Restless legs syndrome in people affected by leprosy

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Summary

Objectives: Restless legs syndrome (RLS) is one of the most commonly encountered sleep disorders. The prevalence of RLS and its association with leprosy have not previously been elucidated. The aims of this study were to investigate the prevalence of RLS in people affected by leprosy and to determine the presence and amount of sleep disruption in leprosy affected people with RLS.

Design: Each leprosy-affected person was matched to two healthy controls for age and sex. A total of 236 leprosy-affected people who lived in Sorokdo and 472 healthy control subjects who lived in Namwon were included in this study. A diagnosis of RLS and a severity assessment were made using the criteria described by the International Restless Legs Syndrome Study Group.

Results: The prevalence of RLS was significantly higher in people affected by leprosy (60/236; 25.4%) than in controls (42/472; 8.8%). Pittsburgh Sleep Quality Index (PSQI) global score was higher in leprosy-affected people than in controls. No significant difference was found between leprosy-affected people and controls with regard to the severity of RLS. Leprosy-affected people with RLS had a poorer sleep quality (higher PSQI global score) than those without RLS, but the Geriatric

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Depression Scale was not different between leprosy-affected people with RLS and those without RLS.

**Conclusions:** The frequency of RLS among leprosy-affected people was significantly higher than that of RLS in the general population. Leprosy-affected people should be examined for RLS and treatment for RLS can potentially improve sleep.

**Introduction**

Restless legs syndrome (RLS) is a common neurological disorder characterised by an urge to move the legs and peculiar, unpleasant sensations deep in the legs. The sensations appear during periods of rest or inactivity, particularly in the evening and at night, and are typically relieved by movement. While pathophysiology of RLS is not fully understood, local dopamine dysfunction within the central nervous system, reduced levels of cerebral iron, and cerebrospinal ferritin appear to play critical roles. RLS occurs more frequently in patients with anemia, uremia, pregnancy, rheumatic disease, and peripheral neuropathy.

Leprosy is one of the important causes of treatable neuropathy worldwide. Infection with *Mycobacterium leprae* leads to chronic granulomatous inflammation of the skin and peripheral nerves. Taking into account the peripheral neuropathy in leprosy and the increased prevalence of anemia for leprosy patients, the prevalence of RLS could be higher in leprosy-affected people than in the general population.

To date, and to our knowledge, the occurrence of RLS in leprosy-affected people has not specifically been studied. We aimed to ascertain the prevalence of RLS in leprosy-affected people, and compare the results with those of healthy controls. We also aimed to determine the presence and amount of sleep disruption in leprosy-affected people with RLS.

**Materials and Methods**

We conducted a cross-sectional house-to-house survey of people affected by leprosy who lived in Sorokdo, an island located in southern area and a major leprosarium in Korea. A total of 236 leprosy-affected people were recruited for the study from January 2011 to August 2011. People were eligible when they were affected by leprosy (multibacillary and paucibacillary), had completed treatment at the time of the interview (time interval from treatment completion to interview: 25 ± 5 years), were living in Sorokdo, were of any age and either gender, were able to give consent and were willing to participate.

The Institutional Review Board of the hospital approved this study. All the participants were informed in full about the purpose and methods of this study, and all of them gave written informed consent.

Each leprosy-affected person was matched for age and sex with two healthy controls. The control population was selected from participants of the Namwon Study. The Namwon Study is an ongoing prospective study designed to investigate the prevalence, incidence, and risk factors for chronic disease in a rural population. The 2005 census reported 33,068 residents (14,960 men and 18,108 women) aged 45–74 in Namwon city. From 2004 to 2007, all eligible subjects aged 45–74 were invited to participate through mailing and telephone calls based on the list of officially registered residents. A total of 10,667 eligible participants of the Namwon Study.
For each participant, the symptoms of RLS were assessed face-to-face by a trained interviewer based on the clinical diagnostic criteria for RLS, established by the International RLS Study Group (IRLSSG).12 Four RLS questions are as follows: 1) Do you have the desire to move your legs, often because of discomfort or restlessness? 2) Does this desire occur or become worse when you are at rest, in other words, when you are sitting or lying down? 3) Do you note any relief of symptoms completely or partly during activity? 4) Do these symptoms occur or worsen only in the evening or at night? Subjects responding affirmatively to all four questions were considered to have RLS. We used the Korean version of a paradigm of questions for epidemiology studies of RLS.13 For the Korean version of the RLS questionnaire for epidemiology studies, the sensitivity was in the range of 75–85% and the specificity was in the range of 94–96%.13 Only patients who fulfilled the four criteria for RLS were asked to complete the 10-question IRLSSG Rating Scale, which was used to assess symptom severity.14 In order to assess the impact of RLS on sleep quality, we asked the subjects to estimate daily sleep duration and the number of nights they had trouble falling asleep for the month prior to the date of questionnaire completion based on the Pittsburgh Sleep Quality Index (PSQI).15 In order to assess depression, each leprosy patient had completed the short form of the Geriatric Depression Scale (GDS-15) by face-to-face interview.16 As a proxy indicator for nerve damage, we checked WHO disability grading for each leprosy patient.17

The statistical software SPSS version 18.0 for Windows was used for all statistical analyses. Continuous data are presented here as mean ± standard deviation (SD) values. The Student’s t-test for continuous variables and the χ² test for categorical variables were used to analyse the demographic and clinical variables between leprosy-affected people and controls. The results were considered statistically significant at a P-value of less than 0.05.

Results

The mean age was 69.15 ± 9.53 in leprosy-affected people and 69.46 ± 7.82 in controls. The proportion of males was more than that of females in both groups. The prevalence of RLS was significantly higher in leprosy-affected people (60/236; 25.4%) than in controls (42/472; 8.8%). The PSQI global score was higher in leprosy-affected people than in controls. No significant difference was found between leprosy-affected people and controls with regard to the severity of RLS. (Table 1)

Comparing the demographic and clinical characteristics of leprosy-affected people with and without RLS, no differences were found in age, sex, GDS-15 and WHO disability

Table 1. The demographic characteristics and diagnosis of restless legs syndrome in people affected by leprosy compared with healthy controls

<table>
<thead>
<tr>
<th></th>
<th>Leprosy affected (n = 236)</th>
<th>Controls (n = 472)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>69.15 ± 9.53</td>
<td>69.46 ± 7.82</td>
<td>NS</td>
</tr>
<tr>
<td>Sex, M/F (female %)</td>
<td>142/94 (39.8)</td>
<td>284/188 (39.8)</td>
<td>NS</td>
</tr>
<tr>
<td>RLS diagnosis (%)</td>
<td>60 (25.4)</td>
<td>42 (8.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PSQI global score</td>
<td>9.38 ± 5.98</td>
<td>6.96 ± 4.74</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IRLSSG-RS score</td>
<td>16.60 ± 5.28</td>
<td>16.12 ± 7.22</td>
<td>NS</td>
</tr>
</tbody>
</table>

M: male, F: female, RLS: restless legs syndrome, PSQI: Pittsburgh Sleep Quality Index, IRLSSG-RS: International RLS Study Group Rating Scale, NS: not statistically significant (P > 0.05)
grading. However, the PSQI global score was higher in leprosy-affected people with RLS than those without RLS. (Table 2)

Comparing the demographic and clinical characteristics of control subjects with and without RLS, no difference was found in age. In contrast to leprosy-affected people, the proportion of women was higher in control subjects with RLS than in those without RLS. Similar to leprosy-affected people, the PSQI global score was higher in control subjects with RLS than in those without RLS. (Table 2)

**Discussion**

The occurrence of RLS has not, to our knowledge, previously been studied specifically for leprosy. Herein we found a markedly higher prevalence of RLS in leprosy-affected people (25.4%) compared with the age- and sex-matched controls. Only 8.8% of the healthy control population included in the present study had RLS. The prevalence of RLS has been reported to be 3–12% in general Western populations,1,18 and 6.5–9.5% in Korean populations.19–22 The present study demonstrated that a relatively high proportion of leprosy-affected people had RLS compared with controls.

The mechanisms of RLS in leprosy-affected people are unclear. It has been hypothesized that primary RLS results from an abnormal dopaminergic transmission as a result of primary iron insufficiency.23 This has been supported by the recent pathological data from human RLS brain tissue.24 The most common causes of secondary RLS include iron deficiency, pregnancy, kidney disease, rheumatic disease, neuropathy, and drugs.1 Infection with *Mycobacterium leprae* leads to chronic granulomatous inflammation in the skin and peripheral nerves.6 Because peripheral neuropathy is one of the causes of secondary RLS,4,25,26 RLS in leprosy-affected people could be due to peripheral neuropathy. The incidence of anemia was increased in leprosy patients treated with dapsone,7,8 and the mean value of serum iron level was significantly lower in untreated patients with active leprosy.9 Therefore, it is possible that RLS in leprosy-affected people is related with anemia.

**Table 2.** The demographic and clinical characteristics in leprosy affected people and controls with and without restless legs syndrome

<table>
<thead>
<tr>
<th></th>
<th>RLS</th>
<th>No RLS</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Leprosy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>60</td>
<td>176</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>68.80 ± 9.57</td>
<td>69.27 ± 9.54</td>
<td>NS</td>
</tr>
<tr>
<td>Sex, M/F (female %)</td>
<td>33/27 (45.0)</td>
<td>109/67 (38.0)</td>
<td>NS</td>
</tr>
<tr>
<td>PSQI global score</td>
<td>10.93 ± 6.13</td>
<td>8.87 ± 5.86</td>
<td>0.024</td>
</tr>
<tr>
<td>GDS-15</td>
<td>5.12 ± 3.78</td>
<td>5.16 ± 4.34</td>
<td>NS</td>
</tr>
<tr>
<td>WHO disability grading</td>
<td>4.92 ± 3.07</td>
<td>5.03 ± 3.69</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Control</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>42</td>
<td>430</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>70.45 ± 6.75</td>
<td>69.36 ± 7.72</td>
<td>NS</td>
</tr>
<tr>
<td>Sex, M/F (female %)</td>
<td>19/23 (54.7)</td>
<td>265/165 (38.3)</td>
<td>0.047</td>
</tr>
<tr>
<td>PSQI global score</td>
<td>9.05 ± 4.90</td>
<td>6.76 ± 4.68</td>
<td>0.003</td>
</tr>
</tbody>
</table>

M: male, F: female; RLS: restless legs syndrome, PSQI: Pittsburg Sleep Quality Index, GDS-15: Geriatric Depression Index short form (15 items), NS: not statistically significant (P > 0.05)
RLS is a subjective disorder and it may be difficult for examiners to evaluate the exact severity of symptoms. However, IRLSSG has recently developed and validated a rating scale aiming at measuring the severity of symptoms. In our study, there was no difference in the IRLSSG rating scale score between leprosy-affected people with RLS and control subjects with RLS. Previous studies showed that the IRLSSG rating scale scores in secondary RLS were similar to or slightly higher than those of the general population. Further analysis is required to determine the relationship between the cause and the severity of RLS.

As for the distribution of RLS according to sex, there seems to be some evidence of a female preponderance in the prevalence of primary RLS. Likewise, our study found the prevalence of RLS in control subjects higher in women as compared with men (12.2% in females, 6.6% in males). In leprosy-affected people, there was a tendency toward female preponderance amongst RLS cases but the prevalence did not vary significantly with sex (28.7% in female, 23.2% in male). In the same way, some previous studies of secondary RLS have shown no significant difference of RLS prevalence between men and women. However, there have been other studies of secondary RLS that report female preponderance in the prevalence of RLS. Further analysis is needed to determine the distribution of secondary RLS according to sex.

The sleep quality of leprosy affected people was worse than that of control subjects. Also, the sleep quality of leprosy-affected people and of controls with RLS was worse than of those without RLS. RLS is a major cause of insomnia, and sleep disruption is a frequent complaint that brings sufferers to consultation. Sleep debt in insomnia and RLS have widespread consequences on the health and overall quality of life. The poorer sleep quality of leprosy-affected people as compared to control subjects is probably due to the higher prevalence of RLS in leprosy-affected people. Previous studies showed that treatment of RLS improved sleep quality. Therefore, the identification and treatment of RLS in leprosy affected people can potentially improve sleep quality.

Primary RLS has been shown to have a strong association with depression in previous studies. The association between secondary RLS and depression is unclear. Our study demonstrated that RLS is not associated with depression in leprosy-affected people. Further study is required to determine the association of secondary RLS with depression.

Neuropathy occurs frequently in leprosy patients, and is one of the causes of secondary RLS. WHO disability grading as a proxy indicator for nerve damage was not different between leprosy-affected people with and without RLS. More detailed nerve conduction study is needed to determine the association of RLS in leprosy patients with neuropathy.

Our study had some limitations. First, the purpose of this study was to evaluate the prevalence of RLS in leprosy affected people, and we did not evaluate the secondary causes of RLS such as iron deficiency, kidney disease, neuropathy, and drugs. We plan to evaluate these related causes in the future. Second, recently it has become clear that the positive predictive value of many questionnaire screens for RLS may be fairly low and that many individuals who are identified by these screens have other conditions that can mimic the features of RLS by satisfying the four diagnostic criteria. Therefore, it has been suggested that exclusion of such RLS-mimics may require further elements in addition to the four-item questionnaire that was used. In our analysis, particular questions relating to the quality of the urge to move the legs, leg position, effects on sleep, and methods used to obtain relief were not specifically asked. This may have erroneously increased our prevalence rate of RLS in leprosy-affected people. However, we used the same diagnostic criteria and questionnaire for control subjects. Therefore, we believe that the comparison of RLS prevalence between the
two groups is meaningful. Also, we believe that the use of a face-to-face interview for all cases minimizes false positives, which may have otherwise been picked up by the four-item questionnaire telephone screening, as previously demonstrated.25

In conclusion, our study demonstrated an association between leprosy and RLS. Comorbid RLS worsens sleep quality in leprosy-affected people. Therefore, leprosy affected people should be examined for RLS and the treatment of RLS can potentially improve sleep. Further studies are needed to clarify the features and pathogenic mechanisms underlying leprosy-related RLS.

Acknowledgements

Authors’ Contributions

Patient consent form: All subjects who participated in this study were enrolled after signing an informed consent form.

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References
