Parkinson's Disease with and without REM Sleep Behaviour Disorder: Are There Any Clinical Differences?

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Key Words

REM sleep behaviour disorder · Parkinson's disease · Autonomic nervous system

Abstract

Rapid eye movement sleep behaviour disorder (RBD) may serve as a useful indicator to approach Parkinson's disease (PD); however, PD patients do not always exhibit RBD. We wondered whether the presence of RBD would be reflected in the expansion of PD lesions and represent the same PD entity. We examined the clinical differences between PD with and without RBD and studied the frequency of RBD-like symptoms (RBD-s) and clinical differences in 150 PD patients, including 81 patients (54.0%) who satisfied the *International Classification of Sleep Disorders, Revised*, minimum clinical criteria for RBD. RBD-s preceding the appearance of parkinsonism were found in 44.4% of patients. Statistically, the presence of RBD-s was associated with ages above 65 years, male gender, constipation, dopa-induced dyskinesia and 'sleep attack', with odds ratios of 3.709, 2.469, 2.184, 5.046 and 6.562, respectively. No differences were found between the 2 groups with regard to symptoms at PD onset, disease duration, Hoehn-Yahr stage, hallucination, dementia, wearing-off, orthostatic hypotension, cerebral blood flow and antiparkinsonism drugs. In the early stage, RBD and autonomic system dysfunction are important factors in the progression of PD.

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Introduction

Rapid eye movement (REM) sleep behaviour disorder (RBD) is characterized by a loss of normal skeletal muscle atonia and involves complex motor activity occurring specifically during REM sleep in association with dream mentation. RBD can be idiopathic or can be associated with degenerative neurological disorders, particularly multiple-system atrophy, dementia with Lewy bodies (DLB) and Parkinson's disease (PD) [1]. In previous studies, the histopathology of patients with RBD revealed incidental Lewy body disease [2], while 38% of RBD patients aged ≥ 50 years were eventually diagnosed with PD [3]. Since RBD may serve as an early indicator of PD, the detection of this symptom could enable the treatment of PD with novel drugs to prevent progression to full-blown PD. However, PD patients do not always exhibit RBD; in fact, this symptom is only observed in approximately one third to one half of PD patients [1, 4, 5]. We wondered whether the presence of RBD would be reflected in the pathology of PD and represent the same PD entity. Therefore, we examined the frequency of RBD-like symptoms (RBD-s) in PD patients and investigated the clinical differences between PD with and without RBD-s by clinical interviews.

Methods and Statistical Analysis

The subjects comprised patients who satisfied Calne's diagnostic criteria for clinically possible or clinically probable PD [6], with Hoehn-Yahr stage I, II, III or IV. PD patients with Hoehn-Yahr stage V were excluded because some patients lived in a nursing home and could not be observed during their nocturnal sleep. Patients with secondary or symptomatic parkinsonism and DLB patients who satisfied the DLB consensus criteria of the Third and Fourth Congress of DLB [7, 8] were also excluded. Clinical interviews were answered by the PD patients and their bed partners or caregivers. We recruited 150 PD patients between June 2006 and May 2007.

The following 3 conditions were investigated: (1) abnormal movements during sleep, assessed by a structured questionnaire to determine the frequency and type of movement (e.g. crying, thrashing the arms and legs about, walking and hitting); (2) a strong urge to move the legs when relaxing and an inability to fall asleep, except during the day (minimal criteria for restless legs syndrome [9]), and (3) 'sleep attack' while engaged in activities such as eating, speaking or driving a car.

The clinical findings were reviewed by board-certified neurologists in our department. The following factors were examined: sex, age, age at onset, initial symptoms, Hoehn-Yahr stage, hallucination, dementia (Mini-Mental Score <23 points), wearing-off, dopa-induced dyskinesia (DID), orthostatic hypotension (pressor medication), constipation (cathartic medication), restless legs syndrome, order of medications and first medication, anaemia (decreased haemoglobin, -2 SD), the heart-to-mediastinum uptake ratio (H/M ratio) of meta-iodobenzylguanidine (MIBG) scintigraphy and cerebral blood flow determined by single-photon-emission computed tomography (SPECT). MIBG scintigraphy using ^{123}I -MIBG (111 MBq) was used to determine the H/M ratio. SPECT with 600 MBq $^{99\text{m}}\text{Tc}$ (Neurorite) was performed and evaluated by a radiological statistical analysis software (Easy Z-Score Imaging System).

RBD-s were confirmed according to the clinical *International Classification of Sleep Disorders, revised* (ICSD-R), minimal diagnostic criteria [10]; however, the current criteria require polysomnography. Therefore, the inter-group differences were examined depending on the presence of RBD-s. The differences in clinical demographic characteristics between PD patients with and those without RBD-s (RBD and non-RBD groups, respectively) were compared using an exact test. The inter-group differences with regard to sex, symptoms at onset, hallucination, dementia, constipation, wearing-off, DID, orthostatic hypotension, first medication and anaemia were investigated using Fisher's χ^2 test. The levodopa, dopamine agonist, amantadine, selegiline and trihexyphenidyl doses and the Hoehn-Yahr stage were analysed by the Wilcoxon test. Age, age at onset, disease duration and blood flow were analysed by an unpaired t test. A multivariate logistic regression analysis was used to study the individual role of each factor, including age, sex, disease duration and Hoehn-Yahr stage, which exhibited statistically significant differences in the t test and Wilcoxon test. Furthermore, the relationship between the history of RBD and factors such as hallucination, dementia, wearing-off, DID, orthostatic hypotension, constipation, 'sleep attack' and each antiparkinsonism drug was investigated using a logistic model adjusted for age, sex, disease duration and Hoehn-Yahr stage. Values of $p < 0.05$ were regarded as statistically significant. These statistical data were analysed using SPSS version 11 for Windows.

Results

The mean age of the 150 PD patients (70 men, 80 women) was 68.5 ± 9.8 years and that at PD onset was 62.0 ± 10.8 years, with a disease duration of 6.4 ± 4.6 years (table 1). The Hoehn-Yahr stage distribution of the patients was as follows: stage I, $n = 3$; II, $n = 26$; III, $n = 96$ and IV, $n = 25$. Of the 150 patients, 13 (8.7%) were not receiving any medication. Levodopa with carbidopa or benserazide was administered as the initial medication to 87 (58.0%) patients and to 123 (82.0%) patients at the time of the interview; the maintenance dose was 330.6 ± 185.0 mg. A dopamine agonist was administered to 19 (12.7%) patients as the initial medication and to 95 (63.3%) patients at the time of the interview. Trihexyphenidyl was administered to 24 (16.0%) patients as the initial medication and to 40 (26.7%) patients at the time of the interview. Amantadine was administered to 9 (6.0%) patients as the initial medication and to 39 (26.0%) patients at the time of the interview. In some cases, these drugs were administered together even at the first medication.

Eighty-one PD patients (54.0%) met the ICSD-R minimal clinical diagnostic criteria for RBD (table 1). The duration of RBD-s was 6.8 ± 10.1 years. RBD-s preceding the appearance of parkinsonism were reported in 36 patients (44.4%) in the RBD group. The mean age was higher in the RBD group (70.6 ± 8.1 years) than in the non-RBD group (66.0 ± 11.1 years; t test, 0.004, $\geq 65/\leq 64$; odds ratio (OR), 3.709; 95% confidence interval (CI), 1.701–8.087; $p = 0.001$). The frequency of RBD-s increased with age ($y = -43.09 + 1.35x$). The mean age at the onset of RBD-s was 64.0 ± 12.2 years. Men exhibited a higher prevalence of RBD-s; 64.3% (45 patients) of men and 45.0% (36 patients) of women had RBD-s (Fisher's exact test, $p = 0.022$; OR, 2.469; 95% CI, 1.214–5.025; $p = 0.013$). The age at PD onset was 63.5 ± 9.5 and 60.2 ± 12.0 years in the RBD and non-RBD groups, respectively (t test, $p = 0.060$). The mean duration of parkinsonism was 6.9 ± 4.9 and 5.8 ± 4.2 years in the RBD and non-RBD groups, respectively (t test, $p = 0.013$, $\geq 6.0/<6.0$; OR, 1.654; 95% CI, 0.804–3.406; $p = 0.172$). The Hoehn-Yahr stage at the examination was 3.0 ± 0.6 and 2.8 ± 0.6 in the RBD and non-RBD groups, respectively (Wilcoxon test, $p = 0.050$). The duration to progress to the next Hoehn-Yahr stage was 3.4 ± 2.3 and 3.3 ± 2.2 years in the RBD and non-RBD groups, respectively. In the RBD and non-RBD groups, the symptoms at onset included tremors in 63.0 and 65.2% of the patients, bradykinesia in 28.4 and 21.7% of the patients and gait disturbance in 4.9 and 10.1% of the patients, respectively. Other symptoms included

Table 1. Patient background and medications according to history and logistic regression of RBD-s

Variables	RBD-s history (+) (n = 81)	RBD-s history (–) (n = 69)	Comparison p value	Logistic regression ¹					
				category point estimate	95% CI	p value			
<i>Background</i>				age at interview					
Age, years				≥65/≤64					
Interview	70.6 ± 8.1	66.0 ± 11.1	0.004 ²	3.709	1.701–8.087	0.001			
PD onset	63.5 ± 9.5	60.2 ± 12.0	0.060 ²						
RBD onset	64.0 ± 12.2	–	–						
Sex				male/female					
Male	45 (55.5)	25 (36.2)	0.022 ³	2.469	1.214–5.025	0.013			
Female	36 (44.5)	44 (63.8)							
Duration of PD at interview, years				≥6.0/<6.0					
Mean ± SD	6.9 ± 4.9	5.8 ± 4.2	0.013 ²	1.654	0.804–3.406	0.172			
Hoehn-Yahr stage				≥III/≤II					
I	1 (1.2)	2 (2.9)	0.050 ⁴	1.083	0.435–2.692	0.864			
II	11 (13.6)	15 (21.7)							
III	52 (64.2)	44 (63.8)							
IV	17 (21.0)	8 (11.6)							
Mean ± SD	3.0 ± 0.6	2.8 ± 0.6							
<i>Medication at interview</i>									
Levodopa, mg/day									
No use	13 (18.0)	14 (20.3)	0.212 ⁴						
<300	34 (42.0)	33 (47.8)							
≥300	34 (42.0)	22 (31.9)							
Pergolide, µg/day									
No use	65 (80.2)	60 (87.0)	0.265 ⁴						
<1,000	8 (9.9)	5 (7.2)							
≥1,000	8 (9.9)	4 (5.8)							
Cabergoline, mg/day									
No use	60 (74.1)	52 (75.4)	0.712 ⁴						
<3.0	11 (13.6)	7 (10.1)							
≥3.0	10 (12.3)	12 (17.4)							
Pramipexole, mg/day									
No use	56 (69.1)	50 (72.5)	0.722 ⁴						
<2.0	15 (18.5)	10 (14.5)							
≥2.0	10 (12.3)	9 (13.0)							
Selegiline, mg/day									
No use	59 (72.8)	52 (75.4)	0.746 ⁴						
<5.0	7 (8.6)	5 (7.2)							
≥5.0	15 (18.5)	12 (17.4)							
Amantagine, mg/day									
No use	55 (67.9)	56 (81.2)	0.078 ⁴						
<150	6 (7.4)	2 (2.9)							
≥150	20 (24.7)	11 (15.9)							
Trihexyphenidyl, mg/day									
No use	58 (71.6)	52 (75.4)	0.616 ⁴						
<4.0	7 (8.6)	5 (7.2)							
≥4.0	16 (19.8)	12 (17.4)							

Figures in parentheses are percentages.

¹ Logistic model adjusted for age, sex, disease duration and Hoehn-Yahr stage. ² t test. ³ Fisher's exact test. ⁴ Wilcoxon test.

Table 2. Symptoms and RBD history

Symptom history after PD onset	History of RBD		Comparison Fisher's exact test	Logistic regression ¹		
	yes (n = 81)	no (n = 69)		OR	95% CI	p value
Hallucination	21 (25.9)	7 (10.1)	0.020	2.469	0.918–6.644	0.074
Dementia	22 (27.2)	9 (13.0)	0.097	1.473	0.574–3.780	0.421
Wearing-off	19 (23.8)	15 (19.2)	0.694	1.515	0.605–3.798	0.375
Dopa-induced dyskinesia	12 (14.8)	3 (4.3)	0.053	5.046	1.148–22.184	0.032
Orthostatic hypotension	5 (6.2)	1 (1.4)	0.218	2.024	0.210–19.504	0.542
Constipation	55 (67.9)	29 (42.0)	0.002	2.184	1.039–4.591	0.039
Restless legs syndrome	10 (12.3)	4 (5.8)	0.260	1.903	0.528–6.851	0.325
Sleep attack	23 (28.4)	3 (4.3)	0.000	6.562	1.747–24.645	0.005

Figures in parentheses are percentages. ¹ Adjusted variables: age at interview, sex, Hoehn-Yahr stage, disease duration.

small voice in 1.2% of the patients in the RBD group and depression in 1.4% of the patients in the non-RBD group. No significant differences were observed between the 2 groups with regard to these symptoms.

Hallucination was present in 25.9 and 10.1% of the RBD and non-RBD groups, respectively ($p > 0.05$) (table 2). Dementia was identified in 27.2 and 13.0% of the RBD and non-RBD groups, respectively ($p > 0.05$). Wearing-off was found in 23.8 and 19.2% of the RBD and non-RBD groups, respectively ($p > 0.05$). DID was identified in 14.8 and 4.3% of the RBD and non-RBD groups, respectively (OR, 5.046; 95% CI, 1.148–22.184; $p = 0.032$). Orthostatic hypotension was found in 6.2 and 1.4% of the RBD and non-RBD groups, respectively ($p > 0.05$). Constipation was present in 67.9 and 42.0% of the RBD and non-RBD groups, respectively (OR, 2.184; 95% CI, 1.039–4.591; $p = 0.039$). The restless legs syndrome was identified in 12.3 and 5.8% of the RBD and non-RBD groups, respectively ($p > 0.05$). 'Sleep attack' was present in 28.4 and only 4.3% of the RBD and non-RBD groups, respectively (OR, 6.562; 95% CI, 1.747–24.645; $p = 0.005$). Anaemia was present in 21.5 and 12.3% of the RBD and non-RBD groups, respectively ($p > 0.05$). MIBG scintigraphy revealed decreased uptake or accelerated wash-out in 80 of the 84 examined cases. Four (10.3%) of the 39 patients in the non-RBD group and none of the 45 patients in the RBD group exhibited negative results in MIBG scintigraphy ($p > 0.05$). SPECT revealed no differences in the uptake by the pons, substantia nigra, red nucleus and occipital lobe and in the total cerebral blood flow between the 2 groups (table 3).

RBD-s resolved over time in 5 PD patients who did not receive clonazepam. In these patients, RBD-s had been

Table 3. SPECT measurement values and history of RBD

SPECT measurements	History of RBD		Comparison t test, p
	yes (n = 81)	no (n = 69)	
Total	23 43.3 ± 5.8	13 44.9 ± 7.0	0.444
Pons right	21 35.7 ± 14.0	13 38.6 ± 16.9	0.580
Pons left	21 35.1 ± 14.2	13 38.1 ± 16.4	0.572
Nigra right	16 34.7 ± 11.2	9 32.7 ± 7.4	0.644
Nigra left	16 30.4 ± 14.6	9 28.3 ± 8.5	0.688
Ruber right	15 33.5 ± 9.6	10 39.7 ± 13.1	0.183
Ruber left	15 33.7 ± 10.9	10 37.3 ± 15.1	0.485
Occipital right	21 38.3 ± 11.1	11 44.7 ± 12.2	0.149
Occipital left	21 42.0 ± 10.4	11 43.1 ± 11.5	0.671

present for more than 5 years, and they disappeared after the onset of PD. The cause of this resolution of RBD-s was unclear in 2 cases. Antiparkinsonism drugs alleviated RBD-s in 2 cases and RBD-s disappeared in 1 case after the dose of cabergoline was decreased.

In PD patients, the effect of antiparkinsonism treatment was examined in the following subgroups: patients without RBD-s and patients with RBD-s after the onset of parkinsonism (table 4). Doses of levodopa, pergolide,

Table 4. Antiparkinsonism drugs and RBD

Variables	Category	OR of positive history of RBD		
		point estimate	95% CI	p value
<i>Background</i>				
Age, years, at interview	≥65/≤64	3.640	1.404–9.438	0.008
Sex	male/female	2.882	1.209–6.868	0.017
Duration of PD, years	≥6.0/<6.0	3.229	1.343–7.762	0.009
Hoehn-Yahr stage	≥III/≤II	1.071	0.338–3.397	0.907
<i>Medication at interview</i>				
Levodopa, mg/day	<300/no use	1.741	0.348–8.702	0.500
	≥300/no use	1.677	0.261–10.788	0.586
Pergolide, µg/day	<1,000/no use	1.320	0.341–5.116	0.688
	≥1,000/no use	1.192	0.278–5.106	0.813
Cabergoline, mg/day	<3.0/no use	0.828	0.222–3.094	0.779
	≥3.0/no use	0.616	0.191–1.983	0.416
Pramipexole, mg/day	<2.0/no use	1.698	0.508–5.678	0.398
	≥2.0/no use	1.849	0.487–7.017	0.366
Selegiline, mg/day	<5.0/no use	1.360	0.271–6.828	0.709
	≥5.0/no use	0.885	0.301–2.598	0.824
Amantagine, mg/day	<150/no use	6.360	0.965–41.894	0.054
	≥150/no use	1.328	0.473–3.729	0.590
Trihexyphenidyl, mg/day	<4.0/no use	0.762	0.171–3.393	0.721
	≥4.0/no use	1.582	0.522–4.793	0.417

Risk for RBD in PD without RBD and with RBD after parkinsonism. Data for drugs were adjusted by variables of age, sex, duration of PD, Hoehn-Yahr stage in logistic regression.

cabergoline, pramipexole, amantadine, selegiline and trihexyphenidyl administered in these 2 subgroups were investigated by logistic regression analysis. The dose of levodopa was considerably higher in patients with RBD-s after parkinsonism than in those without. A comparison by logistic regression analysis revealed no differences in the effect of antiparkinsonism drugs between the 2 subgroups. Moreover, the treatments by antiparkinsonism drugs did not differ between the subgroups.

Discussion

In this study, 54% of PD patients had RBD-s, which is slightly higher than reported in previous studies [1, 4, 5]. RBD-s were not always the preceding symptoms; RBD-s preceded parkinsonism in only 26.0% of all PD patients, and they preceded other symptoms in 44.4% of PD patients with RBD-s. Many PD patients were aware of the symptoms of RBD-s when parkinsonism appeared. Olson et al. [11] reported that 52% of PD patients developed RBD before parkinsonism. Further, in many cases of

neurodegenerative diseases, RBD may precede other symptoms of neurodegenerative diseases. In the PD patients in our study, parkinsonism preceded or was noted at almost the same time as RBD-s.

One of the major limitations of this study was the use of the ICSD-R minimal diagnosis criteria to diagnose RBD because these criteria do not require polysomnography. The sensitivity of specialized interviews for identifying RBD clinically was good (100%) in non-PD patients; however, it was poor (33%) in PD patients [4, 12]. One of the causes for the lower sensitivity in PD patients was the patients' lack of awareness [4]; therefore, we excluded single patients. Although nocturnal sleep behaviour could not be recorded for all patients, we recorded it for 20 subjects (10 patients each from the RBD and non-RBD groups) on HD video (Sony HDR-SR1) to confirm the presence of RBD-s, and these data agreed with those obtained from each questionnaire. Furthermore, in Japan, elderly couples do not always sleep in the same bedroom; therefore, abnormal sleep behaviour not accompanied by loud sounds may not be recognized. Thus, some patients in the non-RBD group may possibly have had

RBD, thereby representing false negatives and causing underestimation of the frequency of RBD.

We expected an increased prevalence in male and elderly patients since similar findings have been reported in the case of idiopathic RBD [13]. The symptoms at the onset of PD did not differ between the RBD and non-RBD groups. No difference was observed in the frequency of dementia between the RBD and non-RBD groups, and the mean age was greater in the RBD group (70.6 years) than in the non-RBD group (66.0 years). In the general Japanese population, the frequency of dementia is reported to be 1.9% in 65- to 69-year-old individuals and 4.5% in 70- to 74-year-old individuals [14]; therefore, no differences were indicated.

Pacchetti et al. [15] reported that the presence of RBD in PD patients was associated with an approximately 3-fold increased risk of psychotic disorders. Arnulf et al. [16] suggested that hallucinations and delusions in non-demented PD patients can result from abnormal REM sleep. A dysfunction in the control system of REM sleep exists in hallucinators, and hallucinations represent illusions of dream imagery during waking hours [15–17]. Brain stem lesions were indicated to occur in hallucination [18]; however, in the present study, we did not find a relationship between RBD-s and hallucination or between hallucination and responsible lesions.

DID was a dominant symptom of the RBD group, and the cause of the risk of DID was unknown. Although only a few patients with RBD-s had DID, prevention of the induction of DID in patients with RBD-s should be considered during the treatment of parkinsonism. ‘Sleep attack’ was a dominant symptom in the RBD group; it might be caused by sleep shortage associated with RBD-s or by the differences in levodopa doses or age. In our study, older patients (OR, 1.143; 95% CI, 1.034–1.265) with RBD-s with PD (OR, 8.532; 95% CI, 1.674–43.488) exhibited a relative risk for sleep attacks. If PD patients exhibited

‘sleep attacks’, we would consider the possibility of RBD-s and initiate clonazepam treatment.

We investigated the relationship between RBD-s and drugs in patients with and without RBD-s after parkinsonism. In other words, we examined the possibility that RBD-s were caused by pharmacotherapy after the onset of PD. Levodopa, dopamine agonists (pergolide, cabergoline and pramipexole), amantadine, selegiline and trihexyphenidyl exhibited no significant differences between the 2 groups. This showed that the antiparkinsonism drugs did not cause RBD-s in PD patients after the onset of parkinsonism. However, differences in age and sex were observed between PD patients with and without RBD-s after parkinsonism.

The theory of Braak et al. [19] on the pathological processes of PD has received considerable attention. This theory states that pathological lesions begin in the medulla and eventually ascend to more rostral structures. The pathophysiology of RBD is believed to involve the nucleus reticularis magnocellularis and peri-locus coeruleus in the pons [12, 20]. These regions correspond to the second-stage lesions of Braak et al., which are pre-symptomatic for PD, and many reports have described sleep symptoms appearing before parkinsonism [2, 11]. Moreover, Braak et al. reported the involvement of parasympathetic preganglionic projection neurons of the vagal nerve in sympathetic preganglionic neurons of the spinal cord, and in postganglionic neurons of the coeliac ganglion [21]. In our study, constipation was more frequent in the RBD group than in the non-RBD group. Early clinical signs of RBD and constipation were important factors in the report by Braak et al. in that unmyelinated parasympathetic and sympathetic nerves might be vulnerable regions in the pathogenesis of PD. In this theory, lesions pathologically progress upwards; however, this pathological progression is not always clinically confirmed in all PD patients.

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