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Original article

Restless legs syndrome, leg motor restlessness and their variants in patients with Parkinson's disease and related disorders

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Abbreviations:
PD=Parkinson's disease; MSA=multiple system atrophy; PSP=progressive supranuclear palsy; BMI=body mass index; MMSE=Mini-Mental State Examination; MDS-UPDRS=Movement Disorder Society revision of the Unified PD Rating Scale; LED=levodopa equivalent dose; SCOPA-AUT=Scales for Outcomes in PD-Autonomic; PDSS-2=PD Sleep Scale-2; ESS=Epworth Sleepiness Scale; BDI-II=Beck Depression Inventory-II; NMSS=Non-Motor Symptom Scale; RLS=restless legs syndrome; LMR=leg motor restlessness; DAT=dopamine transporter scan; SBR=specific binding ratio; MIBG= metaiodobenzylguanidine

Highlights

1. We investigated RLS and LMR and their variants in PD and related disorders.
2. A total of 49.2% of PD patients had any restlessness, including RLS and LMR.
3. LMR variants and RLS variants are rare in PD and related disorders
4. PD with restlessness was related to autonomic, sleep and depressive symptoms

Abstract

Objective: The objective of this study was to investigate the prevalence of restless leg syndrome (RLS), leg motor restlessness (LMR) and RLS/LMR variants and their relationship with clinical factors in patients with Parkinson's disease (PD) and related disorders.

Methods: Sixty-three PD patients, 17 multiple system atrophy (MSA) patients and 11 progressive supranuclear palsy (PSP) patients were included in this study. Through face-to-face interviews, the patients were diagnosed with RLS/LMR, or with RLS/LMR variants in which the symptoms occur predominantly in body parts other than the legs.

Results: The frequency of RLS, LMR, RLS variants and LMR variants was as follows: PD (12.7%, 11.1%, 0% and 1.6%); MSA (5.9%, 11.8%, 0% and 0%); and PSP (0%, 9.1%, 0% and 0%). Restlessness without the urge to move was observed in 25.4% of the PD patients, 11.8% of the MSA patients and 0% of the PSP patients. The PD patients with restlessness exhibited higher Hoehn and Yahr stages and higher scores on the Scales for Outcomes in PD-Autonomic, PD sleep scale-2 and Beck Depression Inventory-II. The olfactory functioning, 123I-MIBG myocardial scintigraphy uptake and dopamine transporter single photon emission computed tomography findings did not differ between the PD patients with restlessness and those without. The severity of RLS was correlated with the autonomic symptoms.

Conclusion: PD with restlessness was characterized by increased autonomic, sleep and depressive symptoms. Further studies including a large sample are warranted to characterize restlessness in PD and related disorders.

Introduction

Patients with Parkinson's disease (PD) show characteristic motor signs, such as bradykinesia, rigidity and rest tremors, due to the progressive degeneration of dopaminergic neurons in the substantia nigra. In addition, a wide range of nonmotor symptoms, such as sleep disturbances, cognitive impairment, olfactory disturbances and autonomic impairment, involve dopaminergic and nondopaminergic systems and are currently considered integral to the disease [1]. Sleep disturbances are common nonmotor symptoms that affect up to 90% of PD patients and are caused by various factors, including nocturnal motor and nonmotor symptoms, sleep-wake impairment related to the disease, comorbid restless legs syndrome (RLS) and rapid eye movement sleep behavior disorders.

RLS is a sleep-related movement disorder characterized by the urge to move one's legs and abnormal leg sensations while resting during the night that interferes with the sleep of sufferers [2]. Dopaminergic dysfunction has been suggested to play a role in RLS based on the clinical responses of patients with RLS to dopaminergic treatment, such as levodopa, ropinirole, rotigotine, pramipexole and cabergoline [3]. Dopaminergic medication mediated by D2 and D3 receptors is likely involved in the short-term improvement of RLS symptoms [4]. In patients with idiopathic RLS, especially severe cases, other body parts (face, trunk or arms) can be involved, but the legs should be more severely impaired than the other body parts. In contrast, RLS variants, such as restless face [5], arms [6] or abdomen [7], in which restlessness is restricted to or predominantly involves regions other than the legs with characteristics identical to those of RLS, has been reported.

In patients with PD, the prevalence of RLS widely varies (0-50%) [8]. A recent

systematic meta-analysis showed that the RLS prevalence in PD patients is approximately 3 times higher than that in healthy controls [9]. A multicenter study showed that the prevalence of RLS among patients with multiple system atrophy (MSA) (28%) was higher than that in patients with PD (14%) and healthy controls (7%) [10]. Patients with progressive supranuclear palsy (PSP) showed severe sleep architecture impairment; however, RLS has not been well studied in PSP patients [11, 12].

Similar to idiopathic RLS, RLS variants, such as restless lower back [13], perianal [14] and genital regions [15], have been described in PD patients. All of these patients responded well to adjunctive dopamine agonist therapy. Untreated patients with PD were 3-times more likely to have “leg motor restlessness” (LMR), which is characterized by the urge to move the legs but does not fulfill the 4 essential features of RLS [16], than healthy controls. Furthermore, we previously reported a patient with PD who presented with restless, uncomfortable sensations in the legs without the urge to move, which did not meet the criteria for RLS or LMR, as the initial manifestation of PD [17].

We hypothesized that patients with PD and related disorders can show various types of restless and abnormal sensations in not only the legs but also other body parts, reflecting the endogenous brain dopamine deficiency. However, no studies have investigated the details of RLS-related symptoms and their clinical correlation in patients with PD and related disorders. The aim of this study was to evaluate the frequency of RLS, LMR and RLS/LMR variants and their relationship with clinical factors in patients with PD and related disorders, including PD, MSA and PSP.

Methods

All study procedures involving human participants were performed in accordance with the ethical standards of the Institutional Research Committee and the 1964 Helsinki Declaration and its subsequent amendments or comparable ethical standards. All subjects enrolled in the study provided written informed consent.

We performed a cross-sectional study investigating RLS and related symptoms in patients with PD and related disorders who visited the Department of Neurology, Dokkyo Medical University Hospital between June 2016 and April 2018. In total, 91 patients with PD and related disorders (63 PD, 17 MSA and 11 PSP) who received a detailed clinical interview and assessment of restlessness were included in this study. The diagnosis of PD was made according to the Movement Disorders Society (MDS) diagnostic criteria for PD [18]. The diagnosis of MSA or PSP was made according to established criteria [19, 20]. Among the 17 patients with MSA, 6 patients had MSA with parkinsonism (MSA-P) symptoms, and 11 patients had MSA with predominant cerebellar ataxia (MSA-C). Patients with secondary parkinsonism due to medication, vascular lesions or trauma were excluded based on a brain imaging study and their clinical history. Patients with dementia, which was defined as Mini-Mental State Examination (MMSE) scores<20, were excluded from the study.

Clinical assessment

All participants completed questionnaires regarding their habits and sleep status. The PD sleep scale (PDSS)-2, which was designed to assess PD-related sleep problems and consists of 15 individual items, was used [21]. Daytime sleepiness was measured by the Japanese version of the Epworth sleepiness scale (ESS) [22]. The autonomic symptoms

were assessed using the Scales for Outcomes in PD-Autonomic (SCOPA-AUT) Japanese version [23]. The nonmotor symptoms were assessed by an interview using the Non-Motor Symptom Scale (NMSS) [24]. The depressive symptoms were evaluated with the Beck Depression Inventory (BDI)-II [25].

RLS was assessed based on the criteria published by the International RLS Study Group (IRLSSG) [2]. The patients were diagnosed with RLS if the following four essential features occurred during the prior year after excluding other RLS mimics: 1) an urge to move the legs that is usually accompanied or caused by uncomfortable and unpleasant sensations in the legs; 2) the urge to move the legs and any accompanying unpleasant sensations begin or worsen during periods of rest or inactivity, such as lying down or sitting; 3) the urge to move the legs and any accompanying unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues; and 4) the urge to move the legs and any accompanying unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues. The severity of restlessness was assessed with the IRLSSG rating scale (IRLS) [26].

The patients were diagnosed with LMR if they had the urge to move the legs during the prior year but did not fulfill the four essential features of RLS [16]. The patients were diagnosed with RLS/LMR variants if the abnormal sensations and restlessness predominantly or solely occurred in body parts other than the legs and their symptoms satisfied the four aforementioned criteria for RLS or LMR when applied in a modified manner to the involved body parts. Conditions that can mimic RLS or LMR, such as positional discomfort, muscle cramps, venous stasis, vascular claudication and

peripheral neuropathy, were excluded, and the diagnosis of RLS or LMR was confirmed [27]. Figure 1 shows the diagnostic flowcharts for RLS, RLS variants, LMR and LMR variants. TM performed detailed clinical interviews and assessments to diagnose the patients with RLS, RLS variants, LMR or LMR variants. If a patient had no urge to move based on the clinical interview but scored ≥1 point (1 or more days per week) on PDSS-2 subitem 4 (nocturnal restlessness), the patient was defined as having restlessness without the urge to move.

The disease severity was rated based on the Hoehn and Yahr (HY) stage. Cognitive functioning was assessed with the MMSE. The levodopa equivalent dose (LED) was calculated according to previously described methods [28]. Parkinsonism was assessed with the Japanese version of the Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale part III [29]. In the patients with PD, the motor complications were assessed with the Japanese version of the MDS-UPDRS part IV. The clinical characteristics of the PD patients with restlessness (positive for RLS, LMR, RLS variants, LMR variants or restlessness without the urge to move) were compared with those of the PD patients without restlessness by DAT SPECT, MIBG cardiac scintigraphy and olfactory testing as described below.

Cardiac 123I-metaiodobenzylguanidine scintigraphy

Chest SPECT and planar images were obtained using a gamma camera 15 minutes (early phase) and 4 hours (delayed phase) after an injection of 111 MBq 123I-MIBG (FujifilmRI Pharma Co., Tokyo, Japan) [30]. Then, the heart-to-mediastinum (H/M) ratio was calculated by dividing the count density of the left ventricular region of

interest (ROI) by that of the mediastinal ROI. We used delayed MIBG imaging in this study.

DAT SPECT

^{123}I FP-CIT-SPECT imaging was performed 3 hours after an injection of 167 MBq (4.5 mCi) [31]. The specific binding ratio (SBR) in the striatum was semiquantitatively determined and analyzed using QSPECT DAT quantification program (Molecular Imaging Labo Inc., Osaka, Japan). In this study, we used the averaged SBR values in the left and right striatum.

Olfactory functioning

A card-type odor identification test (Open Essence (OE), Wako, Japan) was used [32]. The usefulness of the OE test in PD-related disorders has been confirmed [33]. The OE test includes the following 12 different odors that are familiar to the Japanese population: India ink, wood, perfume, menthol, Japanese orange, curry, gas for household use, rose, Hinoki cypress, sweaty socks, condensed milk, and roasted garlic. During the test, when a subject opens the twice-folded card, a microcapsule breaks, and the odor is released. The subjects were asked to choose one of the following 6 possible answers: correct odor, odor closest to the correct odor, odor close to the correct odor, odor very different from the correct odor, detectable but unrecognizable odor, and no odor detected.

Statistical analysis

Chi-square and Fisher's exact tests were used to compare the categorical variables between the groups. Mann-Whitney U test and Student's t-tests were used as appropriate to compare the continuous variables between the two groups. The correlation between IRLS and the other clinical parameters was analyzed with Spearman's rank correlation coefficients. The differences in the continuous variables among the PD, MSA and PSP groups were assessed using the Kruskal–Wallis test, followed by Dunn's post hoc test, or one-way analysis of variance, followed by Bonferroni's post hoc test, as appropriate. A logistic regression analysis using a likelihood ratio forward selection model was performed to determine the contributing factors for restlessness in PD patients, adjusting for other clinical factors such as age, sex, disease duration, HY stage, LED, SCOPA-AUT, PDSS-2, and BDI-II. Two-tailed p-values<0.05 were considered statistically significant. IBM SPSS software V.25.0 (IBM SPSS, Tokyo, Japan) and GraphPad Prism for Windows (V.7.0a; GraphPad Software, San Diego, California, USA) were used for the statistical analyses.

Results

Table 1 shows the clinical characteristics of the patients with PD, MSA and PSP. The PSP patients had higher HY stages than the PD and MSA patients. A total of 41.3% of PD patients, 82.4% of MSA patients and 36.4% of PSP patients were untreated. The MSA patients had lower LED, lower scores on PDSS-2 and higher scores of SCOPA-AUT than the PD patients. The PD patients exhibited higher scores on NMSS

than the MSA and PSP patients. The frequency of RLS, LMR and LMR variants was as follows: PD (12.7%, 11.1% and 1.6%); MSA (5.9%, 11.8%, and 0%); and PSP (0%, 9.1% and 0%) (Table 2A). One MSA patient with RLS was MSA-P, and 2 MSA patients with LMR were MSA-P and MSA-C. None of the patients reported RLS variants. Restlessness without the urge to move, as assessed by PDSS-2 subitem 4, was observed in 25.4% of the PD patients and 11.8% of the MSA patients but was not observed in the PSP patients. Among the untreated groups, RLS, LMR and restlessness without the urge to move were observed in 11.5%, 7.7% and 23.1% of the PD patients and 7.1%, 14.3% and 7.1% of the MSA patients, respectively, while none of the PSP patients showed any restlessness. None of the untreated patients reported RLS variants or LMR variants (Table 2B). In Table 2, statistical comparisons among the groups were not performed due to the small number of MSA and PSP patients.

Among the 8 PD patients with RLS, 4 (50.0%) patients had bilateral symptoms, and 4 (50.0%) patients had unilateral symptoms. Two PD patients with RLS (20.0%) had RLS symptoms on the affected side. One MSA patient with RLS had bilateral symptoms. Among the 7 PD patients with LMR, all (100%) patients had bilateral symptoms. Two MSA patients with LMR had bilateral symptoms, and 1 PSP patient with LMR had bilateral symptoms. One PD patient with LMR variants had unilateral symptoms on the affected side.

Table 3 shows the differences in the characteristics between the PD patients with restlessness (positive for RLS, LMR, RLS variants, LMR variants or restlessness without the urge to move) and those without restlessness. The PD patients with restlessness (49.2%) had higher HY stages and higher scores on SCOPA-AUT, PDSS-2 and BDI-II than the PD patients without restlessness. PD patients with restlessness had

a higher rate of dopamine agonist use and tended to have higher LED. The OE scores, averaged SBR values of the striatum on DAT SPECT and uptake of MIBG cardiac scintigraphy did not differ between the PD patients with and without restlessness. Regarding SCOPA-AUT subitems, there was no significant difference between PD patients with restlessness and those without restlessness, except for gastrointestinal function, which was higher in PD patients with restlessness (4.6±3.7 vs. 2.3±2.2, $p<0.05$). There were no gender differences in the frequency of RLS, LMR, RLS variants and LMR variants among PD patients (Supplementary Table 1). A logistic regression analysis showed that PDSS-2 ($p<0.001$; odds ratio, 1.292; 95%CI, 1.110-1.504) was the sole predictor for restlessness in PD patients, after adjusting for other clinical factors.

Then, we assessed the correlations between the severity of restlessness and the clinical parameters using IRLS among the PD patients with restlessness (n=32). The IRLS scores positively correlated with SCOPA-AUT ($r=0.48$, $p<0.05$).

Discussion

This cross-sectional study was the first to perform detailed assessments of restlessness related disorders, such as RLS, RLS variants, LMR and LMR variants, among patients with PD-related disorders. The frequency of RLS and LMR was 12.7% and 11.1% among the PD patients, 5.9% and 11.8% among the MSA patients and 0% and 9.1% among the PSP patients, respectively. Although no statistical comparison was made among the PD, MSA and PSP groups, the frequency of RLS and LMR in the untreated patients with PD (11.5%, 7.7%) and MSA (7.1%, 14.3%) was likely higher than that in the patients with PSP (0%, 0%), suggesting that restlessness is related to the disease and

is not an effect of the dopaminergic treatment. Gjerstad et al [16] showed that the LMR prevalence in untreated PD patients was higher than that in age-matched healthy controls, but PSP and MSA patients were not included in their study. In our study, LMR variants, which have never been previously studied, were observed in 1.6% of the PD patients but not in the MSA and PSP patients. RLS variants, such as restless lower back [13] and perianal region [14], have been reported in patients with PD; however, we did not find RLS variants in this study in any group. Even though the PSP patients exhibited greater disease severity than the PD and MSA patients, the PSP patients did not report any restlessness (RLS, LMR or LMR variants). The unawareness of restlessness, which could possibly be related to the frontal lobe dysfunction in PSP, could play a role.

Compared with the study by Zhu et al [34], in our study in PD patients, unilateral RLS symptoms were less frequent (50%) and only 1 PD patient had RLS symptoms on the affected side. Our PD patients with LMR all had bilateral symptoms, while the study by Zhu et al showed the majority of patients had unilateral LMR symptoms (94.4%) on the affected side (94.1%). Nomura et al [35] found that 35% of PD patients with RLS showed asymmetrical distribution of RLS symptoms, but there was no correlation between the predominantly affected side of PD and RLS symptoms. Bhalsing et al [11] found that all patients with PD and RLS had bilateral symptoms, despite the PD motor symptoms being asymmetric. A longitudinal study that included 109 drug-naïve PD patients showed RLS prevalence increased from 4.6% at baseline evaluation to 6.5% after 2 years and to 16.3% after 4 years, suggesting disease progression along with increased dopaminergic medication had a role [36]. Although there has been no prospective study on LMR in PD patients, LMR was more common even in untreated PD patients than in healthy controls [16], which suggests that LMR

could represent PD-related sensorimotor symptoms. In our study, PD patients with restlessness tended to show longer PD duration, increased HY severity and LED, suggesting that RLS/LMR are PD-related symptoms. However, the reason for the difference in the rate of unilateral/bilateral RLS/LMR between our study and the study by Zhu et al [34] is unclear, but may be due to differences in the study population.

In a previous study, PD patients with RBD showed reduced MIBG uptake compared with PD patients without RBD [37]. However, the difference in cardiac MIBG uptake between PD with and without restlessness has not been assessed previously. In patients with RLS, the SCOPA-AUT cardiovascular dysfunction domain was significantly impaired compared with control subjects [38], but in our study neither SCOPA-AUT cardiovascular dysfunction domain nor cardiac MIBG uptake were different between PD patients with and without restlessness, suggesting that cardiac autonomic impairment and restlessness are unlikely to be linked in PD patients.

We found that PD patients with restlessness exhibited severe disease severity and increased autonomic, sleep and depressive symptoms compared with those without restlessness. Piao et al [39] reported that compared with PD patients without RLS, PD patients with RLS showed a significantly longer duration, higher disease severity and higher scores for motor symptoms, depression, anxiety, sleep disorders, fatigue and apathy, and increased transferrin and decreased iron, ferritin, dopamine and 5-hydroxytryptamine contents in the cerebrospinal fluid. In their study, the SCOPA-AUT scores tended to be higher in PD patients with RLS compared with PD patients without RLS. The depression rate was higher in PD patients with RLS and LMR compared with those without restlessness [16]. These observations suggest that PD with RLS may be characterized by impaired neurotransmitter systems, such as

dopamine and serotonin, and iron in the brain. In contrast, Moccia et al [36] found a tendency toward the perseveration of dopamine transporter availability in the affected caudate and putamen in PD patients with RLS compared to those without restlessness. Dragan et al [40] also proposed the interesting hypothesis that RLS may delay the onset of PD based on observations that the onset age of parkinsonism was older in the RLS+PD (RLS preceding PD) group than that in the control PD group (without RLS). In this study, we did not find differences in SBR of the striatum on DAT SPECT between PD patients with and without restlessness. The IRLS score and DAT SPECT findings were not significantly correlated in the PD patients with restlessness.

In our study, PD patients with restlessness had a higher rate of dopamine agonist use and tended to have higher LED than those without restlessness. It is possible that chronic dopaminergic treatment unmasked subtle or subclinical RLS in some PD patients. On the other hand, increased dopaminergic medication use in PD patients with restlessness could reflect progressed disease severity as rated by HY stage compared with PD patients without restlessness.

RLS has been reported in 4.7-28% of MSA patients [41]. In MSA patients, RLS was not related to disease severity, LED or excessive daytime sleepiness [10, 42], but the prevalence of RLS tended to be more frequent in MSA-P patients than MSA-C patients [41]. In our study, among the MSA patients, one patient with RLS was MSA-P (1/1, 100%), and 1 of 2 patients with LMR was MSA-P (1/2, 50%).

In our study, none of the PSP patients reported RLS, while the RLS prevalence was 12.7% and 5.9% among the PD and MSA patients, respectively. Similarly, Bhalsing et al [11] found that the prevalence of RLS in PSP patients (3.7%) and MSA patients (4.7%) was lower than that in patients with PD (11.9%). In contrast, in a study

conducted by Gama et al [12] evaluating sleep disorders among patients with PD-related disorders, RLS was the most frequent in patients with PSP (57%), followed by PD (50.0%) and MSA (23.1%), and in PSP patients, the presence of RLS was associated with reduced sleep efficiency and sleep duration as assessed by the subitems on the Pittsburgh Sleep Quality Index. The wide difference in the RLS prevalence in PSP patients may account for the differences in the RLS diagnosis or evaluations employed among studies.

Despite the widespread brainstem pathology in PSP patients, the ESS and PDSS-2 scores did not significantly differ among the PD, MSA and PSP patients. We excluded dementia, and the MMSE scores did not significantly differ among the groups in this study; however, this finding could possibly reflect an impairment in frontal lobe functioning in PSP patients. In PD patients, better cognition was reported to be a factor contributing to nighttime sleep problems [43]. A patient with PSP-parkinsonism who developed RLS after withdrawal from rotigotine has been reported [44]. In our study, no patient had PSP-parkinsonism, but none of the PSP patients had RLS or LMR.

Suzuki et al [45] showed that PD patients with RLS or LMR had an increased rate of sleep-related symptoms. Additionally, in our study, the PD patients with restlessness, including RLS and LMR, exhibited higher scores on the SCOPA-AUT, PDSS-2 and BDI-II than those without restlessness, emphasizing the importance of assessing autonomic, sleep and depressive symptoms in patients complaining of restlessness. Unlike idiopathic RLS, nigrostriatal dopaminergic degeneration is evident in PD and related disorders, suggesting that RLS, LMR and RLS/LMR variants in PD and related disorders could be reflective of nocturnal sensorimotor symptoms and wearing off due to endogenous dopamine insufficiency. Therefore, adding a long acting

dopamine agonist treatment should be first considered. Although evidence is insufficient for PD with RLS, alpha 2 delta ligands (gabapentin, gabapentin enacarbil and pregabalin), which inhibit the release of excitatory neurotransmitters such as glutamate and attenuate postsynaptic excitability [46], should be considered when patients are already receiving high-dose dopaminergic treatment. Istradefylline was recently reported to successfully treat PD patients with RLS [47]. In addition, given that restlessness is related to severe disease severity and increased autonomic, sleep and depressive symptoms in PD patients, detecting restlessness could be a good opportunity to revisit the treatment of motor and other non-motor symptoms.

The lack of statistical power due to the small number of MSA and PSP patients and the absence of healthy controls are the major limitations of the study. Additionally, the onset age of RLS or LMR was not assessed. In our study, we only used MMSE to rule out dementia, but given the various profiles of cognitive impairment in PD [48], additional cognitive assessment batteries are needed to evaluate cognitive function in patients with PD in a future study. A strength of our study was that one author, who is a trained neurologist (TM), carried out all the detailed assessments of restlessness through clinical interviews with all the participants in this study to differentiate RLS or LMR from their mimics.

In conclusion, we evaluated restlessness, including RLS and LMR, in patients with PD, MSA or PSP. Restlessness in the PD patients was associated with the disease severity, autonomic symptoms, sleep disturbances and depressive symptoms. Further studies with larger sample sizes are warranted to characterize restlessness in PD and related disorders.

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Conflicts of interest: The authors declare that they have no potential conflicts of interest in relation to this article.

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Figure legends

Figure 1: Flow chart of RLS/RLS variants, LMR/LMR variants and restlessness without the urge to move in this study

RLS=restless leg syndrome; LMR=leg motor restlessness

Table 1: Clinical characteristics of the patients with PD, MSA and PSP

	PD (n=63)	MSA (n=17)	PSP (n=11)	p-value
Age (years)	68.3±10.1	69.2±9.6	72.7±10.0	0.35
Sex (M/F)	29/34	10/7	4/7	0.69
BMI (kg/m^2)	22.0±4.4	23.2±3.3	21.1±3.9	0.33
Disease duration (years)	4.1±4.3	2.9±3.0	4.2±2.9	0.48
MMSE	26.7±3.3	26.4±3.4	24.1±3.8	0.21
Hoehn and Yahr stage	2.6±1.0	2.6±1.3	3.9±1.2*¶	**0.032**
MDS-UPDRS III	28.2±17.2	19.3±11.6	48.8±24.8	0.059
MDS-UPDRS IV	1.3±3.3	-	-	-
Untreated patients, n (%)	26 (41.3)	14 (82.4)*	4 (36.4) ¶	**0.0076**
LED (mg/day)	244.2±326.3	47.1±117.9*	322.7±453.5	**0.015**
Levodopa, n (%)	31 (49.2)	3 (17.6)	5 (45.5)	0.065
Dopamine agonists, n (%)	22 (34.9)	1 (5.9)*	1 (9.1)	**0.021**
SCOPA-AUT	10.7±7.7	13.9±12.5*	27.0±31.1	0.81
PDSS-2	13.0±8.7	6.1±6.8*	10.0±10.8	**0.029**
ESS	6.4±5.1	7.4±5.3	6.4±10.0	0.46

BDI-Ⅱ	13.5±10.3	13.4±12.8	11.0±17.5	0.47
NMSS	31.0±37.6	15.1±33.1*	21.8±58.0*	**0.0010**

The data are presented as the mean±standard deviation. Significant values ($p<0.05$) are shown in bold.

*$p<0.05$ compared to the PD patient group; ¶$p<0.05$ compared to the MSA patient group.

PD=Parkinson's disease; MSA=multiple system atrophy; PSP=progressive supranuclear palsy; BMI=body mass index; MMSE=Mini-Mental State Examination; MDS-UPDRS=Movement Disorder Society revision of the Unified PD Rating Scale; LED=levodopa equivalent dose; SCOPA-AUT=Scales for Outcomes in PD-Autonomic; PDSS-2=PD Sleep Scale-2; ESS=Epworth Sleepiness Scale; BDI-II=Beck Depression Inventory-II; NMSS=Non-Motor Symptom Scale.

Table 2: Prevalence of RLS, LMR, and RLS/LMR variants in PD and related disorders

(A) Total patients

	PD (n=63)	MSA (n=17)	PSP (n=11)
RLS, n (%)	8 (12.7)	1 (5.9)	0 (0)
LMR, n (%)	7 (11.1)	2 (11.8)	1 (9.1)
RLS variants, n (%)	0 (0)	0 (0)	0 (0)
LMR variants, n (%)	1 (1.6)	0 (0)	0 (0)
Restlessness without the urge to move, n (%)	16 (25.4)	2 (11.8)	0 (0)

(B) Untreated patients

	PD (n=26)	MSA (n=14)	PSP (n=6)
RLS, n (%)	3 (11.5)	1 (7.1)	0 (0)
LMR, n (%)	2 (7.7)	2 (14.3)	0 (0)
RLS variants, n (%)	0 (0)	0 (0)	0 (0)
LMR variants, n (%)	0 (0)	0 (0)	0 (0)
Restlessness without the urge to move, n (%)	6 (23.1)	1 (7.1)	0 (0)

The data are presented as n (%).

PD=Parkinson's disease; MSA=multiple system atrophy; PSP=progressive supranuclear palsy; RLS=restless legs syndrome; LMR=leg motor restlessness

Table 3: Comparison of PD patients with and without restlessness

	PD without restlessness	PD with restlessness*	p-value
Age (years)	68.5±10.5	68.1±9.9	0.89
Sex (M/F)	13/18	16/16	0.52
BMI	22.1±5.0	21.8±3.7	0.75
Disease duration (years)	3.1±2.9	5.0±5.1	0.072
MMSE	27.0±3.0	26.4±3.5	0.48
HY stage	2.2±0.8	2.9±1.1	**0.0095**
MDS-UPDRS III	25.4±14.6	30.9±19.2	0.21
MDS-UPDRS IV	1.0±2.5	1.6±3.9	0.43
Untreated patients, n (%)	15 (48.4)	11 (34.4)	0.26
LED	167.9±271.5	328.1±360.7	0.067
Levodopa, n (%)	14 (45.2)	17 (53.1)	0.53
Dopamine agonist, n (%)	8 (25.8)	14 (43.8)	**0.014**
SCOPA-AUT total	7.9±5.8	13.5±8.2	**0.0046**
PDSS-2	8.0±5.3	17.7±8.8	**<0.001**
ESS	5.1±3.9	7.6±5.9	0.053
BDI-Ⅱ	10.0±7.1	16.6±11.8	**0.013**
NMSS	28.1±29.1	33.8±44.4	0.56
DAT SPECT	4.0±1.5	3.8±1.1	0.61
MIBG cardiac scintigraphy	2.2±1.2	1.8±0.8	0.13
Open Essence	4.5±2.9	3.8±2.4	0.37
IRLS	-	10.2±10.1	-

The data are presented as the mean±standard deviation. Significant values ($p<0.05$) are shown in bold.

*PD with restlessness group consists of RLS, LMR/LMR variants and restlessness without the urge to move.

PD=Parkinson's disease; BMI=body mass index; MMSE=Mini-Mental State Examination; MDS-UPDRS=Movement Disorder Society revision of the Unified PD Rating Scale; LED=levodopa equivalent dose; SCOPA-AUT=Scales for Outcomes in PD-Autonomic; PDSS-2=PD Sleep Scale-2; ESS=Epworth Sleepiness Scale; BDI-II=Beck Depression Inventory-II; NMSS=Non-Motor Symptom Scale; IRLS=International RLS Study Group rating scale.

Table 4: Correlations between the IRLS scores and clinical parameters in PD patients with restlessness

	IRLS score
	correlation coefficient
Age (years)	-0.38
BMI	-0.14
Disease duration (years)	0.04
MMSE	0.13
Hoehn and Yahr stage	0.09
MDS-UPDRS Ⅲ	0.18
MDS-UPDRS Ⅳ	0.13
LED	0.08
SCOPA-AUT	0.48 *
PDSS-2	0.25
ESS	-0.14
BDI-Ⅱ	0.16
NMSS	0.03
DAT SPECT	-0.29
MIBG cardiac scintigraphy	-0.32
Open Essence	-0.17

* $p<0.05$.

IRLS=International Restless Legs Syndrome Study Group rating scale; BMI=body mass index; MMSE=Mini-Mental State Examination; MDS-UPDRS=Movement Disorder Society revision of the Unified PD Rating Scale; LED=levodopa equivalent dose; SCOPA-AUT=Scales for Outcomes in PD-Autonomic; PDSS-2=PD Sleep Scale-2; ESS=Epworth Sleepiness Scale; BDI-II=Beck Depression Inventory-II; NMSS=Non-Motor Symptom Scale.

Figure 1

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