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ORIGINAL ARTICLE

Rapid Eye Movement Sleep Behavior Disorder in Parkinson's Disease: A Preliminary Study

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ABSTRACT

Objective Rapid eye movement sleep behavior disorder (RBD) is associated with α-synucleinopathies, such as Parkinson's disease (PD). We aimed to assess the differences in the clinical characteristics of PD with and without RBD.

Methods Forty-two patients previously diagnosed with PD were evaluated for clinical history, motor and cognitive functioning using the Unified Parkinson's Disease Rating Scale (UPDRS) and Mini-Mental State Examination (MMSE), autonomic symptoms, sleep characteristics using the Pittsburg Sleep Quality Index (PSQI), and the presence of RBD using the Korean version of the RBD screening questionnaire (RBDSQ). The prevalence of RBD and the patients' demographic features were evaluated. The patients were classified into two groups, PD with RBD and PD without RBD, based on the RBDSQ scores. The motor and cognitive functions, as well as other clinical features of the two groups were compared.

Results A total of 42 PD patients were enrolled. Eighteen patients were classified as PD with RBD. Compared to PD without RBD, PD with RBD showed higher scores of rigidity in the UPDRS subscale. Regarding sleep problems, PD with RBD revealed higher sleep disturbance, lower sleep efficiency, and lower overall sleep quality in the PSQI. There was no difference in cognitive dysfunction between the two groups according to the Korean version of the MMSE.

Conclusions PD with RBD was associated with poorer sleep and motor symptoms. Therefore, RBD symptoms in PD are possibly poor prognostic markers.

Key Words Rapid eye movement sleep behavior disorder; Parkinson disease; Rapid eye movement screening questionnaire; Unified Parkinson's Disease Rating Scale; Pittsburg Sleep Quality Index.

Rapid eye movement (REM) sleep behavior disorder (RBD) is characterized by the loss of muscle atonia during REM sleep and dream enactment, which often leads to injury of the patient or the bed partner.[1] Although its precise pathophysiology is unclear, RBD occurs more frequently in patients with neurodegenerative disease than in the general population, and especially in patients with α-synucleinopathy such as Parkinson's disease (PD), multiple systemic atrophy (MSA), and dementia with Lewy bodies (DLB) compared to non-synucleinopathy. A number of studies have attempted to reveal the association between RBD and α-synucleinopathies.[2-4] Up to 81% of the patients initially diagnosed with idiopathic RBD eventually developed neurodegenerative diseases in long-term follow-up studies.[5,6] Therefore, RBD is becoming recognized as a clinical predictive factor for neurodegenerative diseases.[7,8] RBD has been reported to be present in 15–72% of PD patients and is associated with poor parkinsonian symptoms, higher daily levodopa dosage, poor autonomic symptoms and cognitive impairment in PD patients.[2,9-13] In this study, we aimed to assess the differences in the clinical characteristics between PD patients with and without RBD in a Korean population.

Although a definite diagnosis of RBD requires polysomnog-

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raphy (PSG), this technique is unsuitable for studies dealing with large populations or clinical settings because the exam is expensive and requires a skilled examiner. For this reason, various RBD screening tools, including the RBD screening questionnaire (RBDSQ), RBD questionnaire-Hong Kong, Mayo sleep questionnaire, and RBD Severity Scale have been developed and utilized in RBD studies.[14] In 2007, Stiasny-Kolster et al.[15] proposed the RBDSQ, a 10-item, patient self-rating tool that has demonstrated a high sensitivity and reasonable specificity for RBD diagnosis as confirmed by PSG. For this study, the Korean version of the RBDSQ (RBDSQ-K) has been developed and utilized for assessment of RBD in PD patients.

Although the importance of RBD as predicting factor for PD is becoming more recognized and the number of studies examining the clinical characteristics of RBD patients continues to increase, there are only a few RBD studies in the Korean PD population. In this study, we aimed to analyze the differences in the clinical characteristics of PD patients with and without RBD.

MATERIALS & METHODS

Patients

Between August 2013 and February 2015, a total of 42 patients previously diagnosed with PD who visited the outpatient Department of Neurology of Gachon University Gil Hospital were included in the study. Patients were excluded from the study for any of the following reasons: corticobasal degeneration, dementia, or neurologic diseases other than PD; other potential causes of parkinsonism, such as a structural lesion or metabolic derangement, infarction, hemorrhage, tumor, trauma or history of medication known to cause parkinsonism. In addition, patients who could not complete the questionnaire were also excluded.

Study design

All registered patients were assessed and interviewed for their age at the assessment, age at the onset of PD symptoms, duration of PD, total daily levodopa dosage (total LED), motor symptoms, autonomic symptoms, cognitive functions, and sleep disorders. Age at the onset of PD was assessed by interviewing the patient and reviewing the electronic medical record. Total LED was defined as the total equivalent daily dosage of levodopa prescribed to the patient at the time of the assessment. Motor symptoms were assessed with the Unified Parkinson's Disease Rating Scale (UPDRS) part III subscale and the Hoehn and Yahr Scale (H&Y Scale) in the on medication state. The UPDRS part III subscale was further divided into 6 motor domains: tremor, rigidity, bradykinesia, facial, speech, and axial impairment. Autonomic dysfunction was assessed by interviewing the patients for the presence of hyperhidrosis, urination difficulty, urinary incontinence, and severe constipation. Cognitive function was assessed with the Korean Mini-Mental Status Examination (K-MMSE), and sleep dysfunction was assessed with the Pittsburg Sleep Quality Index (PSQI). The PSQI, a self-reported measure of sleep quality, consists of seven subscales: overall sleep quality, sleep duration, sleep latency, day dysfunction due to sleepiness, sleep efficiency, sleep disturbance, medication needed to sleep. The total score of the seven subscales yield the total PSQI score. A total score of 5 or greater is indicative of poor sleep quality.[16]

To assess the presence of RBD in this study, the RBDSQ-K was developed by translating the original RBDSQ, which was validated for its cross-language equivalence by a person fluent in both English both Korean. The RBDSQ is a self-reported 10-item questionnaire with a score that ranges from 0 to 13. The questionnaire was completed by the subjects with aid from their partners if needed. If the subject was unable to read or write, oral answers recorded by the examiner were permitted. The cut-off point for the original version of this scale, which was reported by Stiasny-Kolster et al.,[15] was 4.5; the cut off values for the Japanese version of the RBDSQ (RBDSQ-J) was also 4.5.[17] We defined PD with RBD as having a score of 5 or higher on the RBDSQ-K, whereas PD without RBD was defined as a score of 4 or lower.

Statistical analysis

The demographic features and clinical characteristics of PD with RBD and PD without RBD group were compared in a statistical analysis using IBM SPSS statistics 22 software (SPSS Inc., Chicago, IL, USA). Fisher's exact test was implemented for categorical variables (sex, hyperhidrosis, urination difficulty, urinary incontinence, and severe constipa-

Table 1. Clinical characteristics of total patients with PD

Number of patients	42
Gender (male/female)	18/24
Age (years)	69.7 ± 10.4 (39.0–89.0)
Age at onset of PD (years)	63.7 ± 10.1 (38.0–79.0)
Disease duration (years)	6.1 ± 10.1 (0.5–22.0)
Hoehn and Yahr Scale	2.3 ± 1.3 (1–5)
Total LED (mg/day)	537.5 ± 362.4 (150–1,950)
Hyperhidrosis (%)	13 (10.8)
Urination difficulty (%)	18 (15.0)
Urinary incontinence (%)	13 (10.8)
Severe constipation (%)	19 (15.8)
K-MMSE score	24.0 ± 5.1 (9–30)
RBDSQ-K score	4.4 ± 2.8 (1–12)
UPDRS part III subscale	21.0 ± 17.8 (0–81)
Tremor	4.2 ± 4.6 (0–22)
Rigidity	1.5 ± 2.9 (0–15)
Bradikinesia	9.5 ± 7.8 (0–31)
Facial expression	1.0 ± 1.1 (0–4)
Speech	0.8 ± 1.1 (0–4)
Axial impairment	4.2 ± 4.6 (0–22)
PSQI total	5.9 ± 4.2 (1–19)
Duration of sleep	0.8 ± 1.0 (0–3)
Sleep disturbance	1.5 ± 0.6 (0–3)
Sleep latency	1.3 ± 1.0 (0–3)
Day dysfunction	0.6 ± 0.9 (0–3)
Sleep efficiency	0.4 ± 0.9 (0–3)
Overall sleep quality	1.0 ± 0.9 (0–3)
Need meds to sleep	0.3 ± 0.8 (0–3)

Values are mean ± SD (range), except for gender. PD: Parkinson's disease, total LED: total daily levodopa dosage, K-MMSE: Korean Mini-Mental Status Examination, RBDSQ-K: rapid eye movement sleep behavior disorder screening questionnaire-Korean version, UPDRS: Unified Parkinson's Disease Rating Scale, PSQI: Pittsburg Sleep Quality Index.

tion), and the Wilcoxon/Mann-Whitney U test was implemented for continuous variables (age, age at the onset of PD, duration of PD, total LED, H&Y Scale, K-MMSE score, UPDRS part III subscale scores, and PSQI scores). The level of statistical significance was defined as 0.05.

RESULTS

The demographic and clinical features of all 42 patients are shown in Table 1. There were 18 men and 24 women, and the average age at the assessment was 69.7 years. The averages scores were 21.0 for the UPDRS part III subscale, 24.0 for the K-MMSE, 5.9 for the total PSQI, and 4.4 for the RBDSQ.

The comparison and analysis of the demographic and clinical features of PD patients with and without RBD are presented in Table 2. Eighteen of the 42 patients (42.9%) were classified as PD with RBD. Thirteen patients (29%) had taken benzodiazepine (3 patients, alprazolam 25 mg to 50 mg), antipsychotics (9 patients, quetiapine 25 mg to 100 mg) or an antidepressant (1 patient, escitalopram 10 mg). No patient had taken an antiepileptic drug. There was no statistically significant difference for taking sleep pills between the two groups ($p = 0.14$).

According to the UPDRS score, PD with RBD showed a higher rigidity score. Among the sleep parameters, PD with RBD also showed higher scores in sleep disturbance, sleep efficiency, and overall sleep quality. There was no statistically significant difference between the two groups for sex, age, age at assessment, age at the onset of PD, duration of PD, total LED, autonomic symptoms, and K-MMSE score.

DISCUSSION

The PRIAMO study, a large-scale multi-center study that analyzed 1,027 PD patients, reported that 99% of the PD patients complained of non-motor symptoms including sleep disturbance, daytime sleepiness, dementia, fatigue, and depression.[18] In particular, sleep disturbances including insomnia, restless leg syndrome, sleep apnea, parasomnia, excessive daytime sleepiness, and sleep attacks were present in 60–90% of PD patients. The pathophysiology of sleep disturbances in PD patients is thought to be related to degenerative changes in the sleep-wake related pathways and the sleep regulatory center as PD progresses. Previous studies have reported the prevalence of RBD in PD patients is 25–75%.[9,10,13,19-22] RBD is also known to be more frequent in synucleinopathies, including PD, MSA, and DLB, compared to non-synucleinopathies. In this study, the incidence of RBD in PD was 42.9%, which is similar to previous reports.

Although there was no statistically significant difference in the MMSE score in this study, recent follow-up studies have reported that 45–81% of idiopathic RBD patients eventually developed cognitive impairments or dementia. This finding suggests that RBD is not only a sleep disorder but also a prodromal marker of neurodegenerative diseases.[5,6]

The most significant finding of this study was that the presence of RBD is significantly associated with poorer sleep quality in PD patients. Compared to PD without RBD, PD with RBD had more sleep dis-

Table 2. Comparison between PD patients with and without RBD

	With RBD	Without RBD	*p*-value
Number of patients	18	24	
Gender (male/female)	8/10	10/14	1.00
Age (years)	67.9 ± 10.7 (39–80)	71.1 ± 10.1 (43–79)	0.16
Age at onset of PD (years)	61.4 ± 10.5 (38–75)	65.5 ± 9.6 (43–79)	0.09
Disease duration (years)	6.6 ± 5.6 (0.5–20.0)	5.7 ± 4.9 (1.0–22.0)	0.35
Hoehn and Yahr Scale	2.3 ± 1.1 (1–5)	2.4 ± 1.4 (1–4)	0.43
Total LED (mg/day)	510.1 ± 290.8 (200–1,200)	558.1 ± 413.0 (150–1,950)	0.45
Hyperhidrosis (%)	7 (38.9)	6 (25.0)	0.5
Urination difficulty (%)	9 (50.0)	9 (37.5)	0.53
Urinary incontinence (%)	6 (33.3)	7 (29.2)	1.00
Severe constipation (%)	8 (44.4)	11 (45.8)	1.00
K-MMSE score	23.3 ± 6.1 (9–30)	24.5 ± 4.3 (11–30)	0.43
RBDSQ-K score	7.1 ± 2.1 (5–12)	2.3 ± 0.9 (0–4)	
UPDRS part III subscale	21.7 ± 20.6 (0–81)	20.5 ± 15.7 (1–54)	0.48
Tremor	4.2 ± 5.3 (0–22)	4.1 ± 4.2 (0–13)	0.47
Rigidity	2.1 ± 3.5 (0–15)	1.1 ± 2.4 (0–11)	0.049*
Bradykinesia	10.0 ± 8.4 (0–30)	9.0 ± 7.6 (0–31)	0.39
Facial expression	1.1 ± 1.3 (0–3)	1.0 ± 1.0 (0–4)	0.45
Speech	0.7 ± 1.0 (0–3)	0.9 ± 1.1 (0–4)	0.25
Axial impairment	3.7 ± 4.2 (0–16)	4.5 ± 5.1 (0–16)	0.45
PSQI total	7.0 ± 4.2 (1–19)	5.1 ± 4.0 (1–19)	0.038*
Duration of sleep	1.1 ± 1.1 (0–3)	0.6 ± 0.9 (0–3)	0.094
Sleep disturbance	1.7 ± 0.7 (1–3)	1.3 ± 0.6 (1–3)	0.029*
Sleep latency	1.4 ± 1.1 (0–3)	1.2 ± 0.9 (0–3)	0.25
Day dysfunction	0.7 ± 1.0 (0–3)	0.5 ± 0.9 (0–3)	0.2
Sleep efficiency	0.6 ± 1.0 (0–3)	0.25 ± 0.7 (0–3)	0.045*
Overall sleep quality	1.3 ± 1.0 (0–3)	0.8 ± 0.9 (0–3)	0.021*
Need meds to sleep	0.1 ± 0.2 (0–1)	0.4 ± 1.0 (0–3)	0.14

Values are mean ± SD (range), except for gender. Analyses were performed by Fisher's exact test and Wilcoxon/Mann-Whitney U test.
*$p < 0.05$. PD: Parkinson's disease, RBD: REM sleep behavior disorder, total LED: total daily levodopa dosage, K-MMSE: Korean Mini-Mental Status Examination, RBDSQ-K: REM sleep behavior disorder screening questionnaire-Korean version, UPDRS: Unified Parkinson's Disease Rating Scale, PSQI: Pittsburg Sleep Quality Index, REM: rapid eye movement.

turbances, lower sleep quality, and a higher total PSQI score. Another significant difference between the two groups was observed in the motor symptoms. PD with RBD had significantly more rigidity symptoms compared to PD without RBD.

Two studies of sleep quality in PD patients with RBD have been published so far. A study utilizing the Parkinson's Disease Sleep Scale to compare the sleep quality of PD patients with and without RBD reported that the presence of RBD was associated with poorer sleep quality in PD patients.[23,24] This is consistent with the result of the present study, in which PD with RBD had poorer sleep quality, sleep efficiency, and more sleep disturbances compared to PD without RBD. Whereas, in PD with RBD, better sleep efficiency, longer REM sleep duration, and increased occurrence of periodic limb movements have been reported.[25]

With regard to motor symptoms, rigidity was more severe in PD with RBD than in PD without RBD in this study, whereas no other significant differences in the clinical characteristics were observed. However, there are debates regarding the influence of RBD on the clinical characteristics of PD patients,[9-13,25] RBD has been reported to be associated with a longer PD duration, higher H&Y Scale, higher UPDRS motor symptom scores, more severe motor fluctuation, and higher total LED.[10,25] In a study in the Korean population, PD patients with RBD were older, had a longer duration of PD, a more severe level of disability, a longer duration of antiparkinsonian medication, and a lower proportion of their UPDRS scores accounted for by tremor than those without RBD.[9] Another large-scale study evaluated 944 Korean patients with PD and reported that motor complications and impulse control and other related behaviors were more frequent in patients with RBD than in patients with-

out RBD.[26] Other studies, however, reported inconsistent results, with no significant differences in the age at the onset of PD, duration of PD, H&Y Scale, the UPDRS motor subscale, and total LED between the two groups.[11,27] The discrepancy between this study and the aforementioned studies on the Korean population could be because different criteria were used to diagnose RBD. In the PD-RBD studies involving the Korean population, PD patients were diagnosed with RBD based on the minimal criteria of the International Classification of Sleep Disorder-Revised (ICSD-R).[9] The minimal diagnostic criterion of the ICSD-R is a clinical diagnosis based on clinician's judgement without using objective diagnostic tools. The minimal criteria for RBD in the ICSD-R states that RBD can be diagnosed when the limb or body movement is associated with dream mentation plus at least one of the three following symptoms: harmful or potentially harmful sleep behaviors, dreams appear to be "acted out," or sleep behaviors disrupt sleep continuity.[28] The ICSD-III, on the other hand, allows objective validated RBDSQ to aid in the process of diagnosing RBD.[29] This study used one of the validated RBDSQ, the RBDSQ, which contains detailed questions that assesses the specific symptoms of RBD, such as frequency, dream content, nocturnal movements, injuries to self or bed partner, types of motor behaviors during the night, nocturnal awakenings, sleep disruption, and neurological disease. The recently published RBDSQ-K could discriminate patients with idiopathic RBD from healthy subjects using an optimal cutoff score of 4.5 points, and its sensitivity and specificity was 89.4% and 98.3%, respectively.[30] Miyamoto et al.[17] reported the cut off for the RBDSQ-J was also 4.5, which showed high sensitivity and specificity (88.5% and 96.9%, respectively). Therefore, using a validated RBD questionnaire can improve the diagnostic accuracy of RBD, especially if PSG is unavailable. Further large-scale studies should incorporate a suitable diagnostic tool for RBD, such as the RBDSQ, to elucidate the clinical implications of RBD in Korean PD patients.

One of the limitations of this study was that RBD was diagnosed with a questionnaire and without confirmation of the diagnosis with PSG. Moreover, the cut-off value for RBD was acquired from previous studies involving non-Korean subjects, thus calling for validation studies in Korean patients.[31] Another major limitation of this study was a relatively small sample size and that subjects were recruited from a single institution. Thus, there is a possibility that the study subjects are not a representative sample of the Korean population. Therefore, additional large-scale multi-center studies should be performed with the validated RBDSQ. Nevertheless, the present study is meaningful because we used the questionnaire for RBD in PD patients for the first time. In conclusion, compared to PD without RBD, PD with RBD showed a higher incidence of rigidity and poorer sleep quality. This study partially supports previous studies by demonstrating that RBD is not only a comorbidity but also an associated factor that affects the clinical features of PD. Further studies based on this preliminary study may contribute to a deeper understanding of PD and RBD, as well as prognosis prediction and therapy planning for PD patients with sleep problems.

Conflicts of Interest

The authors have no financial conflicts of interest.

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