# Systemic Lupus and Risk of Restless Legs Syndrome

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*ABSTRACT.* ***Objective.*** To determine the prevalence of restless legs syndrome (RLS) in women with systemic lupus erythematosus (SLE), and to compare this to a rheumatic disease sample without SLE.

***Methods.*** Unselected consecutive female patients were SLE were recruited from a lupus clinic. A RLS questionnaire based on 4 criteria, validated by the International Restless Legs Syndrome Study Group, was administered during a face-to-face interview. Smoking history and height and weight data were collected. Similar methods were used to determine RLS prevalence in a comparator group of women with rheumatic diseases other than SLE. Controls were frequency-matched by age group (in 5-year age bands) to SLE subjects. Controls were otherwise unselected.

***Results.*** We recruited 33 women with SLE and 32 controls. Twelve of 33 female SLE subjects scored positively for RLS (37.5%; 95% CI 22.9, 54.7) compared to 4 of 32 controls (12.5%; 95% CI 5.0, 28.1). Multivariate logistic regression showed that adjusted for age, obesity, and smoking, women with SLE were more likely to have RLS than the female controls (adjusted odds ratio 6.61, 95% CI 1.52, 28.77). In our multivariate analyses of all rheumatic patients, including SLE, the adjusted OR for obesity and RLS was 5.14 (95% CI 1.07, 24.6).

***Conclusion.*** These novel data indicate that RLS is more prevalent in women with SLE than in controls. Although obesity was a significant risk factor for RLS in our sample, the predictive covariates examined were limited. (J Rheumatol First Release Feb 15 2011; doi:10.3899/jrheum.101039)

*Key Indexing Terms:*
SYSTEMIC LUPUS ERYTHEMATOSUS RESTLESS LEGS SYNDROME OBESITY

Restless legs syndrome (RLS) is a neurological disorder characterized by sensory and motor disturbances of the limbs, the lower limbs being the most commonly affected. Patients with RLS complain of uncomfortable sensations in their legs, particularly when resting at night[1]. These sensations thus compromise the affected person's sleep patterns and quality of life. Most studies report that the prevalence of RLS in the general population is 10%–15%[2,3], although in some samples the prevalence in women may approach 20%[4].

Systemic lupus erythematosus (SLE) is a protypic systemic autoimmune rheumatic disease affecting primarily women, with a prevalence of about 1 in 2000 women. A number of studies have shown an elevated incidence of RLS in patients with rheumatic diseases like rheumatoid arthritis (RA)[5,6] and primary Sjögren's syndrome[7]. Studies investigating the prevalence of RLS in SLE have yet to be conducted. Our objective was to determine the prevalence of RLS in SLE, compared to controls with other rheumatic disease.

## MATERIALS AND METHODS

Unselected consecutive patients with SLE were recruited from the McGill University Health Centre (MUHC) lupus clinic. A RLS questionnaire based on 4 criteria, validated by the International Restless Legs Syndrome Study Group (IRLSSG), was administered during a face-to-face interview[1]. Similar methods were used to determine RLS prevalence in a comparator group of persons with rheumatic diseases other than SLE presenting to the MUHC general rheumatology clinics. Female controls were frequency-matched by age group (in 5-year age bands) to the SLE subjects. Controls were otherwise unselected.

We collected information on factors believed to be correlated with RLS in the general population, including smoking[8] and body mass index (BMI)[9]. Multivariate logistic regressions were performed to study the prevalence of RLS in SLE versus controls, adjusting for age, smoking status, and the presence or absence of obesity (defined as BMI > 30)[10].

Our study complied with the Declaration of Helsinki, and the research protocol was approved by the McGill University Health Centre research ethics committee; informed consent was obtained from all subjects.

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## RESULTS

Thirty-three female patients with SLE and 32 female controls (frequency-matched for age group) were recruited. The control population had a variety of rheumatic diseases, the most common being RA (N = 14) and soft-tissue rheumatism (N = 8). Table 1 presents descriptive information on the sample.

Twelve of 33 female SLE subjects scored positively (meeting all 4 IRLSSG criteria) for RLS (37.5%; 95% CI 22.9, 54.7) compared to 4 of 32 controls (12.5%; 95% CI 5.0, 28.1). Multivariate logistic regression (Table 2) adjusted for age, obesity, and smoking showed that women with SLE were more likely to have RLS than the female controls (adjusted OR 6.61, 95% CI 1.52, 28.77). In our multivariate analyses of all rheumatic patients, including SLE, the adjusted OR for obesity and RLS was 5.14 (95% CI 1.07, 24.6).

## DISCUSSION

The prevalence of RLS in the general population is believed to be about 10%, although the prevalence in women is twice as high as that in men. A number of studies have shown an elevated incidence of RLS in patients with rheumatic diseases like RA and primary Sjögren's syndrome; to our knowledge, ours is the first study investigating the prevalence of RLS in SLE. The results suggest that over a third of female SLE patients (37.5%) have RLS, about 3 times higher than that in women without SLE. This is an important contribution, especially given the recent study of Iaboni, *et al* regarding sleep in patients with SLE[11] where an increase in periodic limb movement syndrome (PLMS) was observed. Although RLS and PLMS are considered different entities, some similarities do exist.

*Table 1*. Characteristics of female patients with systemic lupus erythematosus (SLE) and controls.

| Characteristic | SLE, N = 33 | Controls, N = 32 |
|---|---|---|
| Average (SD) | | |
| Age, yrs | 43.0 (13.8) | 40.3 (15.7) |
| Body mass index | 24.3 (5.0) | 26.7 (7.2) |
| N (%) | | |
| Age ≥ 50 yrs | 9 (27.3) | 10 (30.3) |
| Obesity* | 5 (15.2) | 9 (27.3) |
| Smoker | 5 (15.2) | 7 (21.2) |

* Body mass index ≥ 30.

*Table 2*. Univariate and multivariate effects of variables on the reports of restless legs syndrome in our sample of women.

| Factor | Univariate (95% CI) | Multivariate (95% CI) |
|---|---|---|
| Age ≥ 50 yrs | 1.71 (0.52, 5.63) | 1.38 (0.35, 5.45) |
| Obesity* | 3.15 (0.89, 11.14) | 5.14 (1.07, 24.6) |
| Smoker | 1.05 (0.25, 4.47) | 1.44 (0.28, 7.45) |
| With systemic lupus erythematosus** | 4.14 (1.17, 14.65) | 6.61 (1.52, 28.77) |

* Body mass index ≥ 30. ** Compared to rheumatology clinic controls without SLE.

We chose controls from the general rheumatology clinic for several reasons. First, this choice helped to ensure that our control subjects represented the same catchment area as our SLE patients. Also, since RLS has already been demonstrated to be elevated in other rheumatic disease populations, we considered that it would be more relevant to use this population as a control, rather than a healthy control population. However, this likely could have biased our results toward showing a less impressive increase in RLS compared to controls. Indeed, the prevalence of RLS in our controls was on the higher side of available population estimates, which is to be expected given that they were drawn from a rheumatic disease clinic. Hence, our estimate of the relative increase of RLS in SLE may be considered conservative.

Until recently, RLS was only poorly described in the literature, and many patients likely still remain undiagnosed for long periods of time. Once diagnosis is confirmed, RLS can be treated with dopamine agonists; opioids, benzodiazepines, and gabapentin are also used. Certain lifestyle changes can help alleviate RLS symptoms: exercising before going to sleep and avoiding alcohol and caffeine, for example. Thus, it is important for rheumatologists to be aware of this potential complication in their patients, in order to be able to offer treatment. The best diagnostic tool for definite RLS at present is the IRLSSG questionnaire[1], in which an individual must fulfill all of 4 criteria, which include the following: (1) An urge to move the legs, usually accompanied by uncomfortable and unpleasant sensations. (2) The symptoms begin/worsen during periods of rest or inactivity such as lying or sitting. (3) The symptoms are at least partially relieved by movement (e.g., walking/stretching), at least for the duration of the activity. (4) The symptoms occur (or are worse) only in the evening/night versus the daytime. (When symptoms are very severe, the worsening at night may not be noticeable but must have been present previously.)

Although the pathogenesis of RLS remains unclear, it is widely accepted that there is an underlying genetic component that may cause abnormalities in central dopamine pathways (leading to hypo-dopaminergic states). The chromosomes implicated (as either autosomal dominant or recessive traits) to date include 12q, 14q, 9p, 20p, 4q, and 17p[12]. Interestingly, there is evidence that in the MRL-lpr mouse model of SLE, systemic autoimmunity affects the central dopaminergic system, destroying dopaminergic pathways[13]. Serum antibodies against dopaminergic cells in SLE have been described in at least one case report[14]. This suggests that abnormalities in dopaminergic pathways could drive an increased risk of RLS in SLE.

Obesity appeared to be a risk factor for RLS across our sample, that is, in both lupus and control patients. Several investigations suggest that the dopaminergic system may be altered in obesity; among obese individuals, the number of dopamine receptors appears to be inversely correlated with BMI[15]. This is of potential importance in SLE, where a high predominance of obesity has been demonstrated in some samples (up to 25%)[16].

Iron deficiency is also a known factor correlated with RLS. Although mild anemia did occur in some of our SLE patients, all patients with significant anemia had been screened to rule out iron deficiency. Due to power issues, we were unable to demonstrate associations between these laboratory indices and the presence of RLS in the SLE sample. Similarly, it would be interesting to consider other variables, such as neuropsychiatric involvement, renal disease, serology, fibromyalgia, and drugs such as antihistamines and corticosteroids. Again, however, we had limited power in this pilot study to investigate these variables in multivariate models.

SLE is a condition that often affects women in their child-bearing years, although many of the subjects in our study were older. RLS can be a complication of pregnancy, but there were no recent pregnancies in our small sample. It is of interest that although Berger, *et al*[4] showed higher prevalence of RLS in women, in that study nulliparous women actually had prevalence equal to that of men. It is a limitation of our study that we did not specifically collect obstetrical history, but since women with SLE are more likely than women without SLE to be nulliparous[17], this limitation should only serve to produce a conservative estimate of the relative increase in RLS among SLE patients compared to controls.

As a final potential limitation, we had background information on race/ethnicity in the SLE cohort but unfortunately did not specifically collect such information in the controls. Although our center does serve a relatively diverse population, the majority of the clients are Caucasian; certainly in the SLE subjects, the majority (approximately 75%) were Caucasian.

Our study suggests that women with SLE may be at high risk for RLS. This suggests the need for more research on the causes, progression, and possible treatment of RLS and related issues (such as sleep disturbances, fatigue, and neurologic involvement) in persons with rheumatic diseases like SLE. Although obesity was a significant risk factor for RLS in our sample, the predictive covariates examined were limited; additional study is warranted.

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