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The relationship between restless legs syndrome and motor subtype in patients with de novo Parkinson's disease

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Abstract

Background: Restless legs syndrome (RLS) is a common sleep-related complication in patients with Parkinson's disease (PD). The aim of this study was to assess the clinical characteristics associated with the occurrence of RLS in patients with de novo PD. *Methods:* Our study included 346 patients with de novo PD. The motor and non-motor status of each patient was assessed using the appropriate scales, and RLS was diagnosed through face-to-face interviews. *Results:* The incidence of RLS in patients with PD was 12.7% (44/346), while relative proportion of different motor subtypes was significantly different between PD patients with and without RLS. PD patients with RLS had lower rates of tremor-dominant subtype (25.0% vs. 36.4%) and higher rates of akinetic-rigid subtype (59.0% vs. 54.6%) (P<0.001) than those without RLS. PD patients with the akinetic-rigid subtype had a higher prevalence of RLS (13.6%) than those with tremor-dominant subtype (9.0%) (P=0.020). The significant factors associated with the presence of RLS were modified Hoehn-Yahr stage, motor subtype, and Pittsburg Sleep Quality Index total scores.
Conclusion: Our findings indicated a significant relationship between RLS and motor subtype in patients with PD and revealed that the motor subtype is a significant predictor of RLS in patients with PD.

Keywords: Parkinson's disease, restless legs syndrome, subtype

INTRODUCTION

Restless legs syndrome (RLS) is a common neurological condition characterized by an unpleasant sensation in the legs along with an urge to move them.[1] Some patients manifest RLS symptoms secondary to other disease processes including Parkinson's disease (PD).[2] Recent studies have shown the relationship between PD and RLS and have indicated that RLS affects motor and non-motor symptoms in patients with PD.[3,4]

RLS and PD share a common pathophysiology via the dopaminergic pathway.[4,5] Previous RLS studies had included patients with PD who were taking dopaminergic medication, which was a limitation[6-9] because the differences in the prevalence of RLS in patients with PD and the relationship between RLS and motor or non-motor symptoms in patients with PD could result from the confounding effects of dopaminergic medication.[3]

The clinical factors related to RLS development in patients with PD and the relationship between the two disorders remain controversial. Therefore, the aim of this study was to assess the clinical characteristics associated with the presence of RLS in patients with de novo PD.

METHODS

Subjects

We recruited patients from the Movement Disorders Clinic of our hospital from 2011 to 2017. The patients were diagnosed with PD according to the United Kingdom Parkinson's Disease Society Brain Bank clinical diagnostic criteria[10], and the diagnoses were confirmed by a movement disorder specialist (SM Choi). At the time of the clinical evaluation, no patient was treated with anti-parkinsonian or anti-dopaminergic agents. These patients were subsequently followed-up regularly for at least a year, during which they showed a positive response to levodopa. RLS was diagnosed

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through face-to-face interviews, based on the International Restless Legs Syndrome Study Group (IRLSSG) criteria.[1] Exclusion criteria were as follows: atypical or secondary parkinsonism, poor response to levodopa, presence of clinically significant lesions on brain magnetic resonance imaging, inability to complete the clinical evaluations, and diseases that could cause secondary RLS such as peripheral neuropathy, spinal cord lesion, chronic renal disease, iron deficiency anemia, pregnancy, rheumatologic disease, and medication-induced RLS.

All the patients provided written consent for their participation. This study was approved by the Institutional Review Board of the Hospital and was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Clinical evaluation

All the clinical evaluations were performed by interviewing patients prior to the start of dopaminergic medication. The patients underwent detailed neurologic examinations and were queried about their age at symptom onset, formal education duration, and any past and current medication use. The parkinsonism motor states and activities of daily living (ADL) were assessed using the modified Hoehn-Yahr (mHY) stages[11], and the motor (part III) and ADL (part II) subscores of the Unified Parkinson's Disease Rating Scale (UPDRS).[12] The motor subtype was classified as tremor-dominant (TD), mixed (MX), and akinetic-rigid (AR) according to the previously reported method.[13] Briefly, motor subtypes were defined according to the ratio of each patient's UPDRS III tremor score (sum of items 20 - 21 divided by 4) to the patient's mean UPDRS III AR score (sum of items 22 - 27 and 31 divided by 15). The TD, MX, and AR groups were defined as patients having a ratio of > 1.0, between 0.80 and 1.0, and < 0.80, respectively. The non-motor symptoms of the patients were assessed using the Korean version of the Mini-Mental State Examination (MMSE)[14], Beck Depression Inventory (BDI)[15], Non-Motor Symptoms Scale (NMSS) for PD[16], and Pittsburgh Sleep Quality Index (PSQI).[17] Patients who fulfilled the diagnostic criteria for RLS were requested to complete the 10-question IRLSSG Rating Scale, which was used to assess symptom severity.[18]

Statistical analysis

SPSS, version 20.0 for Windows (IBM Corp., Armonk, NY, USA) was used to perform all statistical analyses. Data with $p < 0.05$ were considered statistically significant. Independent sample Student's t-test for continuous variables and $\chi 2$ test for categorical variables were used to determine the significance of any differences in the clinical characteristics between PD patients with and without RLS and between PD patients with TD subtype and AR subtype. Statistically significant characteristics in the aforementioned analyses were subsequently included as dependent variables in the logistic regression analysis to explore the factors associated with the presence of RLS in patients with PD.

RESULTS

The study included 346 patients with de novo PD. The clinical characteristics of PD patients with and without RLS are shown in Table 1. Forty-four out of 346 (12.7%) patients with PD had RLS. No significant differences were found in age, sex, duration of disease, and age at symptom onset between PD patients with and without RLS. Further, there were no differences in the scores of motor states and ADL. However, the relative proportions of TD, MX, and AR motor subtypes were 36.4%, 8.9%, and 54.6%, respectively, in PD patients without RLS and 25.0%, 15.9%, and 59.0%, respectively, in PD patients with RLS. PD patients with RLS had lower rates of TD subtype and higher rates of AR subtype than those without RLS. There were no significant differences concerning non-motor symptoms such as MMSE, BDI, and NMSS; however, the PSQI scores were significantly different between the two groups. PD patients with RLS had a higher PSQI global score than PD patients without RLS.

The clinical characteristics of PD patients with TD subtype and AR subtype are shown in Table 2. No difference was found in the demographic variables between the two groups. Scores related to motor states and ADL including mHY stage, UPDRS III, and UPDRS II were significantly higher in PD patients with AR subtype than in those with TD subtype. The prevalence of RLS was higher in PD patients with AR subtype (13.6%) than in those with TD subtype (9.0%). No significant difference was observed between the two groups in other non-motor symptom scores such as MMSE, BDI, and NMSS.

The results of logistic regression analysis for predicting the presence of RLS are presented in Table 3. The significant predictors were mHY stage, motor subtype, and PSQI total scores.

Table 1: Clinical characteristics of the Parkinson's disease patients with and without restless legs syndrome

	All patients (n = 346)	No RLS (n = 302)	RLS (n = 44)	p-value
Age (years)	65.5 ± 9.7	65.5 ± 9.0	65.5 ± 9.8	0.987
Sex (female : male)	178 : 168	153 : 149	25 : 19	0.445
Duration of disease (months)	17.7 ± 13.8	18.2 ± 13.9	14.2 ± 12.8	0.071
Age at onset (years)	64.1 ± 9.7	64.3 ± 8.9	64.0 ± 9.8	0.840
mHY stage	1.8 ± 0.8	1.8 ± 0.8	1.7 ± 0.7	0.454
UPDRS part III score	20.1 ± 10.3	20.0 ± 10.3	21.0 ± 10.6	0.550
UPDRS part II score	6.8 ± 5.4	6.6 ± 5.4	8.1 ± 5.3	0.100
Subtype (TD/MX/AR)	121/34/191	110/27/165	11/7/26	**<0.001**
MMSE	25.9 ± 3.5	25.9 ± 3.5	25.8 ± 3.9	0.901
BDI	11.9 ± 9.6	11.7 ± 9.8	13.4 ± 8.7	0.291
NMSS total	42.5 ± 32.6	41.6 ± 32.8	49.0 ± 30.5	0.160
PSQI global	6.6 ± 3.5	6.4 ± 3.3	7.8 ± 4.2	**0.017**

Values are mean ± standard deviation.
RLS, restless legs syndrome; TD, tremor-dominant; MX, mixed; AR, akinetic-rigid; mHY, modified Hoehn-Yahr; UPDRS, unified Parkinson's disease rating scale; MMSE, mini-mental state examination; BDI, Beck depression inventory; NMSS, non-motor symptoms scale for Parkinson's disease; PSQI, Pittsburgh sleep quality index

DISCUSSION

Our study on the clinical characteristics associated with RLS in patients with de novo PD revealed that the relative proportion of motor subtype was significantly different between PD patients with and without RLS. PD patients with RLS had higher rates of AR subtype than those without RLS, and the prevalence of RLS was higher in AR subtype than in TD subtype. The results of logistic regression analysis showed that the motor subtype was a significant predictor of RLS in patients with PD.

PD is one of the causes of secondary RLS, and the prevalence of RLS symptoms is three to six times higher in patients with PD than in the general

Table 2: Comparison of clinical characteristics between Parkinson's disease patients with tremor-dominant and akinetic-rigid subtypes

	TD subtype (n = 121)	AR subtype (n = 191)	p-value
Age (years)	64.7 ± 10.4	65.8 ± 9.1	0.358
Sex (female : male)	64 : 57	93 : 98	0.343
Duration of disease (months)	16.9 ± 14.6	18.3 ± 13.8	0.404
Age at onset (years)	63.3 ± 10.4	64.2 ± 9.1	0.415
mHY stage	1.5 ± 0.7	1.9 ± 0.8	**< 0.001**
UPDRS part III score	17.8 ± 9.7	21.4 ± 10.6	**0.003**
UPDRS part II score	5.4 ± 4.2	7.7 ± 5.9	**< 0.001**
MMSE	25.9 ± 3.4	26.0 ± 3.7	0.889
BDI	11.3 ± 10.0	12.6 ± 9.5	0.237
NMSS total	38.5 ± 29.8	45.4 ± 33.7	0.065
PSQI global	6.4 ± 2.9	6.8 ± 3.7	0.284
Patients with RLS (%)	11 (9.0)	26 (13.6)	**0.020**
IRLSSG rating scale	14.4 ± 6.2	14.5 ± 7.9	0.974

Values are mean ± standard deviation.
TD, tremor-dominant; AR, akinetic-rigid; mHY, modified Hoehn-Yahr; UPDRS, unified Parkinson's disease rating scale; MMSE, mini-mental state examination; BDI, Beck depression inventory; NMSS, non-motor symptoms scale for Parkinson's disease; PSQI, Pittsburgh sleep quality index; RLS, restless legs syndrome; IRLSSG, international restless legs syndrome study group

Table 3: Logistic regression analysis on factors associated with the presence of restless legs syndrome in patients with Parkinson's disease

	OR (95% CI)	p-value
mHY stage	0.479 (0.237 – 0.967)	**0.040**
UPDRS part III score	1.036 (0.985 – 1.090)	0.165
UPDRS part II score	1.037 (0.974 – 1.105)	0.257
Motor subtype (TD/MX/AR)	2.369 (1.063 – 6.554)	**0.037**
PSQI total	1.097 (1.003 – 1.200)	**0.042**

OR, odds ratio; CI, confidence interval; mHY, modified Hoehn-Yahr; UPDRS, unified Parkinson's disease rating scale; TD, tremor-dominant; AR, akinetic-rigid; PSQI, Pittsburgh sleep quality index

population.[3] Accordingly, when compared to an earlier study that included the general population,[2] our study indicated that the prevalence of RLS (12.7 %) was higher in patients with PD.[2] The prevalence of RLS in PD patients in our study was higher than that in Asian PD patients (12%) and lower than that in non-Asian PD patients (16%).[19] A lower rate of RLS among Asian PD patients compared to non-Asian PD patients is similar to observations in populations without PD.[20]

Our study showed that there are no differences in age, sex, disease duration, and age at symptom onset between PD patients with and without RLS. This is consistent with the results of previous studies, which showed no difference in the demographic variables between PD patients with and without RLS.[5,6] However, previous studies reported that RLS is more prevalent among female patients with PD than among male patients with PD[7] and that age at symptom onset is lower in PD patients with RLS than in those without RLS.[8]

Regarding motor symptoms, we could not find any difference in the mHY stage, UPDRS motor scores, and ADL scores between PD patients with and without RLS. Likewise, other studies have shown no differences in parkinsonian motor symptoms between the two groups.[8,21] However, one study showed a higher HY stage with more severe limb parkinsonism and rest tremor in PD patients with RLS than in those without RLS.[5]

The clinical manifestations of PD are heterogeneous and its clinical subtypes have been empirically defined based on the prominent motor symptoms. There are various methods to classify the subtypes of PD in addition to the subtype classification based on the prominent motor symptoms; however, the validity of these methods remains controversial.[22] The TD/AR classification is one of the most commonly used classifications of PD motor subtypes[13], and the AR group appears to have more advanced neurodegeneration and less favorable outcomes than the TD group.[23] Similarly, in our study, PD patients with AR subtype had higher scores in motor and ADL scales than those with TD subtype. Additionally, the prevalence of RLS was higher in PD patients with AR subtype than in those with TD subtype. These results show that non-motor symptoms as well as motor symptoms occur more frequently in AR subtype than in TD subtype. It is unclear why RLS is more common in the AR subtype. To our knowledge, there has been no report on the association between motor subtypes and RLS in PD patients to date. The higher prevalence of RLS in PD patients with the AR subtype observed in our study is consistent with the results of a previous study, which reported that sleep-related symptoms are more prevalent in the non-TD subtype than in the TD subtype.[24]

Regarding non-motor symptoms, we found a significant difference in the sleep-related score between PD patients with and without RLS. The PSQI global score was considerably higher in PD patients with RLS than in those without RLS. These results are consistent with those of other studies, which show that RLS is an important factor causing sleep disturbance in patients with PD.[8,9]

This study has some limitations: First, we enrolled patients from the outpatient clinic of a single tertiary referral center; hence, the study participants may not have been representative of the general PD population. Second, we did not include a control group. Third, the potential confounders that could affect RLS in patients with PD were not considered. Fourth, as this was a cross-sectional study, the associations observed herein cannot be considered as definitive evidence of causal associations.

In conclusion, our findings indicated a significant relationship between RLS and motor subtype in patients with de novo PD and revealed that AR subtype was associated with PD patients

with RLS. Thus, the motor subtype is an important predictor of RLS, and further studies are essential to understand this correlation in patients with PD.

DISCLOSURE

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Conflicts of interest: None

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