Exploring the Relationship Between Parkinson Disease and Restless Legs Syndrome

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Background: Restless legs syndrome (RLS) and Parkinson disease (PD) are common neurological conditions that respond to dopaminergic therapy. To our knowledge, the relationship between the two has not been thoroughly explored.

Methods: We consecutively queried 303 patients with PD seen in our clinic for the presence of RLS symptoms, and evaluated their condition with the Epworth Sleepiness Scale and other demographic and sleep measures. We then looked for predictors of RLS in these patients with PD. We also compared a larger group of patients with PD/RLS with a group of patients with RLS alone.

Results: Of 303 patients with PD, 63 (20.8%) had symptoms of RLS. Neither PD patient demographics nor PD treatments could reliably predict the development of RLS symptoms; however, lower serum ferritin levels were associated with RLS symptoms in our patients with PD (P=.01). In 34 (68%) of the 79 total patients with PD/RLS (including additional patients with PD/RLS seen in the clinic) with reliable age-at-onset data, the PD symptoms preceded the RLS symptoms (x² test, P<.001). Compared with patients with idiopathic RLS (N=146), patients with PD/RLS (N=109) were older at RLS onset (P<.001), were less likely to have a family history of RLS (P<.001), and had lower serum ferritin levels (P=.01).

Conclusions: Symptoms of RLS are common in patients with PD; however, except in patients with a family history of RLS, they seem to reflect a secondary phenomenon, perhaps in relation with lower ferritin levels. There is no evidence that RLS symptoms early in life predispose to the subsequent development of PD.

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PATIENTS AND METHODS

Consecutive patients with PD (new and established) examined at the Parkinson’s Disease Center and Movement Disorders Clinic, Baylor College of Medicine, Houston, Tex, completed written surveys during a 4-month period. Parkinson disease was diagnosed by the presence of 2 of 3 cardinal features (rigidity, bradykinesia, and tremor). To our knowledge, no patient refused to participate. The survey asked about the symptoms of RLS: (1) the urge to move legs or arms associated with an unpleasant sensation, (2) motor restlessness, (3) worsening with inactivity and temporary improvement with activity, and (4) worsening at night.15 A positive diagnosis of RLS was based on an affirmative response to all 4 questions. Those patients who answered affirmatively to all 4 of the paraphrased cardinal criteria for the diagnosis of RLS were subsequently interviewed to corroborate the diagnosis of RLS. The survey also included the Epworth Sleepiness Scale.16 Additional input from the spouse or caregiver was allowed, and specifically encouraged in cases in which the patient could not competently answer all questions. If patients were not able to complete the entire questionnaire in the clinic or left some questions unanswered, they were subsequently interviewed over the telephone or in person.

Medical records were reviewed to corroborate the diagnosis of PD; to collect information about current medications and treatment history, the duration and severity of PD (Hoehn and Yahr stage), and prior diagnosis of RLS; and to assess for the presence of dementia. Patients were classified as having dementia if they had a documented Mini-Mental State Examination score of less than 25, neuropsychologic testing results that concluded dementia, or a formal diagnosis of dementia in our clinic but no formal neuropsychologic testing. Additional interviews were later obtained for all patients originally included in the survey who were subsequently seen by one of the investigators (W.G.O.). This ranged from 3 to 10 months after completion of the survey. At that time, patients were again asked about RLS symptoms. If they then met the criteria for RLS, they were included in that group during analysis.

Data were incorporated into a database, and statistical analysis was performed using Statistical Product and Service Solutions, version 10.0 (SPSS Inc, Chicago, Ill). Prediction of RLS used a stepwise regression model, including the following: (1) duration of PD, (2) age, (3) Hoehn and Yahr stage, (4) sex, (5) dementia, (6) use of levodopa, (7) use of any dopamine agonist, (8) Epworth Sleepiness Scale score, (9) history of pallidotomy, and (10) history of deep brain stimulation. To minimize any misinterpretation of predictor exclusion (as predictors may be highly correlated with the outcome), the criterion for inclusion and exclusion of a variable was set at a level of α=0.05 and α=0.15, respectively. Furthermore, stepwise selection of predictors was specified where predictors were removed from the equation one at a time, but could be retained if doing so would help prediction. Analysis was performed using Statistical Product and Service Solutions’ Logistic Regression program (SPSS Inc). We also compared ferritin levels (RLS positive vs RLS negative) in the subgroup of patients in whom they were obtained (analysis of variance).

We next wanted to compare the clinical features of patients with PD/RLS with those of patients with only RLS. We combined the group of patients with PD/RLS from the original cohort (n=63) with additional patients with PD/RLS from our database whom we collected during a 3-year period in our clinic (n=46). These 46 patients were not necessarily collected systematically. Therefore, we compared demographic features between the original prospective PD/RLS group and the database PD/RLS group to assess for any differences. Within this larger group of patients with PD/RLS (N=109), we then compared those with a family history of RLS with those patients without a family history of RLS.

We next compared the total PD/RLS group (N=109) with a group of patients diagnosed as having only RLS (N=146) from our database, for demographics and ferritin levels. Patients with RLS secondary to renal dysfunction were excluded from the “RLS only” group. All but one patient with RLS only were referred to our clinic for RLS. The other was referred for essential tremor.

Comparisons made among the patients with PD/RLS, and between patients with PD/RLS and those with RLS only, used analyses of variance, t tests, and χ² tests when appropriate. The Levene correction (α=0.02) was applied when homogeneity of variances was violated. Data are given as mean±SD unless otherwise indicated.

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Began first in 54 and RLS began first in 25; 8 had a concurrent onset of RLS who confidently recalled their symptom onset, PD (F1,134 = 6.52, P < .005). In the 87 total patients with PD/RLS who confidently recalled their symptom onset, PD began first in 54 and RLS began first in 25; 8 had a concurrent onset (\( \chi^2 = 3.73, P < .001 \)). This contrasts with those patients with PD/RLS who do have a family history of RLS (n = 21 with reliable data), in whom the onset of RLS preceded the onset of PD in 11 (P = 1.0).

Of the 146 patients with RLS only identified from our database, a family history was reported in 96. When compared with this RLS only group, the total PD/RLS group (N = 109) had a lower incidence of family history (\( \chi^2 = 41.9, P < .001 \)), an older age at onset of RLS (F1,231 = 64.5, P < .001), and lower serum ferritin levels (F1,134 = 6.52, P < .001) (Table). This contrasts with the PD/RLS group (N = 109) which had a higher incidence of family history (\( \chi^2 = 40.0, P < .001 \)), an older age at onset of PD (F1,134 = 6.52, P < .001) (Table). This contrasts with the PD/RLS group (N = 109) which had a lower incidence of family history (\( \chi^2 = 4.0, P < .05 \)).

**COMMENT**

Restless legs syndrome occurred in 20.8% of our patients with PD. We could not, however, identify any specific demographic or PD treatment factors associated with RLS symptoms, except that patients with PD who also had RLS had lower serum ferritin levels than patients with PD who did not have RLS. Symptoms of RLS were not associated with higher Epworth Sleepiness Scale scores in the population with PD. Compared with patients with isolated RLS, patients with PD/RLS had an older age at onset and were much less likely to report a family history of RLS. Those patients with PD/RLS who did have a family history of RLS, however, tended to have RLS demographic features more similar to those with idiopathic RLS.

Although we did not formally quantify the severity of RLS symptoms in the population with PD, they anecdotally appeared to have milder symptoms compared with those seen in patients with idiopathic RLS. Often, their RLS symptoms were ephemeral, inconsistent, and difficult to subjectively differentiate from other sensory and motor symptoms associated with PD. We took special care to segregate RLS from akathisia, dystonia, and other sensory symptoms seen in patients with PD. Patients did not usually reveal RLS symptoms unless specifically asked, as demonstrated by our low percentage of a prior diagnosis. Patients usually believed that the RLS symptoms were part of their PD symptom complex. Furthermore, it appears that written questionnaires are neither specific nor sensitive enough to correctly identify RLS in this population.

An association between PD and RLS is not entirely unexpected because overlap between the two is suggested by several observations. Both conditions respond to dopaminergic medications.17-19 and both result in an increased number of periodic limb movements of sleep.20 Furthermore, functional imaging suggests modest similarities, such as reduced dopaminergic functioning in the striatum.21,22 Pathologic examination of the substantia nigra pars compacta in 2 patients with RLS, however, did not reveal dopaminergic cell depletion, but instead showed iron store depletion (reduced ferritin staining) in dopaminergic areas.23 In contrast, patients with PD have an elevated iron content in the basal ganglia.24 Therefore, preliminary evidence suggests that RLS results from reduced dopamine cellular function secondary to local iron deficiency, rather than dopamine cell depletion. It has been suggested that RLS specifically involves separate diencephalic dopaminergic systems.25 These dopamine cells, however, also degenerate to a lesser degree in patients with PD.26,27 One could speculate that the RLS symptoms associated with reduced dopaminergic system functioning would be accentuated in patients with PD who have fewer dopaminergic cells. Because RLS symptoms in patients with sporadic PD/RLS usually occur after PD symptoms, it could be proposed that PD is a risk factor for RLS symptoms, perhaps in combination with other risk factors, such as low ferritin levels.

Weaknesses of this study include the delay in obtaining ferritin levels and the fact that the ferritin level was not obtained in all patients. We, however, have no reason to believe that the group in whom we did obtain ferritin levels differed from the entire group. Our center, a tertiary referral center, may reflect a more severe or complicated population with PD/RLS. Finally, historical information is always subject to recall biases. Nevertheless, we believe that our data do suggest that RLS is more common in patients with PD than what has been

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**Summary of Results**

<table>
<thead>
<tr>
<th>Variable</th>
<th>With PD and Without RLS (n = 240)</th>
<th>With PD/RLS (n = 63)</th>
<th>Total Cohort</th>
<th>With RLS Only (n = 146)</th>
<th>Without a Family History of RLS (n = 96)</th>
<th>With a Family History of RLS (n = 64)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>67.5 ± 11.0</td>
<td>67.0 ± 9.8</td>
<td>67.9 ± 10.0</td>
<td>59.8 ± 15.1</td>
<td>59.3 ± 14.9</td>
<td>60.9 ± 15.6</td>
</tr>
<tr>
<td>Age at the onset of RLS</td>
<td>NA</td>
<td>62.5 ± 12.8</td>
<td>56.6 ± 18.6</td>
<td>35.6 ± 19.8</td>
<td>29.8 ± 17.5</td>
<td>46.5 ± 19.5</td>
</tr>
<tr>
<td>Those with a family history of RLS</td>
<td>NA</td>
<td>17.5</td>
<td>20.2</td>
<td>65.8§</td>
<td>100.0</td>
<td>0</td>
</tr>
<tr>
<td>Male sex†</td>
<td>62.5</td>
<td>52.4</td>
<td>48.6</td>
<td>35.4</td>
<td>40.0</td>
<td></td>
</tr>
<tr>
<td>Ferritin level, ng/mL</td>
<td>88.4 ± 67.5 (n = 32)</td>
<td>50.7 ± 46.6 (n = 25)</td>
<td>58.8 ± 51.0 (n = 46)</td>
<td>86.3 ± 63.0 (n = 90)</td>
<td>96.4 ± 64.5 (n = 64)</td>
<td>61.5 ± 54.1 (n = 26)</td>
</tr>
</tbody>
</table>

*Data are given as mean ± SD unless otherwise indicated. RLS indicates restless legs syndrome; PD, Parkinson disease; and NA, data not applicable.
†P < .05 (t test) for PD/RLS vs RLS only.
‡Data are given as percentage of patients.
§P < .001 (analysis of variance) for PD/RLS vs RLS only.
P < .05 (t test) for PD without RLS vs PD/RLS.
¶P < .01 (analysis of variance) for PD/RLS vs RLS only.
previously reported in normal populations\textsuperscript{9,10} and that, except in patients with a family history of RLS, this is consistent with a "secondary RLS" that occurs after the onset of PD.

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Author contributions: Study concept and design (Dr Ondo); acquisition of data (Mr Vuong); analysis and interpretation of data (Dr Jankovic); drafting of the manuscript (Dr Ondo); critical revision of the manuscript for important intellectual content (Mr Vuong and Dr Jankovic); statistical expertise (Mr Vuong); administrative, technical, and material support (Dr Ondo); and study supervision (Dr Jankovic).

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