Parkinsonism and Related Disorders 19 (2013) 355–358

Contents lists available at SciVerse ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Short communication

Restless legs syndrome in Korean patients with drug-naïve Parkinson's disease: A nation-wide study

Hee-Young Shin [a,1], Jinyoung Youn [b,1], Won Tae Yoon [c], Ji Sun Kim [b], Jin Whan Cho [b,*]

[a] Center for Health Promotion, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea
[b] Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, 50, Irwon-Dong, Gangnam-Gu, Seoul 135-710, Republic of Korea
[c] Department of Neurology, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

ARTICLE INFO

Article history:
Received 23 April 2012
Received in revised form
6 September 2012
Accepted 18 September 2012

This manuscript is dedicated to the loving memory of Won Young Lee, who designed and conducted this study.

Keywords:
Restless legs
Parkinson
Drug-naive
Dopamine
Iron

ABSTRACT

Background: Restless legs syndrome is a common neurologic disorder, and there is increasing evidence for a dopaminergic link between Parkinson's disease and restless legs syndrome. However, most previous studies did not take into account the effects of dopaminergic medication. We conducted a nation-wide, cross-sectional study to determine the prevalence and clinical characteristics of restless legs syndrome in Korean drug-naïve Parkinson's disease patients.
Methods: One hundred and fifty-one drug-naïve patients with Parkinson's disease were enrolled from 18 centers in South Korea over the course of one year. Clinical profiles of parkinsonism, restless legs syndrome, psychiatric symptoms, and laboratory data were collected. The findings of subjects with and without restless legs syndrome were compared.
Results: The prevalence of restless legs syndrome in drug-naïve patients with Parkinson's disease was 16.5%. Subjects with restless legs syndrome had a higher mean Hoehn and Yahr stage and more severe limb parkinsonism, especially tremor. There was, however, no difference in iron metabolism between patients with and without restless legs syndrome. Analysis demonstrated that Beck's depression inventory score was associated with the severity of restless legs syndrome.
Conclusion: Our study demonstrated an increased prevalence of restless leg syndrome in drug-naïve patients with Parkinson's disease than in the general population. Based on the association between parkinsonism and restless legs syndrome, and the unique characteristics of restless legs syndrome in patients with Parkinson's disease, we suggest that the pathophysiology of restless legs syndrome in Parkinson's disease differs from that in patients without Parkinson's disease.

1. Introduction

Although Restless legs syndrome (RLS) and Parkinson's disease (PD) have frequently been considered related disorders that share a common pathophysiology via the dopaminergic pathway [1], the exact prevalence of RLS in PD patients and the relationship between the two disorders remains controversial.

In spite of many studies examining RLS in PD patients, none adjusted for the effect of dopaminergic medication or enrollment of patients with advanced PD who could have fluctuations due to both medication effects and disease progression [2–6]. Therefore, the diverse prevalence of RLS in PD patients could result from these confounding effects of medications in each study [2–6].

Recently, two studies were conducted on the prevalence of RLS in drug-naïve PD patients to eliminate the confounding effect of dopaminergic medication [7,8]; however, these studies failed to report a similar prevalence of RLS (5.5% vs. 15.5%). Therefore, to exclude the effect of this major confounder and assess the nature of the correlation between RLS and PD, we conducted a nation-wide, cross-sectional study to determine the prevalence of RLS in drug-naïve early-stage PD patients.

2. Methods

2.1. Subjects

Early-stage drug-naïve patients with PD were enrolled at outpatient movement disorder clinics in 18 community-based hospitals in Korea between March 2009 to February 2010. PD was diagnosed by specialists in movement disorders using the United Kingdom PD Society Brain Bank criteria. RLS was diagnosed when patients met the four essential criteria of the International Restless Legs Syndrome Study Group (IRLSSG) [9]. We excluded patients with diabetes, chronic obstructive pulmonary disease, rheumatoid arthritis, uremia, neuropathy, anemia or medication

* Corresponding author. Tel.: +82 2 3410 1279; fax: +82 2 3410 0052.
E-mail address: jinwhan.cho@samsung.com (J.W. Cho).
[1] These authors have equally contributed to this study as co-first authors.

1353-8020/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.parkreldis.2012.09.009

history including neuroleptics, antidepressants, anxiolytics or sleep medication to rule out symptoms mimicking RLS such as akathisia, and secondary RLS. Patients with cognitive deterioration (an MMSE-K score of <24 out of 30) and those who failed to complete the study questionnaires were also excluded. All patients signed informed consent, and the study was approved by the Institutional Review Boards of all participating institutions.

2.2. Measurement instruments

All patients were examined for demographic variables. PD symptom and severity were evaluated with Hoehn and Yahr (H&Y) stage and Unified Parkinson Disease Rating Scale–motor scale (UPDRS part III). Subjects were classified into three groups based on UPDRS patterns: an akinesia-rigidity predominant (AR) group, a tremor-predominant (TR) group, and a mixed (MX) group [10]. Parkinsonism in limb was measured by the sum of the scores from the item number 20 to 26, axial parkinsonism by the sum of the scores from the item number 27 to 30 and bradykinesia by the sum of the scores from the item number 23 to 26 in UPDRS part III. The Korean version of the mini-mental status examination (MMSE-K) was used to evaluate cognitive function, and the PD sleep scale (PDSS) to evaluate sleep status. Psychological assessments were performed in all subjects using Beck's Anxiety Inventory (BAI) and Beck's Depression Inventory (BDI). RLS severity was assessed using the International RLS rating scale (IRLSRS) [11]. Blood laboratory tests were performed to assess hematologic factors, liver function, and renal function, including fasting glucose, iron, ferritin, and transferrin levels.

2.3. Statistical analysis

All data are presented as means ± standard deviations. Differences between the two groups were evaluated using the unpaired Student's *t*-test or the Mann–Whitney *U* test for continuous and ordinal variables, and Pearson's chi-square test or Fisher's exact test for categorical variables. Spearman correlation and partial correlation tests were used to analyze relationships among possible contributing factors and the severity of RLS. *P*-values of <0.05 were considered statistically significant. All statistical analyses were conducted using commercially available software (SPSS for Windows, version 18.0; SPSS Inc., Chicago, IL, USA).

3. Results

We enrolled one hundred and fifty-one drug-naïve PD patients. Mean subject age was 63.5 ± 10.6 and 55 were male (36.4%). The mean age at PD onset was 61.9 ± 10.8 years old, and mean PD duration was 17.7 ± 12.4 months. The mean UPDRS part III score was 15.0 ± 8.4 and H&Y stage was 1 (57.6%) or 2 (42.4%) in all subjects (Table 1). Four patients (2.7%) had a family history of PD.

3.1. Prevalence and demographic data of RLS in drug-naïve PD patients

Of the 151 study subjects, 25 were diagnosed as having RLS (16.5%). In subjects with RLS, mean duration of PD was 17 ± 13.0 months and mean RLS duration was 23.5 ± 10.5 months. Although the duration of RLS was longer than that of PD, these values were not significantly different. Mean severity of RLS symptoms using the IRLSRS was 18.0 ± 7.6. Nineteen RLS patients (76%) complained of leg symptoms, 2 (8%) of arm symptoms, and 4 (16%) of both arm and leg symptoms. Only seven patients (28%) had bilateral RLS symptoms. Of the other 18 patients with unilateral RLS symptoms, only 2 patients had RLS symptoms in the side contralateral to the dominant parkinsonism side. Among the 4 patients with family history of PD, only 1 subject had RLS.

Table 1
Characteristics of drug-naïve PD patients.

Characteristics	Patients
No. patients	151
Sex, male/female (% male)	55/96 (36.4)
Age (years)	63.5 ± 10.6
Duration of PD (months)	17.7 ± 12.4
Age at onset (years)	61.9 ± 10.8
UPDRS part III	15.0 ± 8.4
Hoehn and Yahr stage (%), 1/2	57.6/42.4
PD subgroup (%), AR/TR/MX	57.6/22.5/19.9
K-MMSE	27.0 ± 2.3
PDSS	121.4 ± 22.8

PD, Parkinson disease; UPDRS, unified Parkinson disease rating scale; AR, Akinesia-rigidity predominant group; TR, tremor-predominant group; MX, mixed group; K-MMSE, Korean version of a mini-mental status examination; PDSS, Parkinson disease sleep scale.

3.2. Characteristics in drug-naïve PD patients with RLS

No significant difference was observed between drug-naïve PD subjects with and without RLS in terms of demographics (Table 2). However, when we assessed parkinsonism, subjects with RLS had a more severe H&Y stage, in limb parkinsonism, especially resting tremor. Although mean PDSS score was significantly lower in subjects with RLS, there was no difference between two groups when we eliminated scores of questions about RLS in total PDSS scores.

3.3. Factors that influenced RLS symptoms in drug-naïve PD patients

In drug-naïve PD patients with RLS, no significant differences in IRLSRS score were found between men and women. Correlation analysis demonstrated statistical significance only in BDI and PDSS with RLS severity. No association was found between RLS severity and parkinsonism such as H&Y stage and scores for parkinsonism, which were significantly more severe in patients with RLS. Moderately significant correlations were found between IRLSRS scores and PDSS scores ($r = -0.487$, $p = 0.047$) and BDI scores ($r = 0.618$, $p = 0.001$). However, when we eliminated the scores in questions about RLS, there was no correlation between IRLSRS scores and PDSS scores. There was a correlation between BDI scores and IRLSRS scores using partial information regardless of age, sex, UPDRS and H&Y stage ($r = 0.649$, $p = 0.002$).

Table 2
Characteristics of drug-naïve PD patients with and without RLS.

Characteristics	RLS ($n = 25$)	No RLS ($n = 126$)	*p*-value
Age (years)	64.8 ± 12.6	63.2 ± 10.2	0.240
Sex, male/female (% male)	6/19(24)	49/77(36.4)	0.158
Duration of PD (months)	17 ± 13.0	17.9 ± 12.5	0.628
Age at PD onset (years)	63.2 ± 13.1	61.7 ± 10.4	0.281
Family history of PD, *n* (%)	1 (4)	3 (2.4)	0.519
Hoehn and Yahr stage (%), 1/2	28/72	63.5/36.5	0.001*
PD subgroup (%), AR/TR/MX	48/16/36	59.5/23.8/16.7	0.083
UPDRS part III	17.4 ± 8.2	14.5 ± 8.4	0.060
Axial parkinsonism	1.7 ± 1.6	1.7 ± 1.9	0.783
Parkinsonism in Limb	13.4 ± 6.5	10.6 ± 6.6	0.022*
Bradykinesia	6.6 ± 4.0	5.3 ± 4.0	0.066
Resting tremor	2.2 ± 1.7	1.5 ± 1.6	0.029*
Rigidity	3.4 ± 2.8	2.8 ± 2.2	0.457
PDSS	117.0 ± 16.8	122.2 ± 23.7	0.047*
PDSS except scores on RLS	101.3 ± 15.1	104.3 ± 20.8	0.103
K-MMSE	26.3 ± 2.2	27.0 ± 2.3	0.211
BAI	32.9 ± 8.6	30.0 ± 6.9	0.092
BDI	13.9 ± 10.4	10.5 ± 8.1	0.095
Hemoglobin	13.3 ± 1.4	13.5 ± 1.4	0.257
Hematocrit	39.3 ± 4.1	40.0 ± 3.9	0.411
Serum iron	91.0 ± 34.2	85.5 ± 33.9	0.410
Ferritin	121.9 ± 80.2	99.9 ± 79.0	0.008
Transferrin	237.6 ± 47.7	228.2 ± 70.0	0.947

PD, Parkinson disease; AR, Akinesia-rigidity predominant group; TR, tremor-predominant group; MX, mixed group; UPDRS, unified Parkinson disease rating scale; PDSS, Parkinson disease sleep scale; K-MMSE, Korean version of a mini-mental status examination; BAI, Beck's anxiety inventory; BDI, Beck's depression inventory. *p*-value was calculated by unpaired Student's *t*-test, Mann–Whitney *U* test, Chi-square test and Fisher's exact test. *p-value < 0.05.