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Characterizing restless legs syndrome and leg motor restlessness in patients with Parkinson's disease: A multicenter case-controlled study

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ABSTRACT

Background: We investigated the prevalence and impact of restless legs syndrome (RLS) and leg motor restlessness (LMR) in patients with Parkinson's disease (PD) in a multicenter study.
Methods: A total of 436 PD patients and 401 age- and sex-matched controls were included in this study. RLS was diagnosed based on four essential features. LMR was diagnosed when a participant exhibited the urge to move his or her legs but did not meet the four essential features of RLS.
Results: The RLS prevalence did not differ between PD patients and controls (3.4% vs. 2.7%), while LMR prevalence was significantly higher in PD patients than in controls (12.8% vs. 4.5%). PD patients with RLS or LMR had a higher prevalence of excessive daytime sleepiness (EDS) (50.7%, vs. 6.9%), probable REM sleep behavior disorder (38.0% vs. 3.4%) and PD-related sleep problems (49.3% vs. 20.7%) than controls with RLS or LMR. RLS/LMR preceding PD onset was related to an older age of PD onset.
Conclusion: Our study revealed an increased prevalence of LMR but not RLS in PD patients. LMR could be an early manifestation of PD; however, whether LMR is within the range of RLS or whether LMR and RLS constitute different entities in PD requires further studies.

1. Introduction

Restless legs syndrome (RLS) is a sensorimotor disorder characterized by an urge to move the legs accompanied by abnormal sensation; bouts occur predominantly during rest and evenings and can lead to insomnia [1]. In Asia, RLS prevalence in the general population has been reported to be 1–4% [2,3]. Increased prevalence of RLS in PD patients compared with controls and favorable responses to dopaminergic drugs in both RLS and PD have been reported by several studies, suggesting a link between these disorders. However, in untreated patients with PD, RLS prevalence has been reported to be similar to that in controls [4,5]. Additionally, a recent systematic review of RLS and major diseases showed a possible association between RLS and dopaminergic drug-treated PD but not untreated PD [6]. In contrast, leg motor restlessness (LMR), a condition in which an urge to move the legs exists but symptoms do not fulfill the four essential features of RLS, has attracted attention due to observations of increased LMR prevalence even in drug-naïve PD patients compared with controls [5] and the negative impact of RLS on sleep in PD patients [7]. However, few studies have characterized LMR in PD patients.

In this study, we aimed to investigate the prevalence and characteristics of RLS and LMR in a large sample of PD patients from

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a multicenter, case-controlled study.

2. Patients and methods

Between September 2014 and April 2016, a multicenter study was performed to assess NMS of PD, which included 8 University Hospitals in the Kanto region of Japan. The Kanto region consists of 7 prefectures, which include the capital Tokyo and the Greater Tokyo Area with an approximate population of 42.6 million, accounting for one-third of the entire Japanese population according to the 2010 Population Census of Japan, Preliminary Counts of the Population and Households.

3. Patients

Among an initial sample of 490 PD patients (age, 69.4 ± 8.0 years; 225 M), 436 PD patients (age, 69.3 ± 7.8 years; 197 M) were included after excluding dementia defined as Mini-Mental Status Examination scores lower than 24 and missing data. Bedridden patients and patients who were unable to answer the questionnaire were also excluded from this study. Age- and sex-matched control subjects with no history of any neurological or psychiatric diseases (n = 401; age, 69.2 ± 8.6 years; 187 M) recruited from the medical staff and their friends and family participated in this study.

4. Methods

All patients were assessed by board-certified neurologists who were experienced in movement disorders, and a diagnosis of PD was made according to the UK Brain Bank Clinical Diagnostic Criteria. Brain imaging was performed to exclude atypical Parkinsonian syndrome or vascular parkinsonism. Drug-induced parkinsonism was also excluded based on clinical history. Disease severity was evaluated by Hoehn and Yahr (HY) staging. All PD patients were evaluated based on the Japanese version of the MDS-UPDRS part II (motor experiences of daily living), III (motor examination) and IV (motor complications).

All participants completed questionnaires regarding their habits, education and sleep status. The PD sleep scale (PDSS)-2, consisting of 15 individual items for nocturnal non-motor and motor problems, was used to evaluate PD-related sleep problems [8]. Three domain scores of the PDSS-2 were also evaluated: “disturbed sleep” (items 1–3, 8, and 14), “motor symptoms at night” (items 4–6, 12, and 13), and “PD symptoms at night” (items 7, 9–11, and 15) [9]. PDSS-2 scores ≥18 were defined as clinically relevant PD-specific sleep disturbances [10]. Daytime sleepiness was measured by using the Japanese version of the Epworth sleepiness scale (ESS) [11]. Excessive daytime sleepiness (EDS) was defined as an ESS score of 10 or greater. The Japanese version of the RBD screening questionnaire (RBDSQ-J) was used, and RBDSQ-J scores of 5 or greater were defined as probable RBD (pRBD) [12]. RLS was determined by the presence of the four essential features outlined in the questionnaire: 1) an urge to move the legs usually accompanied by 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 during rest or inactivity only occur or are worse in the evening or night than during the day. RLS mimics such as positional discomfort, muscle cramp, venous stasis, vascular claudication and peripheral neuropathy were excluded by the questionnaire, and the diagnosis of RLS was confirmed by board-certified neurologists [13]. LMR was diagnosed when a participant exhibited the urge to move his or her legs but did not meet the four essential features of RLS. Regarding the onset of RLS or LMR in relation to the onset of PD, we further classified the PD patients with RLS or LMR into 2 groups: RLS/LMR preceding PD and RLS/LMR following PD. The former was defined as PD patients exhibiting a history suggestive of RLS or LMR before the onset of PD, and the latter was defined as PD patients developing RLS or LMR at the same time of the diagnosis of PD or after the diagnosis of PD. The semi-structured Mini International Neuropsychiatric Interview (MINI) based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, was administered to participants to assess depression (minor and major depression) [14]. The levodopa-equivalent dose (LED) was calculated based on previously reported conversion factors [15].

This study was conducted in accordance with the Declaration of Helsinki. The study was approved by the institutional review boards of the participating facilities, and written informed consent was obtained from all participants enrolled in the study.

5. Statistical analysis

Mann-Whitney U tests or Student's t-tests were used where appropriate to compare continuous variables, and chi-squared or Fisher's exact tests were used to compare the categorical variables between the patients with PD and controls. The demographic characteristics of the no restlessness, RLS and LMR groups were compared using one-way analysis of variance (ANOVA) for continuous variables and chi-squared tests for categorical variables. Because of the exploratory nature of our study, adjustments for multiplicity for the multiple tests in this study were not performed. Two-tailed p values of <0.05 were considered statistically significant. IBM SPSS software, version 24.0 (IBM SPSS, Inc., Tokyo, Japan) was used for statistical analyses, and GraphPad Prism for Windows (Version 5.01; GraphPad Software, San Diego, USA) was used to generate figures.

6. Results

The demographics and characteristics of PD patients and control subjects are shown in Table 1. The mean disease duration and HY

Table 1
The demographics and characteristics of PD patients and controls.

	PD (n = 436)	Controls (n = 401)	P value
n (M/F)	436 (197/239)	401 (187/214)	0.67
Age (y)	69.3 ± 7.8	69.2 ± 8.6	0.38
Education (y)	12.5 ± 2.8	12.2 ± 2.8	0.10
Caffeine intake, n (%)	381 (87.4)	342 (85.3)	0.38
Caffeine (cup/day)	2.5 ± 2.0	2.5 ± 2.3	0.97
Alcohol, n (%)	196 (45.0)	217 (54.1)	0.0081
Smoking, n (%)	35 (8.0)	71 (17.7)	<0.0001
Disease duration (y)	7.4 ± 5.3	–	–
Onset age of PD (y)	61.9 ± 9.5	–	–
Hoehn and Yahr stage, n (%)			
Stage 1	41 (9.4)	–	–
Stage 2	254 (58.3)	–	–
Stage 3	120 (27.5)	–	–
Stage 4	20 (4.6)	–	–
Stage 5	1 (0.2)	–	–
MDS-UPDRS part II	12.6 ± 8.9	–	–
MDS-UPDRS part III	28.6 ± 13.3	–	–
MDS-UPDRS part IV	2.0 ± 3.3	–	–
De novo, n (%)	34 (7.8)	–	–
LED (mg/day)	488.3 ± 360.0	–	–

PD=Parkinson's disease; MDS-UPDRS=Movement Disorder Society revision of the Unified Parkinson's Disease Rating Scale; LED = levodopa-equivalent dose.

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