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

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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 among the PD patients with restlessness.

*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.

## 1. 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 non-motor 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 disorder (RBD).

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

*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

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is restricted to or predominantly involves regions other than the legs with characteristics identical to those of RLS, have 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.

## 2. 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.

### 2.1. 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 only occur or are worse in the evening or night than during the day. 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]. Fig. 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 $\geq 1$ 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 (MDS-UPDRS) 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.

### 2.2. Cardiac 123I-metaiodobenzylguanidine scintigraphy

Chest SPECT and planar images were obtained using a gamma camera 15 min (early phase) and 4 h (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.

### 2.3. DAT SPECT

$^{123}$I FP-CIT-SPECT imaging was performed 3 h 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.

### 2.4. Olfactory functioning

A card-type odor identification test (Open Essence (OE), Wako,