Critique.

Kenji Wada-Isoe: Research project Conception, Organization, Execution, Statistical Analysis Design, Execution, Manuscript Review and Critique.

Satoko Nakashita: Research project Execution.

Kenji Nakashima: Research project Conception, Organization, Execution, Manuscript Review and Critique.

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Brief Communication

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

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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].

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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).

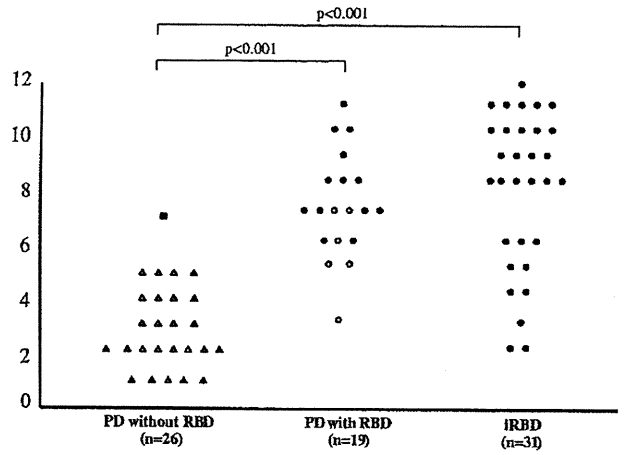

Fig. 1. Comparison of RBDSQ-J scores among the three groups. symbols indicate individual RBDSQ-J scores for each patient among the subject groups (PD without RBD, PD with RBD, iRBD). ●, Violent RBD symptoms; ○, non-violent RBD symptoms; ■, non-violent symptoms without RWA; ▲, RWA with no RBD symptoms;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

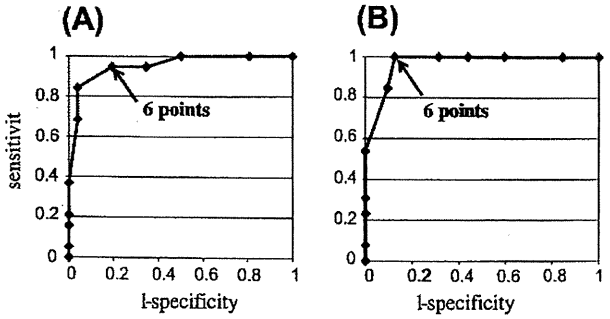

Fig. 2. Receiver-operator characteristics (ROC) curves of PD patients. Curves show distributions of sensitivity and specificity for the existence of any RBD symptom (A) and violent RBD symptoms only (B). The cut-off value of RBDSQ-J scores for the existence of any RBD symptoms in PD patients was 6 points, 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.

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特集 レストレスレッグス症候群

9．二次性レストレスレッグス症候群について

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はじめに

レストレスレッグス症候群(restless legs syndrome：RLS)は，原因不明の特発性と，他疾患に合併して症状が出現する二次性とに分類される．また，一般的にRLSは比較的若年で発症するものと中年期以降に発症するものに分けられるが，二次性RLSは特に中年期以降に発症するRLSに多くみられる．特発性RLSでは家族歴を有する例が多いが，50歳以前のRLSの家族歴が39%であるのに対して，50～64歳では23%，65歳以上では8%と低下していく[1]こともこの事実を表している．

二次性RLSの原因としては多岐にわたるが，神経疾患としてはパーキンソン病(Parkinson's disease：PD)，ミエロパチー，ニューロパチー，遺伝性脊髄小脳変性症(spinocerebellar ataxia：SCA)などが挙げられ，腎障害，リウマチ性疾患，妊娠，鉄欠乏などでも多い(表1)．鉄欠乏は腎障害や妊娠とも関連している可能性がある．最近，RLSの認識が増すとともに，新たな疾患とRLSの合併も報告されている．

表1 二次性RLSの背景

神経疾患	鉄欠乏
パーキンソン病	妊娠
ミエロパチー	その他の内科疾患
ニューロパチー	クローン病
脊髄小脳変性症	慢性肝疾患
多発性硬化症	慢性閉塞性肺疾患
ハンチントン病	サルコイドーシス
家族性痙性対麻痺	原発性副甲状腺亢進症
腎障害	
リウマチ性疾患	
関節リウマチ	
シェーグレン症候群	
線維筋痛症	
強皮症	

PDとRLS

PDとRLSはいずれもドパミン製剤で治療されるため関連性が疑われているが，結論は出ておらず，頻度についても一定していない(表2)．

Ondoらは20.8%[2]，Krishnanらは7.9%[3]，われわれは12%[4]と，PDでRLSの頻度が健常対照群より多い傾向にあるとの報告を行った．

最近，Gomez-Estebanらは21.9%[5]，Leeらも16.3%[6]と報告しており，健常成人より多い傾向にあることを支持している．

一方，TanらはPDにおいてRLSがみられなかったと報告し[7]，CalzettiらもPDとコントロールに差がないと報告している[8]．この相違はRLS症状をwearing off徴候と見誤る可能性があるとともに，既にPD患者が内服している抗パーキンソン病薬がRLS症状を抑制している可能性も示唆される．

PDとRLSの関連因子としては，Ondoらは血清フェリチンの低値を挙げており[2]，Leeらは抗パーキンソン病薬の長期使用をリスク因子[6]と報告している．われわれは特発性RLSとPD合併RLSの比較より，PD合併RLSでは少ない家族歴，

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表2 パーキンソン病患者におけるRLSの有病率

報告者(発表年)	調査地	有病率(%)
Ondo et al(2002)[2]	アメリカ	20.8
Krishnan et al(2003)[3]	インド	7.9
Tan et al(2002)[7]	シンガポール	0
Nomura et al(2006)[4]	日本	12
Gomez-Esteban et al(2007)[5]	スペイン	21.9
Lee et al(2009)[6]	韓国	16.3
Calzetti et al(2009)[8]	イタリア	12.7

表3 腎不全患者によるRLSの有病率

報告者(発表年)	調査地	有病率(%)
Winkelman et al(1996)[10]	アメリカ	20
Takaki et al(2003)[11]	日本	20
Mucsi et al(2005)[12]	ハンガリー	14
Kawauchi et al(2006)[13]	日本	23

少ない周期性四肢運動(periodic leg movements in sleep：PLMS)，治療の反応性の悪さを特徴として確認した[9]．

このように，ドパミン機能障害としてはRLSとPDには類似性があるが，特発性RLSとPD合併RLSは異なった側面をもっている．

腎障害とRLS

RLSの有病率について，慢性腎不全，特に血液透析を導入した患者においては，最近14～23%とする報告がある(表3)[10-13]．また人種差はないと思われていたが，アフリカ系アメリカ人の方が白人よりRLSの頻度が少なかったという報告がある[14]．この点に関しては，さらなる大規模な検討が必要である．

慢性腎不全透析患者におけるRLS発症機序については，透析患者がRLSを発症する時期は血液透析の開始直後が最も多く，透析患者の腎移植によりRLS症状が消失し，腎不全の再増悪につれて再び出現したとの報告や，透析時間の延長や血液透析の導入によりRLS症状が改善する症例もあることなどが報告されている．透析の開始自体がRLSの発症に関与するレベルまで慢性腎不全が進行していることを反映しており，尿毒症性の要因がRLSの発症に関連するとの考えが妥当であるが，鉄欠乏や貧血，遺伝，生活様式の要因も関連が考えられる[15]．

さらに，慢性腎不全に至る背景疾患の関与も考慮される．特に腎不全の原因として糖尿病が最も多いことから，糖尿病性ニューロパチーや尿毒症性ニューロパチーの合併もあり得る．したがって，これらのニューロパチーがRLSの発症に関与している可能性も考慮すべきである．

このように腎障害では，種々の原因でRLSが引き起こされている可能性がある．透析患者においてもRLSやPLMSがQOLを悪化させるため[16]，注意が必要である．

リウマチとRLS

RLS患者は下肢の痛みとして症状を訴えることがあり，リウマチ性疾患は鑑別診断として考慮する必要がある一方，リウマチ性疾患でのRLSの報告も稀であるが存在する[17]．

関節リウマチ(rheumaoid arthritis：RA)の患者では，RLSが25%と高率にみられ，背景因子の検討では，変形性関節症患者と比較した結果から，RLS患者では血清フェリチンが低値で，ニューロパチーが高頻度にみられると報告されている[18]．

Gudbjornssonらは，シェーグレン症候群では24%にRLSがみられたのに対し，RAではわずか

表4　妊婦におけるRLSの有病率

報告者(発表年)	調査地	有病率(%)
Goodman et al(1988)[22]	イギリス	19
Suzuki et al(2003)[23]	日本	20
Manconi et al(2004)[24]	イタリア	26

に2%にみられたのみであったと報告している[19]．線維筋痛症でも患者の25%と高率にRLSがみられたと報告され[20]，強皮症の22%がRLSと報告されている[21]．

このような結果には，RLS診断基準作成以前のものも含まれており，診断精度が低い可能性がある．しかしながら，まだまだ他疾患と比べても検討は少なく，RLSの認知を広め，さらなる検討が必要である．

妊娠とRLS

一般的に妊婦では19～26%のRLS有病率の報告がある(表4)[22-24]．日本での検討でもRLSは20%であったと報告されている[23]．また妊娠前0%であったRLSが妊娠後期には23%まで上昇した報告もあり[25]，妊娠とともにRLSが出現する例が多く，出産6カ月後には6%まで軽快した報告もある[24]．このことより，女性では妊娠中にRLSを発症することが多いといえる．初回の妊娠でRLSを発症し出産後にいったん症状が消失しても，妊娠を繰り返すたびに症状が徐々に増悪し，慢性化する症例もあるため，注意が必要である．

妊婦では鉄欠乏を生じやすい状態にあることから，RLSへの鉄欠乏の関与が指摘されているが，妊婦では血清フェリチン値は低下するもののRLS発現との関連が乏しく，むしろ血清葉酸の低下が妊娠中のRLS発症と関連するとの報告もあり[26]，一定の見解は得られていない．

このように，妊娠はRLSのリスク因子として挙げられる．

鉄欠乏とRLS

貧血や鉄欠乏もRLSとの関係が古くから疑われている．鉄欠乏症は高齢患者におけるRLS発症の重要な寄与因子で，鉄サプリメントにより症状が軽減する可能性が示唆されている[27]．RLSの病態における鉄の役割については，中枢神経における鉄の動態が関与していると考えられている．頭部MRIにて線条体や赤核の貯蔵鉄減少の報告や[28]，RLS患者での脳脊髄液中のフェリチン濃度の低下の報告がある[29]．鉄はドパミン合成過程における律速酵素であるチロシン水酸化酵素の補因子として必要であるとともに，鉄がドパミンD_2レセプターの構成要素であることなどより[30]，中枢の鉄欠乏がドパミン系の障害を引き起こしている可能性が考えられる．

これらの病態では，血清フェリチンが50 μg/L以下のときに鉄の投与で軽快する例が多く，RLS患者には精査が必要である．

ミエロパチーとRLS

ミエロパチーによるRLSとしては，外傷による脊髄損傷，脊髄空洞症，炎症性疾患，腫瘍性疾患などによる一過性，あるいは持続性の症状発現の報告がある．RLSの機序として，脊髄に入力しているA11ドパミン神経の関与も考慮されているため(図1)[31]，ミエロパチーでのRLS出現は注意すべきであり，RLSの主な病態機序に関わっている可能性があり得る．

ニューロパチーとRLS

ニューロパチーとRLSの関連についても，一定の見解は得られていない．糖尿病で17.7～27%とRLSの報告があり[32,33]，ポリニューロパチーが増悪因子として挙げられている[34]．

両者の鑑別が困難な場合には，電気生理学的評価が有用であり，ニューロパチーの程度や原因を詳細に把握することが重要である．

SCAとRLS

遺伝性脊髄小脳変性症(SCA)のCAGリピート

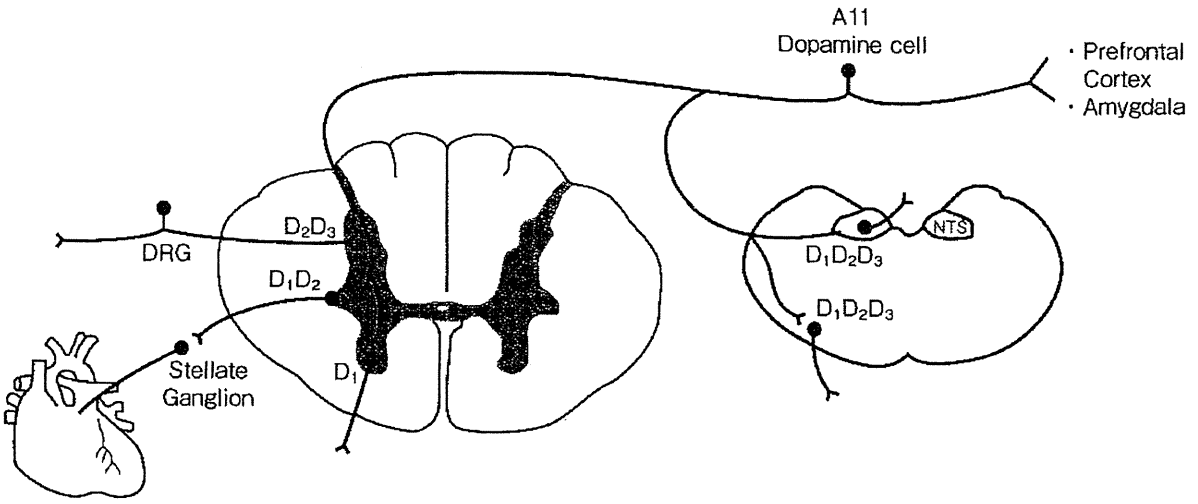

図1　A11ドパミンサーキット[31]

表5　脊髄小脳変性症(SCA)患者におけるRLSの有病率

報告者(発表年)	SCA 1 (%)	SCA 2 (%)	SCA 3 (%)	SCA 6 (%)
Schols et al (1998)[35]	0	18	45	5
Abele et al (2001)[36]	23	27	30	NA
Iranzo et al (2003)[37]	NA	NA	50.5	NA
Boesch et al (2006)[38]	NA	NA	NA	40
Boesch et al (2006)[39]	NA	0	NA	NA
Reimold et al (2006)[40]	25	25	100	NA

SCA：spinocerebellar ataxia，NA：データなし　　Iranzo et al，2007[41]

は脳内の鉄イオンチャンネル機能障害に関連がある．そのためRLSとの関連も示唆されるが，SCAでの調査も小規模なものしかない．その中でSCA 3が最も高頻度であり，30～100%と報告されている(表5)[35-40]．SCAではRLS症状は軽度であり，L-ドーパ治療への反応も良好で，PLMSが高頻度出現することが特徴である．しかし，CAGリピート数や発症年齢，電気生理検査での異常とは関連がなかった．SCAでのRLS出現の病態は明らかでないが，中枢性ドパミン機能障害が疑われる[41]．

その他の神経疾患とRLS

多発性硬化症(multiple sclerosis：MS)では，19%にRLSの合併の報告がある．高齢，長いMSの病歴，原発性進行性タイプ，錐体路徴候などが危険因子として挙げられるが，神経の炎症性損傷が原因と考えられる[42]．またハンチントン病の1家系でのRLSの報告があり[43]，最近RLS症状の4年後にハンチントン病と診断した症例の報告がある[44]．少数の報告であるが，ハンチントン病の早期症状として注意する必要があるのかもしれない．さらに，遺伝性痙性対麻痺の20.5%でRLSの報告もある[45]．このように，神経疾患においてもRLSの合併は多く，今後他疾患での報告の可能性もある．

その他の内科疾患とRLS

神経疾患と同様に，いくつかの内科疾患でのRLS合併の報告がある．クローン病の42.7%[46]，慢性肝疾患の62%[47]，慢性閉塞性肺疾患の29.1%[48]，サルコイドーシスの52%にRLSを認めたとの報告もある[49]．さらに原発性副甲状腺機能亢進症での症例報告もあり[50]，RLSの認知が広がるとともにその他の疾患での報告も増える可能性がある．

おわりに

RLSは頻度の高い病気であることがわかり，病気の認識も広がっている．二次性のRLSには多種の疾患があるが，特発性RLSとの病態が関連している病気も含まれているため，今後も合併疾患との検討が必要であるとともに，RLS症状に注意して診療を行う必要がある．

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多系統萎縮症における睡眠障害—レム睡眠行動障害を含めて*

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Key Words: excessive daytime sleepiness, sleep apnea syndrome, REM sleep behavior disorder

はじめに

多系統萎縮症（multiple system atrophy：MSA）はパーキンソニズム，自律神経障害，小脳症状，錐体路症状等の臨床症状を呈し，レボドパの反応性が乏しく，（黒質線条体，オリーブ橋小脳，自律神経系）等の神経細胞の消失，グリオーシス，嗜銀性細胞封入体の病理変化を特徴とする孤発性の神経変性疾患である．細胞レベルの病因の解明により現在MSAはParkinson病（PD）やLewy小体型認知症と同様にシヌクレイノパチーと分類されている[1]．MSAではしばしば睡眠障害の合併がみられる．PDの51%が睡眠障害を訴えるのに対してMSAでは70%が睡眠障害を訴えている．睡眠分断の訴えが最も多く，53%の患者が睡眠分断を訴えており，早朝覚醒（33%），不眠（20%）と続く[2]．主観的な訴えは客観的な終夜脳波（polysomnography：PSG）で睡眠時間の減少，睡眠効率の低下，レム睡眠や徐波睡眠の減少として確認されている[3~6]．原因としてはLvodopaの低反応による無動症状，疼痛，夜間排尿，周期性四肢運動が睡眠の分断を引き起こし，PSGでの異常として捉えられる[5,7,8]．MSAに特徴的な睡眠障害としては，睡眠関連呼吸疾患とレム睡眠行動障害（REM sleep behavior disorder：RBD）がある．これらは頻度も高く，MSAの一症状と考えられている[1]．

Ⅰ．睡眠関連呼吸疾患

睡眠関連呼吸疾患はMSAに頻度が高く，臨床的にも重大な問題となる[2,5,9~11]．睡眠時呼吸障害は多彩な病像を呈しており，閉塞性無呼吸障害，中枢性無呼吸，脳幹障害による呼吸リズム異常，中枢神経原性の肺胞低換気，低酸素血症における化学受容体の障害[12]などのほか，後輪状披裂筋の神経原性変化による声帯外転麻痺（Gerhardt症候群），および球麻痺や気道感染に基づく呼吸障害であり，これらはしばしば突然死の原因にもなり，生命予後にもかかわる重要な徴候である．夜間の喘鳴や閉塞性無呼吸（objective sleep apnea：OSA）は最も共通の症状であり[4,5]，病態が異なっていてもしばしば同時に起こっている[13]．臨床検査やオーディオモニター付きのPSGで喘鳴は簡単に確認でき，グーグーという低音のいびきのほか，ヒーヒーという高音で“ロバのいななき”と形容される[2,7,11]．喉頭鏡検査で喉頭の狭窄は評価できるが，覚醒時の検査では感度が低く，夜間喘鳴のある患者の声帯運動は正常であったと報告されている[10,11]．そのため，睡眠時を含めた声帯喉頭機能の積極的な評価が必要である．声帯外転麻痺の重症度の評価および治療方針の決定に

* Sleep Disturbances in Multiple System Atrophy Including REM Sleep Behavior Disorder.

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Table 1 Stage and therapy on abductor dysfunction of cord in multiple system atrophy

Stage of abductor paralysis of cord	Movement of cord		Severity of paralysis	Therapy
	Awake	Sleep		
0	normal	No change	normal	observe
1	normal	Paradoxical movement	mild	Nasal CPAP Tracheotomy
2	Limit of abductor	Paradoxical movement	moderate	Tracheotomy
3	Persistent of midline	Persistent of midline	severe	Tracheotomy

は磯崎の分類[14]が有用である．宮本らが示した治療方針をしめす（**Table 1**）[15]．また，この睡眠中の上気道の閉塞の評価には，食道内圧のモニタリングが最も適している[10]．

MSA患者の喘鳴，OSAの正確な頻度は報告によりばらつきがある．多数例の検討では喘鳴はMSAの13～69%[5,16]，OSAは15～37%[4,5]と報告されている．MSA-PよりMSA-Cに喘鳴の頻度が高いとの報告[5]があるが，反対の報告もある[6]．52人に行った検討ではインタビューで19%に夜間の喘鳴があり[2]，PSGで39人に認めていた[4]．MSAの高頻度のOSAは無呼吸による睡眠分断に起因していた[5]．無動症状の重症度を考慮しても重症のMSAが臥位で寝ることが高値のapnea hypopnea index（AHI）に関連していると考えられる．OSA患者の夜間の閉塞イベントは側臥位にすることで改善するとも報告されている[7]．MSAの睡眠呼吸障害の特徴としてMSAでは病気の進行とともにAaDO2開大を伴う低酸素血症が出現し増悪すると共に，声帯のみならずさまざまな部位に気道閉塞が生じていること，無呼吸の指標として頻用されるAHIは罹病期間と相関せず重症度の指標として必ずしも有用でないこと等が示されている[17]．

MSAの睡眠関連呼吸疾患の病因としてもPDと同様に上気道筋の夜間の無動症状である可能性もある[18]．さらに，声帯外転筋の萎縮や麻痺を引き起こす疑核の変性はMSAの吸気性喘鳴を起こすと考えられる[19]．しかし，最近の病理検討でもこれらの所見は確定できていない[20]．また，少数例の筋電図検討（electromyogram：EMG）では，ジストニアと同様に吸気時の声帯内転筋の持続する筋緊張を示し，喉頭の狭窄，吸気流の制限を引き起こしていることが示唆された[21～23]．しかし，大多数のEMGでは麻痺なのか，ジストニアなのかは明らかになっていない．また，喘鳴の存在は死亡率と関連があり，喉頭の閉塞の結果と予想できる突然死のリスクがあげられている[11]．MSAでは，低酸素に対する呼吸応答の障害[12]や睡眠中の呼吸機能を制御するセロトニンやコリン神経の枯渇[24]が呼吸制御の機能障害を起こし，呼吸症状が出現し，喘鳴や無呼吸の増悪をおこしている可能性がある．橋脚被蓋核（pedunclopontine nucleus：PPN）や外背側被蓋核からのコリン神経の変性が視床のコリン神経の欠乏を起こしMSAでの重度なOSAとなっているという報告がある[25]．動物実験の結果の結果もPPNの呼吸パターンの影響が指摘されている[26]．しかし，明確な機序は確立していない．

喘鳴に対する治療としては，気管切開や声門開大術のような侵襲的な治療が現実である．少数例にはボツリヌス毒素が有効であったと報告されているが[23]，日常的な適応には至っていない．現在，喘鳴や無呼吸に対しての非侵襲的な治療としては，continuous positive airway pressure（CPAP）だけが有効な治療である[6,7]．しかし，気管切開術やCPAPでも突然死を完全には防げず，上気道閉塞以外のメカニズムでも突然死が生じることが示されている[27]．さらに，MSAでは睡眠中に中枢性呼吸調節異常が生じ，その結果低酸素血症に伴

う重症不整脈や低酸素脳症，呼吸停止が生じる可能性があることが考えられている[28]．このように，運動症状の重症度が長期間のCPAP治療の制限因子となっているのが現実である[6]．しかし，CPAP療法を行うにあたり治療の効果を十分に発揮しかつ突然死の予防のためにも，CPAPマスクの確実な装着とコンプライアンスの状況に十分な注意が必要である[15]．

II. レム期睡眠行動障害

レム期睡眠行動障害（REM sleep behavior disorder：RBD）はレム睡眠随伴症状であり，MSAで多く認められる睡眠関連症状である．2005年に作成された睡眠障害国際診断分類（international classification of sleep disorders：ICSD）第二版の診断基準[29]において，夢内容の行動化により怪我をしたり，怪我をしてもおかしくないような睡眠中の行動化の病歴があるか，PSG実施中にREM睡眠期に異常な行動化があるかの少なくともどちらかの事象があると共に，PSG上REM sleep without atonia（RWA）の存在が確認されることがRBD診断の必須項目となっている．RBDの約60%は特発性であるが，RBDはシヌクレイノパチーにしばしば関連がある[30]．MSAでは90～100%がPSG確定のRBDである[4,5,31]．特発性RBDの38%までがParkinson関連疾患に発展していた[32]．このように，RBDはパーキンソニズムに数年先行する場合がある[33]．それゆえに，RBDはシヌクレイノパチー等の神経変性疾患の早期症状と考えられている．我々のMSA16人の検討では，11例（68.8%）にRWAを認め，7人が発症前にRBD症状を認めており，発症後にはRWAの出現量は増えるのに対してRBD症状は消失していた．この傾向はTachibanaらにより一症例のMSAで報告されている[34]．この変化は広範な神経変性によるものと考えられる．

現在においてもRBDの病態生理は明らかでない．BoeveらはREM睡眠を促進するREM on（下外側背側核，前青斑核）とREM睡眠を抑制するREM off（中脳水道周辺腹外側灰白質，外側橋被蓋）が相互に干渉してREM睡眠の制御を行い，REM睡眠時には下外側背側核より直接，間接（延髄網様体を介して）的に脊髄前角細胞に抑制を行っているが，下外側背側核の障害により情動系からの出力への抑制が弱くなり，RWAの出現，夢内容の行動化が起こると仮説を立てている（**Fig. 1**）[35]．MSAでは中脳橋のコリンREM on細胞の消失，青斑核ノルアドレナリン細胞の消失，縫線核セロトニン細胞の保持等REM睡眠制御細胞の障害がREM異常を起こしている[36]．このコリンの病態は特発性RBDでのアセチルコリンエステラーゼ阻害薬のdonepezilの効果でも考えられる[37]．また，RBDがドパミン欠乏疾患の一部と考える研究者もいる．機能画像では特発性RBDで黒質線条体のドパミン投射の減少を示している[38,39]．MSA患者でもRBDの重症度と線条体のモノアミン神経の消失とが関連していた[25]．ドパミンの関連は特発性RBDの病理例で黒質，青斑核の神経細胞消失でも見られる[40]．さらに，PDでもRBDはlevodopaの治療後に改善したとの報告もある[41]．黒質線条体投射はPPNへの下方連結によってRBDに関連し，REM制御に重要な役割を示す[42]．MSAでは基底核の機能障害やPPN自体の機能障害，PDと同様の病態である基底核に関連する他の脳幹機能障害があり，RBDの原因となっているのかもしれない[42,43]．動物実験より黒質網様体からPPNへのGABA投射はREM atoniaの制御をしていると考えられている[44]．それゆえに，Parkinson関連疾患で基底核からPPNへのGABAの過剰出力がRBDを引き起こしている可能性はある．しかしながら，MSAでのRBD出現の機序も明確にはなっていない．

RBD治療としては，二重盲検試験は行われていず，RBD関連脱同調を起こすmelatoninの有効性も確立していない[30]．clonazepamはbenzodiazepineがRBDを改善する正確な機序が明らかでなく，OSAを増悪する可能性があるが，治療として選択される[45]．MSAでのアセチルコリンエステラーゼ阻害薬の有効性は不明であるが，検討する価値はあると思われる[30,37]．さらに，ドパミンアゴニストであるpramipexoleで特発性RBDが改善した報告もある[46]が，PDに合併したRBDには効果がなかったとの報告もある[47]．このようにMSAのRBDに対する治療の報告はないが，特発性RBDでの報告より考えると，