Restless Legs Symptoms and Periodic Leg Movements in Sleep Among Patients with Parkinson’s Disease

Donald L. Bliwise, Ph.D., Elias G. Karroum, M.D. Ph.D., Sophia A. Greer, M.P.H., Stewart A. Factor, D.O., Lynn Marie Trotti, M.D., MSc.

aDepartment of Neurology, Emory University School of Medicine, Atlanta, Georgia
bDepartment of Neurology, George Washington University School of Medicine, Washington, D.C.
cSchool of Medicine, University of Missouri, Columbia, Missouri

Abstract

BACKGROUND: The association between Restless Legs Syndrome (RLS) and Parkinson’s Disease (PD) remains controversial, with epidemiologic and descriptive evidence suggesting some potential overlap while mechanistic/genetic studies suggesting relative independence of the conditions.

OBJECTIVE: To examine a known, objectively measured endophenotype for RLS, periodic leg movements (PLMS) in sleep, in patients with PD and relate that objective finding to restless legs symptoms.

METHODS: We performed polysomnography for one (n = 8) or two (n = 67) consecutive nights in 75 PD patients and examined the association of PLMS with restless legs symptoms.

RESULTS: We found no association between restless legs symptoms and PLMS in PD. Prevalence of both was similar to data reported previously in other PD samples.

CONCLUSIONS: We interpret these results as suggesting that restless legs symptoms in PD patients may represent a different phenomenon and pathophysiology than RLS in the non-PD population.

Keywords
restless legs; periodic leg movements in sleep; Parkinson’s Disease

Correspondence: Donald L. Bliwise, Ph.D., Department of Neurology, Emory University School of Medicine, Sleep Center, 12 Executive Park Drive, Room 435, Atlanta, Georgia 30329, 404-712-7241 (phone), 404-712-8145 (FAX), dbliwis@emory.edu.

CONFLICTS OF INTEREST
The authors have no conflict of interest to report relevant to this work.
Conflicts of interest outside the scope of this work are shown below:
Bliwise: Honoraria: Eisai, Ferring, Huxley, Idorsia, Merck
Karroum: None
Greer: None
Factor: Honoraria: Lundbeck, Sunovion, Biogen, Impel, Acorda, CereSpir; Grants: Medtronic, Boston Scientific, Sun Pharmaceuticals Advanced Research Company, Biohaven, Impax, Lilly, US World Meds, Sunovion Therapeutics, Neurocrine, Vaccinex, Voyager, Jazz, CHDI Foundation, Michael J. Fox Foundation, Parkinson Foundation; Royalties: Demos, Blackwell Futura, Springer, UpToDate; Other: Sinaia Health (Bracket Global LLC), CNS Ratings LLC
Trotti: Dr. Trotti is a member of the Board of Directors of the American Academy of Sleep Medicine (AASM). Views expressed are those of the authors and do not necessarily reflect those of the AASM.
INTRODUCTION

Although epidemiologic data have suggested that Restless Leg Syndrome (RLS) may be a harbinger for incident Parkinson’s Disease (PD) [1,2] or its pre-motor symptoms (e.g., constipation) [3], these findings remain controversial, since pathophysiologically, the two conditions appear very different. Evidence for regarding disparate pathophysiology includes neuroimaging studies, which have suggested that, in contrast to PD, persons with RLS may have intact dopamine transport [4] and, relative to controls, enhanced pre-synaptic dopaminergic release [5]. Additionally, post-mortem data have not shown evidence of alpha-synucleinopathy in RLS [6], and genetic studies similarly have suggested divergent diathesis for the two conditions [7-9]. Despite this considerable evidence of their relative independence, many case-control studies have shown higher prevalence of RLS in PD than in controls [e.g., 10-13], though some studies do not concur and imply that prior exposure to dopaminergic medications may underly the apparently higher prevalence of RLS in PD [e.g., 14-16]. Recent reviews [17-19] have described this complex, and often conflicting, literature in greater detail. None of these studies examined Periodic Limb Movements in sleep (PLMS), an objectively measured, intermediate endophenotype of RLS [20].

In this report, we examined the prevalence of RLS in PD, and with availability of two consecutive nights of overnight polysomnography (PSG), we also examined PLMS as a possible correlate. We hypothesized that, as has been well-established for decades in the non-PD population [21], symptoms of restless legs in PD should be associated with PLMS.

MATERIALS AND METHODS

Patients with idiopathic PD (n = 75; 50 men; 25 women; X (SD) age = 62.5 (9.6) years) taking part in a larger study of sleep and alertness completed questions about RLS and underwent either two consecutive nights (N = 67) or a single night (N = 8) PSG in a research-dedicated sleep laboratory. Details of PSG recordings are described elsewhere [22]. In one case, recording malfunction on the first night of sleep lab recording resulted in Night 2 as the single recording night analyzed.

All patients underwent examination by a board-certified neurologist who rated each patient on the Unified Parkinson’s Disease Rating Scale (UPDRS) motor subscale [23]. For patients on dopaminergic medications (n = 49), UPDRS ratings were completed in the “On” state, typically between 8 AM and 11 AM the morning after their first night in the lab. Levo-dopa dose equivalences were computed for all patients, taking into account combined doses of all forms of daily levo-dopa, dopamine agonists and COMT inhibitors, using standard conversions [22,24]. PD patients had been diagnosed for a mean of 5.2 years (SD = 3.6) at time of evaluation and had a mean UPDRS part 3 motor scale score of 17.4 (SD = 8.2). Twenty-six patients were not taking nor had prior exposure to either levo-dopa or dopamine agonists at time of study. Of the remaining 49, 42 received levodopa, 31 were taking dopamine agonists and 25 received both. The mean daily levodopa equivalent for the 49 medicated patients was 582.0 mg (SD = 322.5; median = 556.3; range 100 to 1333).
Restless legs symptoms were assessed with two questions used previously in an epidemiological study \[25\]. The first of these ("At bedtime, how often does restlessness in your legs delay your falling asleep?") assessed symptoms possibly affecting the onset of sleep, whereas the other ("When you wake up during the night, how often do you feel unpleasant sensations in your leg muscles that require you to move your legs or walk in order to be more comfortable?") assessed RLS during the nighttime period. Both questions could be answered with the following categories: “Never,” “Occasionally,” “Often,” or “Very Often.” An indication for restless legs symptoms was considered a response of “Often” or “Very Often.” For analyses, we employed two definitions, depending on whether a patient endorsed either item alone (but not the other) (non-restrictive definition) or whether a patient endorsed both items (restrictive definition).

PSG recordings were conducted with an Embla Flaga A10 digital acquisition system and consisted of central and occipital electroencephalography, left and right monopolar electrooculography referenced to the opposite mastoid, mentalis electromyography (EMG) from surface placements, single lead electrocardiography, respiratory airflow and effort, pulse oximetry and bilateral leg surface EMG recordings from electrodes placed over the left and right anterior tibialis. Records were scored manually by trained research staff in 30-second epochs for PLMS using conventional criteria \[26\]. The total number of PLMS were divided by total sleep time to yield a PLMS Index.

**RESULTS**

Responses to the two restless legs questions were associated strongly (Chi square = 36.7, p < .0001) with 8 individuals (10.7 %) endorsing the beginning-of-night item and 17 (22.7 %) endorsing the middle-of-night item. A total of 18 cases (24.0 %) endorsed at least one (non-restrictive definition), and 7 (9.3 %) endorsed both (restrictive definition). Table 1 provides a comparison of demographics, clinical variables, and PSG-derived variables between those patients with and without restless legs symptoms. There were no significant differences in UPDRS motor score between individuals with and without symptoms using either definition. There were also no differences in the proportions of the groups using levo-dopa or dopamine agonists or in PSG sleep measures, including PLMS. Using Night 1 data with the unrestricted definition, PLMS Index > 15 was present in 27.8% of RLS cases versus 25.5% of non-RLS cases (chi square = .04, p = .85). Using Night 2 data with the unrestricted definition, PLMS Index > 15 was present in 29.4% of RLS cases versus 24.0% of non-RLS cases (chi square = .20, p = .66). Using Night 1 data with the restricted definition, PLMS Index > 15 was present in 14.3% of the RLS cases versus 39.6% of non-RLS cases (p = .67 with Fisher’s exact). Using Night 2 data with the restricted definition, PLMS Index > 15 was present in 16.7% of the RLS cases versus 26.2% of the non-RLS cases (p = .100 with Fisher’s exact). Because of known night-to-night variability in PLMS [27], we also computed the absolute difference in PLMS Index between Nights 1 and 2 (Table 1), but this was unrelated to either definition.

Because mimics such as dopaminergic-induced dyskinesias can often resemble RLS symptoms and our RLS assessments relied exclusively on self-report, we also evaluated current dopaminergic dose and years with diagnosis as possible correlates of RLS. Among
patients using dopaminergic medications (n = 49), levo-dopa dose equivalents did not differentiate PD patients with and without RLS using either the unrestricted definition (X = 592.7 [SD = 363.4] mg vs. X = 577.9 [SD = 310.3] mg; t = .13, p = .89) or the restricted definition, (X = 530.5 [SD = 306.0] mg vs. X = 589.3 [SD = 327.6] mg; t = .44, p = .66; see Table 1). Years with PD diagnosis also did not differentiate patients with and without RLS using the unrestricted definition (X = 4.9 [SD = 2.6] years vs. X = 6.9 [SD = 3.5] years; t = 1.72, p = .094) or the restricted definition, (X = 4.2 [SD = 1.6] years vs. X = 6.7 [SD = 3.5] years; t = 1.70, p = .097).

Among the drug-naïve PD patients, RLS prevalence was marginally, but not significantly, lower than in the patients already receiving dopaminergic therapy (for unrestricted definition, 4/26, 15.4%, versus 14/49, 28.6%, p = .26 with Fisher’s exact; for restricted definition, 1/26, 3.9% % versus 6/49, 12.2% %, p = .41 with Fisher’s exact). The proportion of unmedicated cases having PLMS Index > 15 on either (or both) lab nights (42.3%) was similar to the proportion of medicated cases having PLMS Index > 15 on either (or both) lab nights (37.5%) (chi-square = .16, p = .69). Similarly, in the unmedicated group, PLMS Index did not differ between cases having versus not having RLS (for Night 1: 12.3 [11.4] versus 10.3 [13.1] per hour, t = .32, p = .75; for Night 2: 21.7 [43.3] versus 10.7 [12.4] per hour, t = .50, p = .61; unrestricted definition).

DISCUSSION

Using different PD populations, we [28] and others [29] have reported previously that PLMS are more common in PD relative to other neurodegenerative conditions or age-matched controls. The levels of PLMS observed in our PD patients here were consistent with this. Similarly, our observed prevalence of apparent RLS, which occurred in between 9.3% (restrictive definition) and 22.7% (unrestrictive definition) of our PD patients, was consistent with results from a recent meta-analysis, which, after correcting for high heterogeneity across studies, suggested a weighted prevalence in PD of 14% (95% confidence interval: 0.10-0.16) [17], with slightly lower prevalence noted within Asian populations and in men and higher prevalence in patients with prior exposure to pharmacologic anti-Parkinsonian therapy. One population-based, longitudinal study reported the prevalence of RLS rising from 4.6% in do novo PD to 16.3 % at four years subsequent to initial diagnosis but noted that effect was not mediated by pharmacologic treatment [30], in contrast to what has been reported elsewhere [14,17]. Our data also suggested that RLS in PD was unlikely related to usage of dopaminergic medications, since our medicated patients tended to report less RLS, and among medicated patients, levo-dopa dose equivalents did not differentiate those with and without RLS.

Interestingly, despite our broadly replicative results involving prevalence of both apparent RLS and PLMS in these PD patients, the two phenomena were unrelated in our sample. By contrast, in the general population, strong overlap between the subjective experience of RLS and the sleep-measured endophenotype of PLMS has been noted frequently [21,27]. Lack of association between PLMS and RLS was noted originally in more severely affected PD patients [31] and recently confirmed in more mild patients [31], similar in disease severity level in the current study. Our data could imply that RLS in PD patients represent a different
phenomenon than RLS in non-PD populations. For example, PD is associated with high rates of many kinds of sleep-related EMG activity, including PLMS [28] but also brief, phasic EMG activity, which can occur in both REM and NREM [33, 34]. Thus, attribution of PLMS as a specific endophenotype for RLS in PD patients may not be definitive.

Limitations of this study include the assessment of restless legs symptoms exclusively by questionnaire, rather than standardized interview. The questions used, although employed in an early seminal epidemiologic study of RLS [25], did not distinguish between RLS and conditions that may mimic RLS [35, 36], such as neuropathy, dystonia or dyskinesia, nor did they differentiate RLS in PD from a general motor restlessness (akathisia) that often characterizes this condition [36]. Medication-induced dyskinesia, not an infrequent occurrence in a population regularly taking dopaminergics, constitutes a problem particularly recalcitrant to unequivocal interpretation. Among those patients receiving such medications, however, we found no evidence that either higher medication dose or greater number of years since original PD diagnosis were related to more likely endorsement of RLS questions, implying that positive responses to these items were unlikely to reflect dyskinesias. The standard for RLS assessment is the International Restless Legs Study Group RLS rating scale [37], though this has seen greater usage and likely has more validity in clinical trials as an outcome for potential RLS treatments than as a population-based screening tool. Other questionnaires, such as the Cambridge-Hopkins questionnaire [38], which were published after our study was initiated, may be a more viable approach to distinguish true RLS from conditions that may otherwise appear similar to it. Despite this, a limited number of questions have often been used in epidemiologic studies to assess RLS [e.g., 39, 40] and, in our data, there was relatively strong concordance between the responses to the two RLS questions, one reflecting motor restless at the beginning of sleep and one referring to phenomena during the night. Additionally, we have shown elsewhere [41] that these items, when placed in the context of a larger questionnaire collecting self-reported sleep features in PD, load very strongly on a single unique factor, which is independent from other components of disturbed sleep. Additional limitations of this study include the absence of neuroimaging of the dopamine transporter (i.e., DAT), to more definitively elucidate pre-versus post-synaptic dopaminergic dysfunction, and the fact that the data were collected only cross-sectionally, thus precluding our knowing whether restless legs symptoms anticipated PD in these patients. Within these limitations, we found no evidence that restless legs symptoms in PD were corroborated by the simultaneous presence of PSG-defined PLMS.

ACKNOWLEDGEMENTS

This research was supported by NS 050595 (DLB); NS 077366 (SAF); NS 083748 (LMT); NS 111280 (LMT)

REFERENCES


J Parkinsons Dis. Author manuscript; available in PMC 2023 January 01.


Table 1
Demographic, Clinical and Polysomnographic Data on Patients with and without Symptoms of Restless Legs

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unrestricted Definition</th>
<th></th>
<th></th>
<th>Restricted Definition</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With RLS (n = 18)</td>
<td>Without RLS (n = 57)</td>
<td>Comparison</td>
<td>With RLS (n = 7)</td>
<td>Without RLS (n = 68)</td>
</tr>
<tr>
<td>Age</td>
<td>61.7 (10.9)</td>
<td>62.7 (9.2)</td>
<td>t = .38, p = .70</td>
<td>59.9 (9.2)</td>
<td>62.8 (9.7)</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>66.7</td>
<td>66.7</td>
<td></td>
<td>71.4</td>
<td>66.2</td>
</tr>
<tr>
<td>UPDRS Motor Score</td>
<td>16.8 (7.0)</td>
<td>17.5 (8.6)</td>
<td>t = .31, p = .76</td>
<td>16.0 (9.5)</td>
<td>17.5 (8.2)</td>
</tr>
<tr>
<td>% Receiving levo-dopa</td>
<td>66.7</td>
<td>52.6</td>
<td>Chi-square = 1.09, p = .30</td>
<td>71.4</td>
<td>54.4</td>
</tr>
<tr>
<td>% Receiving dopamine agonist</td>
<td>44.4</td>
<td>40.4</td>
<td>Chi-square = .09, p = .79</td>
<td>71.4</td>
<td>38.2</td>
</tr>
<tr>
<td>% Receiving neither levo-dopa nor dopamine agonist</td>
<td>22.2</td>
<td>38.6</td>
<td>Chi-square = 1.62, p = .20</td>
<td>14.3</td>
<td>36.8</td>
</tr>
<tr>
<td>Levo-dopa equivalent (in mg) for those receiving medications (n = 49)</td>
<td>592.7 (363.4)</td>
<td>577.9 (310.3)</td>
<td>t = .13, p = .89</td>
<td>530.5 (306.0)</td>
<td>589.3 (327.6)</td>
</tr>
<tr>
<td>Total Sleep Time, (mins), Nt 1</td>
<td>306.5 (99.8)</td>
<td>291.8 (119.9)</td>
<td>t = .47, p = .64</td>
<td>330.6 (70.9)</td>
<td>291.7 (118.3)</td>
</tr>
<tr>
<td>Total Sleep Time, (mins), Nt 2</td>
<td>316.3 (87.7)</td>
<td>325.6 (100.2)</td>
<td>t = .34, p = .74</td>
<td>298.5 (80.0)</td>
<td>325.7 (98.3)</td>
</tr>
<tr>
<td>Sleep Efficiency (%), Nt 1</td>
<td>67.5 (21.5)</td>
<td>60.6 (23.3)</td>
<td>t = 1.10, p = .27</td>
<td>69.1 (16.8)</td>
<td>61.6 (23.5)</td>
</tr>
<tr>
<td>Sleep Efficiency (%), Nt 2</td>
<td>68.8 (19.3)</td>
<td>67.5 (19.8)</td>
<td>t = .24, p = .81</td>
<td>62.7 (16.9)</td>
<td>68.3 (19.8)</td>
</tr>
<tr>
<td>REM (%), Nt 1</td>
<td>18.6 (11.9)</td>
<td>12.9 (11.5)</td>
<td>t = 1.81, p = .08</td>
<td>16.1 (13.9)</td>
<td>14.1 (11.6)</td>
</tr>
<tr>
<td>REM (%), Nt 2</td>
<td>19.6 (13.6)</td>
<td>15.8 (13.3)</td>
<td>t = .90, p = .37</td>
<td>14.8 (12.9)</td>
<td>16.9 (13.5)</td>
</tr>
<tr>
<td>Apnea/Hypopnea Index (events per hour), Nt 1</td>
<td>5.5 (5.9)</td>
<td>6.7 (9.3)</td>
<td>t = .63, p = .53</td>
<td>6.8 (7.2)</td>
<td>6.4 (8.7)</td>
</tr>
<tr>
<td>Apnea/Hypopnea Index (events per hour), Nt 2</td>
<td>5.0 (6.5)</td>
<td>6.9 (8.7)</td>
<td>t = .83, p = .41</td>
<td>4.4 (4.5)</td>
<td>6.6 (8.5)</td>
</tr>
<tr>
<td>PLMS Index (movements per hour), Nt 1</td>
<td>18.5 (33.3)</td>
<td>12.4 (26.2)</td>
<td>t = .80, p = .43</td>
<td>21.0 (46.4)</td>
<td>13.2 (25.7)</td>
</tr>
<tr>
<td>PLMS Index (movements per hour), Nt 2</td>
<td>18.3 (35.2)</td>
<td>11.9 (21.6)</td>
<td>t = .70, p = .49</td>
<td>6.9 (9.3)</td>
<td>14.2 (26.6)</td>
</tr>
<tr>
<td>PLMS Index (absolute difference)</td>
<td>14.7 (17.7)</td>
<td>9.3 (11.3)</td>
<td>t = 1.18, p = .25</td>
<td>9.1 (7.8)</td>
<td>10.8 (13.8)</td>
</tr>
</tbody>
</table>

NOTES:
All data shown as mean and standard deviation, except where indicated as percentage. Comparisons for continuously measured variables shown as two-group t-tests adjusting for unequal variances using Satterthwaite correction.

Nt 1: Night 1; Nt 2: Night 2
N = 75 but numbers of cases for some variables varied. Demographics and medication status available on all patients. UPDRS available on 68 cases. Polysomnography (PSG) performed on two consecutive nights for 66 patients. Additional single night PSG data (N = 9), reflecting night 1 for 8 cases and night 2 for 1 case (owing to technically inadequate night 1 study), used for computation of PSG variables. One patient showed 0
minutes of sleep on first night, allowing calculation of Total Sleep Time and Sleep Efficiency (as zero) but other polysomnographic data treated as missing for that case.