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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.

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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).

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

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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.

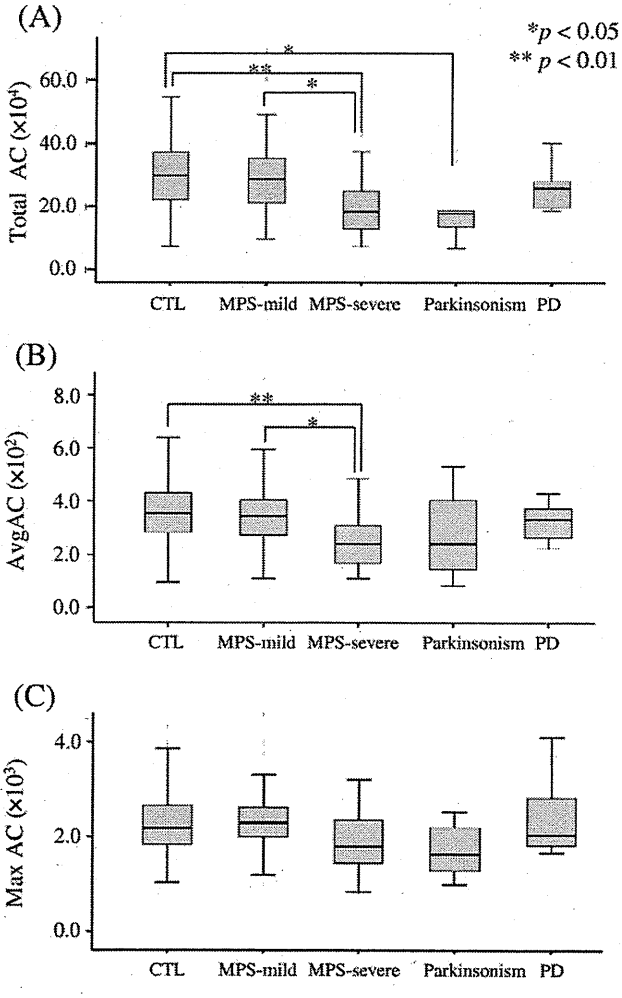

Fig. 1. Comparison of physical activity. The box plots show the median values (thick lines), 25th percentile (lower line of box), and 75th percentile (upper line of box). T bars indicate the 10th and 90th percentiles. Statistical differences were calculated using an ANOVA followed by Tukey tests. CTL: 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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References

[1] Ross GW, Petrovitch H, Abbott RD, Nelson J, Markesbery W, Davis D, et al. Parkinsonian signs and substantia nigra neuron density in decendents elders without PD. Ann Neurol 2004;56:532–9.
[2] Louis ED, Benett DA. Mild parkinsonian signs: an overview of an emerging concept. Mov Disord 2007;22:1681–8.
[3] Liu Y, Stern Y, Chun MR, Jacobs DM, Yau P, Goldman JE. Pathological correlates of extrapyramidal signs in Alzheimer's disease. Ann Neurol 1997;41:368–74.
[4] Louis ED, Tang MX, Schupf N. Mild parkinsonian signs are associated with increased risk of dementia in a prospective, population-based study of elders. Mov Disord 2010;25:172–8.
[5] Louis ED, Brickman AM, DeCarli C, Small SA, Marder K, Schupf N, et al. Quantitative brain measurements in community-dwelling elderly persons with mild parkinsonian signs. Arch Neurol 2008;65:1649–54.
[6] Geroldi C, Ferrucci L, Bandinelli S, Cavazzini C, Zanetti O, Guralnik JM. InCHIANTI Study. Mild cognitive deterioration with subcortical features: prevalence, clinical characteristics, and association with cardiovascular risk factors in community-dwelling older persons (The InCHIANTI Study). J Am Geriatr Soc 2003;51:1064–71.
[7] Zhou G, Duan L, Sun F, Yan B, Ren S. Association between mild parkinsonian signs and mortality in an elderly male cohort in China. J Clin Neurosci 2010;17:173–6.
[8] Bennett DA, Beckett LA, Murray AM, Shannon KM, Goetz CG, Pilgrim DM, et al. Prevalence of parkinsonian signs and associated mortality in a community population of older people. N Engl J Med 1996;334:71–6.
[9] Louis ED, Luchsinger JA, Tang M-X, Mayeux R. Parkinsonian signs in older people: prevalence and associations with smoking and coffee consumption. Neurology 2003;61:24–8.
[10] Louis ED, Schupf N, Manly J, Marder K, Tang MX, Mayeux R. Association between mild parkinsonian signs and mild cognitive impairment in a community. Neurology 2005;64:1157–61.
[11] Wada-Isoe K, Uemura Y, Suto Y, Doi K, Imamura K, Hayashi A, et al. Prevalence of dementia in the rural island town of Ama-cho, Japan. Neuroepidemiology 2009;32:101–6.
[12] Tanner CM, Gilley DW, Goetz CG. A brief screening questionnaire for parkinsonism. Ann Neurol 1990;28:267–8 Abstract.
[13] Niino N, Imaizumi T, Kawakami N. A Japanese translation of the Geriatric Depression Scale. Clin Gerontol 1991;10:85–6.
[14] Schreiner AS, Hayakawa H, Morimoto T, Kakuma T. Screening for late life depression: cut-off scores for the Geriatric Depression Scale and the Cornell Scale for Depression in Dementia among Japanese subjects. Int J Geriatr Psychiatry 2003;18:498–505.
[15] Buysse DJ, Reynolds III CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 1989;28:193–213.
[16] Stiasny-Kolster K, Mayer G, Schäfer S, Möller JC, Heinzel-Gutenbrunner M, Oertel WH. The REM sleep behavior disorder screening questionnaire—a new diagnostic instrument. Mov Disord 2007;22:2386–93.
[17] 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.
[18] de Rijk MC, Rocca WA, Anderson DW, Melcon MO, Breteler MM, Maraganore DM. A population perspective on diagnostic criteria for Parkinson's disease. Neurology 1997;48:1277–81.
[19] Hughes AJ, Ben-Shlomo Y, Daniel SE, Lees AJ. What features improve the accuracy of clinical diagnosis in Parkinson's disease: a clinical pathological study. Neurology 1992;42:1142–6.
[20] Louis ED, Tang M, Mayeux R. Factor structure of parkinsonian signs in the community-dwelling elderly. Mov Disord 2004;19:268–72.
[21] Richards M, Stern Y, Mayeux R. Subtle extrapyramidal signs can predict the development of dementia in elderly individuals. Neurology 1993;43:2184–8.
[22] McPartland RJ, Kupfer DJ, Foster FG, Reisler KL, Matthews G. Objective measurement of human motor activity: a preliminary normative study. Biotelemetry 1975;2:317–23.
[23] Katayama S. Actigraph analysis of diurnal motor fluctuations during dopamine agonist therapy. Eur Neurol 2001;46:11–7.
[24] van Someren EJ, Vonk BF, Thijssen WA, Speelman JD, Schuurman PR, Mirmiran M, et al. A new actigraph for long-term registration of the duration and intensity of tremor and movement. IEEE Trans Biomed Eng 1998;45:386–95.
[25] Whitehead DL, Davies AD, Playfer JR, Turnbull CJ. Circadian rest-activity rhythm is altered in Parkinson's disease patients with hallucinations. Mov Disord 2008;15:1137–45.
[26] Comella CL, Morrissey M, Janko K. Nocturnal activity with nighttime pergolide in Parkinson disease: a controlled study using actigraphy. Neurology 2005;64:1450–1.
[27] Kuzuya M, Masuda Y, Hirakawa Y, Iwata M, Enoki H, Hasegawa J, et al. High prevalence rate of depression among community-dwelling frail elderly Japanese. Nippon Ronen Igakkai Zasshi 2006;43:512–7.
[28] Wada T, Ishine M, Sakagami T, Okumiya K, Fujisawa M, Murakami S, et al. Depression in Japanese community-dwelling elderly—prevalence and association with ADL and QOL. Arch Gerontol Geriatr 2004;39:15–23.
[29] Colenda CC, Legault C, Rapp SR, DeBon MW, Hogan P, Wallace R, et al. Psychiatric disorders and cognitive dysfunction among older, postmenopausal woman: results from the Women's Health Initiative Memory Study. Am J Geriatr Psychiatry 2010;18:177–86.
[30] Rosness TA, Barca ML, Engedai K. Occurrence of depression and its correlates in early onset dementia patients. Int J Geriatr Psychiatry 2010;25:704–11.
[31] Ownby RL, Crocco E, Acevedo A, John V, Loewenstein D. Depression and risk for Alzheimer disease: systematic review, meta-analysis, and metaregression analysis. Arch Gen Psychiatry 2006;63:530–8.
[32] Tolosa E, Compta Y, Gaig C. The premotor phase of Parkinson's disease. Parkinsonism Relat Disord 2007;13:S2–7 Suppl.
[33] Mayo NE, Fellows LK, Scott SC, Cameron J, Wood-Dauphinee S. A longitudinal view of apathy and its impact after stroke. Stroke 2009;40:3299–307.

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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.
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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 ⩾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).

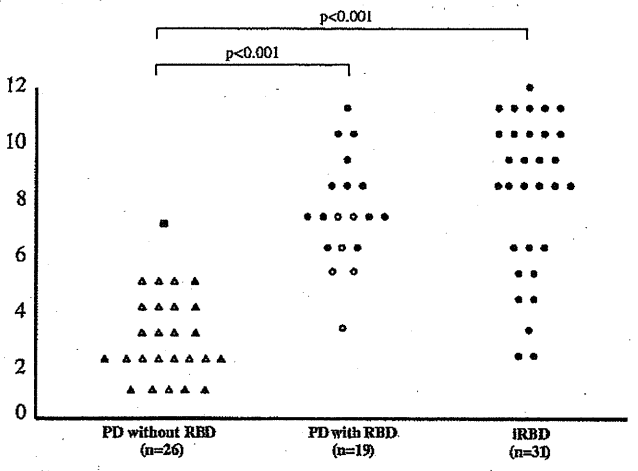

Fig. 1. Comparison of RBDSQ-J scores among the three groups. symbols indicate individual RBDSQ-J scores for each patient among the subject groups (PD without RBD, PD with RBD, iRBD). ●, Violent RBD symptoms; ○, non-violent RBD symptoms; ■, non-violent symptoms without RWA; ▲, RWA with no RBD symptoms;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

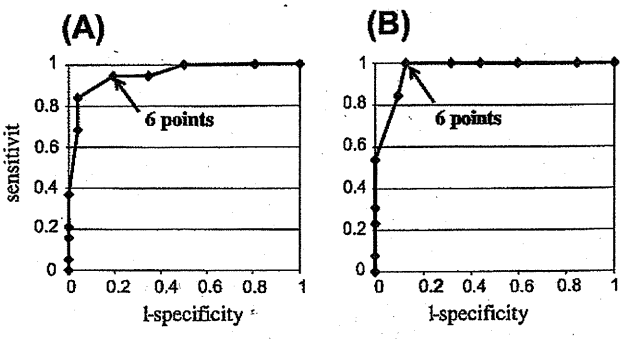

Fig. 2. Receiver-operator characteristics (ROC) curves of PD patients. Curves show distributions of sensitivity and specificity for the existence of any RBD symptom (A) and violent RBD symptoms only (B). The cut-off value of RBDSQ-J scores for the existence of any RBD symptoms in PD patients was 6 points,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

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Regular Article

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

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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

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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

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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.

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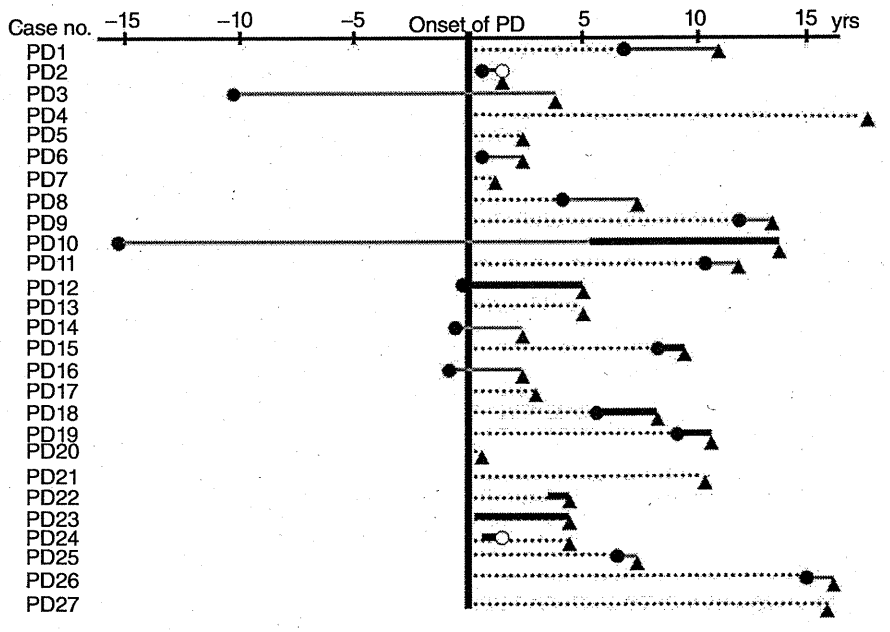

Figure 1. Self-reported onset and course of rapid eye movement (REM) sleep behavior disorder (RBD) symptoms in Parkinson's disease (PD) patients with REM sleep without atonia on polysomnogram ($n = 27$). Dotted lines (·····) indicate symptom-free periods for RBD. Thick black lines (▬) indicate periods 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

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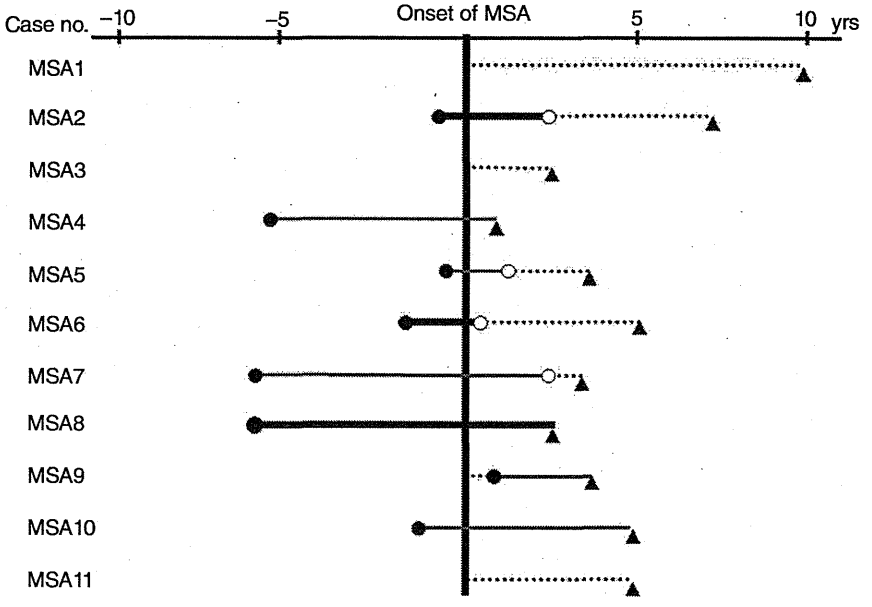

Figure 2. Self-reported onset and course of rapid eye movement (REM) sleep behavior disorder (RBD) symptoms in multiple system atrophy (MSA) patients with REM sleep without atonia on polysomnogram ($n = 11$). Dotted lines (.....) indicate symptom-free periods for RBD. Thick black lines (▬) indicate periods 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.

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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.

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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.

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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.

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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.

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Large-scale replication and heterogeneity in Parkinson disease genetic loci

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Editorial, page 619

Supplemental data at www.neurology.org

Supplemental Data

ABSTRACT

Objective: Eleven genetic loci have reached genome-wide significance in a recent meta-analysis of genome-wide association studies in Parkinson disease (PD) based on populations of Caucasian descent. The extent to which these genetic effects are consistent across different populations is unknown.

Methods: Investigators from the Genetic Epidemiology of Parkinson's Disease Consortium were invited to participate in the study. A total of 11 SNPs were genotyped in 8,750 cases and 8,955 controls. Fixed as well as random effects models were used to provide the summary risk estimates for these variants. We evaluated between-study heterogeneity and heterogeneity between populations of different ancestry.

Results: In the overall analysis, single nucleotide polymorphisms (SNPs) in 9 loci showed significant associations with protective per-allele odds ratios of 0.78–0.87 (*LAMP3*, *BST1*, and *MAPT*) and susceptibility per-allele odds ratios of 1.14–1.43 (*STK39*, *GAK*, *SNCA*, *LRRK2*, *SYT11*, and *HIP1R*). For 5 of the 9 replicated SNPs there was nominally significant between-site heterogeneity in the effect sizes (I^2 estimates ranged from 39% to 48%). Subgroup analysis by ethnicity showed significantly stronger effects for the *BST1* (rs11724635) in Asian vs Caucasian populations and similar effects for *SNCA*, *LRRK2*, *LAMP3*, *HIP1R*, and *STK39* in Asian and Caucasian populations, while *MAPT* rs2942168 and SYT11 rs34372695 were monomorphic in the Asian population, highlighting the role of population-specific heterogeneity in PD.

Conclusion: Our study allows insight to understand the distribution of newly identified genetic factors contributing to PD and shows that large-scale evaluation in diverse populations is important to understand the role of population-specific heterogeneity. ***Neurology*® 2012;79:659–667**

GLOSSARY

CI = confidence interval; **GEO-PD** = Genetic Epidemiology of Parkinson's Disease; **GWAS** = genome-wide association studies; **HWE** = Hardy-Weinberg equilibrium; **MALDI-TOF** = matrix-assisted laser desorption/ionization time-of-flight; **MSA** = multiple system atrophy; **OR** = odds ratio; **PD** = Parkinson disease; **SNP** = single nucleotide polymorphism.

Genome-wide association studies (GWAS) have provided tangible gains in understanding the genetic architecture of complex diseases,[1,2] including Parkinson disease (PD).[3] Several GWAS have been conducted in PD in Caucasian populations and only 1 in the Asian population.[3–11] Consistent and reproducible association signals were confirmed in α-synuclein (*SNCA*), leucine-rich repeat kinase 2 (*LRRK2*), and microtubule-associated protein tau (*MAPT*), thus underscoring the importance of these 3 genes in the pathophysiology of the common sporadic forms of PD.[3–10,12] In addition to that, different studies have provided some evidence for an association for *BST1*, *GAK*, and *HLA-DRB5* with PD.[6–9,13]

A recently published GWAS meta-analysis in PD increased the number of identified PD genetic loci to 11.[14] This study reported significant between-study heterogeneity for some of the 11 genetic loci[14] even though data were restricted to Caucasian descent populations.

It is important to establish whether the 11 genetic loci that have been postulated to be associated with PD are replicated when tested with direct genotyping in a larger spectrum of diverse populations. The consistency or lack thereof of the genetic effects of these genetic

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variants across different populations may help to determine whether they represent genuine loci for PD susceptibility and whether they can be used for risk prediction across these diverse populations.[15] To gain further insight into genetic factors contributing to PD across different populations and define the implications of between-population heterogeneity, we performed a large-scale replication study within the GEO-PD consortium.

METHODS

Consortium. Investigators from the Genetic Epidemiology of PD (GEO-PD) Consortium were invited to participate in this study. A total of 21 sites representing 19 countries from 4 continents agreed to contribute DNA samples and clinical data for a total of 17,705 individuals (8,750 cases and 8,955 controls). Healthy individuals matched for age and gender served as controls. They underwent neurologic examination and were excluded from the study whenever there was clinical evidence for any extrapyramidal disorder.

Genotyping. We selected 1 SNP per each gene locus, exactly as they were proposed by the recently published GWAS meta-analysis.[14] Genotyping was performed by a central genotyping core (Department of Human Genetics, Helmholtz Zentrum, Munich). Each site provided 100–200 ng of DNA to the laboratory core. In total 11 SNPs located in and around the genes encoding *SYT11*, *ACMSD*, *STK39*, *LAMP3*, *GAK*, *BST1*, *SNCA*, *HLA-DRB5*, *LRRK2*, *HIP1R*, and *MAPT* were genotyped. The genotyping core was blinded to case-control status of each site. Genotyping was performed using a matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry on a MassArray system (Sequenom, San Diego, CA). Cleaned extension products were analyzed by a mass spectrometer (Bruker Daltronik, USA) and peaks were identified using the MassArray Typer 4.0.2.5 software (Sequenom). Assays were designed by the AssayDesigner software 4.0 (Sequenom) with the default parameters for the iPLEX Gold chemistry and the Human GenoTyping Tools ProxSNP and PreXTEND (Sequenom). All variants were genotyped in 1 multiplex assay. An experienced investigator blinded to case or control status of the samples visually checked genotype clustering. The average call rate of the variants was >97%.

In order to further enrich the samples of Asian ancestry populations, we also included GWAS data from a Japanese population (988 cases, 2,521 controls).[6] We used r^2 threshold of 0.8–1.0 to select proxy SNPs from the Japanese GWAS. Using this threshold, we were able to capture only 3 SNPs from *BST1*, *SNCA*, and *LRRK2* genes.

Standard protocol approvals, registrations, and patient consents. The local Ethics Committee approved the study. All participants signed an informed consent.

Analysis. An exact test was used to assess whether the genotype distributions for each SNP deviated from Hardy-Weinberg equilibrium (HWE) among controls; each site was tested separately and deviation from HWE was considered significant at <0.01. We excluded data from sites where the missing rate was >5%. For our analysis, we adhered to the same allele coding as in the previous GWAS meta-analysis.[14]

For consistency effect estimates based on minor vs major allele contrast were computed. We used an additive model adjusted for age and gender to obtain effect estimates. Results were then synthesized using fixed and random effects models. Fixed effect models assume that the genetic effect is the same in populations from different sites and that observed differences are due to chance alone. For associations showing between-study heterogeneity, fixed effect estimates yield narrower confidence intervals (CIs) and smaller p values as compared to random effects models, which incorporate between-study heterogeneity.[16–18] Fixed effects analysis tests the null hypothesis of no association in all studied populations that are analyzed. Routinely, this assumption is used in GWAS settings to increase the power of meta-analysis to detect associations that may exist in some (at least 1) population. However, in presence of heterogeneity the effects may differ substantially in different populations and not all populations may show a genetic effect for the variant of interest. Random effects models allow the genetic effects might be different due to genuine heterogeneity that may exist across different sites. Random effects calculations take into account the estimated between-study heterogeneity. We used the inverse variance method for fixed effects models. Cochran Q test of homogeneity and the I^2 metric were used to evaluate the between-site heterogeneity. The Q statistics follows χ^2-based distribution with k −1 degrees of freedom (k = number of studies). I^2 is estimated by the ratio (Q-df)/Q, where *df* is degrees of freedom. The I^2 metric ranges from 0% to 100% and measures the proportion of variability that is beyond chance. Typically estimates of I^2 <25% are considered to reflect little or no heterogeneity, 25%–50% moderate heterogeneity, 50%–75% large heterogeneity, and >75% very large heterogeneity. It should be acknowledged that I^2 can have large uncertainty in its estimation especially for variants with low minor allele frequency. Therefore, we also estimated the 95% CI of I^2.[17]

The overall main analysis considered all sites and populations irrespective of ancestry. Then, we separately analyzed Caucasian and Asian sites and we compared the genetic effects in these 2 major ancestry groups.

The SNPs evaluated in the recently published GWAS meta-analysis are common with minor allele frequencies varying from 13% to 46%,[14] except for SNP, rs34372695 (SYT11) where the minor allele frequency is 2%. Therefore, based on minor allele frequency and effect estimates obtained in the GWAS meta-analysis,[14] power calculations showed that our study would have at least 99% power to detect an allele-based odds ratio (OR) of 1.2 for minor allele frequencies of 10% or higher for $\alpha = 0.05$. Based on genome-wide significance level ($\alpha = 5 \times 10^{-8}$), our study would have 43% power to detect an allele-based OR of 1.2 for minor allele frequency of 10%, but it would be 99% for same minor allele frequency and on OR of 1.4. Power would be only 69% for a minor allele frequency of 2% and OR of 1.2, but it would be 99% for the same minor allele frequency of 2% and an OR of 1.5.

Meta-analyses were performed using STATA 9.0 (Stata Corp., College Station, TX) and Review Manager 4.2.7. p Values are 2-tailed.

RESULTS

Characteristics of sites and overall database. Twenty-one sites contributed a total of 8,750 cases and 8,955 controls. Characteristics of all participating sites are shown in table 1. Most sites contributed participants of Caucasian ancestry (n = 16); 5 sites (counting also the GWAS performed in the Jap-

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Table 1 Description of datasets contributed by each study site

Site	Country	No.	Case	Control	Male (%)	Female (%)	Mean AAO	Mean age at study	Diagnostic criteria
Annesi	Italy	394	197	197	204 (51.7)	190 (48.2)	61.5	63.7	UKPDBB
Brice[a]	France	505	272	233	302 (59.8)	203 (40.1)	47.6	57.8	UKPDBB
Bozi	Greece	222	114	108	107 (48.1)	115 (51.8)	69.9	74.5	UKPDBB
Wszolek	US	1,518	692	826	794 (52.3)	724 (47.6)	64.4	71.7	UKPDBB
Garraux	Belgium	82	68	14	45 (54.8)	37 (45.1)	62.1	69.6	UKPDBB
Hadjigeorgiou	Greece	714	357	357	379 (53.0)	335 (46.9)	63.4	63.7	UKPDBB
Jeon	Korea	749	408	341	314 (41.9)	435 (58.0)	57.6		UKPDBB
Opala	Poland	629	352	277	340 (54.0)	288 (45.7)	50.2	68.1	UKPDBB
Lynch	Ireland	740	368	372	340 (45.9)	400 (54.0)	50.5	70.7	UKPDBB
Lin	Taiwan	320	160	160	160 (50)	160 (50)	62.0	70.8	UKPDBB
Facheris	Italy	181	114	67	86 (47.5)	95 (52.4)	63.0		UKPDBB
Maraganore	US	1,024	801	223	600 (58.5)	361 (35.3)	59	74.7	Bower
Mellick	Australia	2,024	1,012	1,012	1,042 (51.4)	981 (48.4)	59	72.2	Bower
Morrison[a]	England	1,120	766	354	606 (54.1)	514 (45.8)	66.1		UKPDBB
Mok	China	436	260	176	264 (60.5)	170 (38.9)		63.5	UKPDBB
Aasly	Norway	1,278	656	622	721 (56.4)	557 (43.5)	58.8	72.9	UKPDBB
Wirdefeldt	Sweden	299	83	216	147 (49.1)	152 (50.8)	65.8	71.4	Gelb
Van Broeckhoven	Belgium	1,010	501	509	500 (49.5)	509 (50.3)	60.5	66.3	Pals/Gelb
Rogaeva	Canada	560	387	173	303 (54.1)	257 (45.8)	49.7	64.2	UKPDBB
Tan	Singapore	391	194	197	244 (62.4)	147 (37.5)	59.7	54.0	UKPDBB
Toda	Japan	3,509	988	2,521	1,844 (52.6)	1,665 (47.4)	58.7	66.0	UKPDBB
Total		17,705	8,750	8,955			59.5	67.6	

Abbreviations: AAO = age at onset; GWAS = genome-wide association studies; UKPDBB = UK Parkinson's Disease Brain Bank.
[a] Also included in the previously published GWAS.[7,8]

anese population[6]) included participants of Asian ancestry. We excluded 1 site with 114 cases and 67 controls from the analysis due to a plate layout error. The median age at onset was 59 years and median age at examination was 67 years.

We observed that for one site, effect estimates for all SNPs were "inverse" as compared to other Caucasian sites. Allele flipping for one particular site in the same Caucasian descent might reflect error in sampling ascertainment and is unlikely to reflect genuine effects.[19] This site (n = 181) was therefore excluded from further analyses. Overall, genotype call rates were >97%. The genotype distribution for each SNP in the controls of each site showed no departure from HWE, except for rs6599388 (*GAK*) in samples from 4 Asian sites. We therefore excluded this SNP (rs6599388) from analyses in the Asian population.

Overall data synthesis. We observed consistent and reproducible associations for *SNCA*, *LRRK2*, *MAPT*, *BST1*, *GAK*, *STK39*, *SYT11*, *LAMP3*, and *HIP1R* loci but not for *ACMSD* (rs10928513) or *HLA-DRB5* (rs3129882) where the per-allele OR was very close to the null (1.02 and 0.95, respectively) and statistically nonsignificant (table 2). Thus we provide unequivocal support for the involvement of these newly identified genetic loci in the pathogenesis of PD.

Summary effect estimates were generally comparable with the previous GWAS meta-analysis results (table 2), although effect estimates in this study were stronger for STK39 and somewhat weaker for *LRRK2* compared to the previous GWAS meta-analysis.[14] Exclusion of 1,625 samples that overlap with the previously published GWAS did not change any of the estimates (table e-1 on the *Neurology*® Web site at www.neurology.org). The protective per-allele OR ranged from 0.78 to 0.87 (*LAMP3*, *BST1*, and *MAPT*) and the susceptibility per-allele OR ranged from 1.14 to 1.43 (*STK39*, *GAK*, *SNCA*, *LRRK2*, *SYT11*, and *HIP1R*). Cochran Q statistics were nominally significant for *STK39*, *LAMP3*, *BST1*, and *SNCA* with I^2 estimates ranging from 39% to 48%. The heterogeneity reflected primarily differences in the magnitude of the effect sizes across different sizes, while the direction of the effect was consistent in all sites, with rare exceptions.

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