CED
Clinical and Experimental Dermatology

Increased frequency of restless legs syndrome in atopic dermatitis

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doi:10.1111/j.1365-2230.2012.04356.x

Summary

Background. Restless legs syndrome (RLS) is characterized by an unpleasant sensation in the legs, which is difficult to describe, but produces an urge to move the legs frequently.

Aim. To assess the prevalence and severity of RLS in patients with atopic dermatitis (AD) and patients with psoriasis, and to investigate the factors potentially associated with RLS.

Methods. In total, 253 people were enrolled (120 with AD, 50 with psoriasis and 83 healthy controls). A diagnosis of RLS was made according to the criteria of the International RLS Study Group (IRLSSG), and severity was assessed using the IRLSSG severity scale.

Results. RLS was significantly more common in patients with AD (40.8%) than in patients with psoriasis (18.0%) or in controls (10.8%) ($P < 0.01$ and $P < 0.001$, respectively). Prevalence of RLS was higher in patients with active AD than in those with inactive AD (55.3% vs. 23.6%) or controls. There was a significant difference in RLS prevalence between patients with active and those with iactive AD, between patients with active AD and healthy controls, between patients with active AD and patients with psoriasis, and between patients with inactive AD and healthy controls ($P < 0.001$, $P < 0.001$, $P < 0.001$, $P = 0.04$, respectively). There was no significant difference in RLS prevalence between patients with active AD and patients with psoriasis, or between patients with psoriasis and healthy controls ($P > 0.05$). Of patients who were positive for RLS, 56.9% had a family history of atopy and 40.3% had a family history of RLS, and there was a significant relationship between the presence of RLS and family history of atopy or RLS ($P < 0.001$ for both).

Conclusions. RLS is common in patients with AD, particularly in those with active disease.

Introduction

Restless legs syndrome (RLS) is a chronic sensorimotor disorder characterized by an unpleasant sensation in the legs, which patients report as difficult or impossible to describe, but that produces an urge or a need to move the legs frequently.[1,2] RLS usually occurs in the legs and rarely in the arms. The symptoms typically occur at rest or before sleep, and are alleviated by activity. The disease worsens intermittently, and there may be long, asymptomatic periods.[1,2] Epidemiological studies indicate that 5–15% of the population has RLS. Its prevalence in women is twice that in men, and it is more common in the elderly (> 65 years).[1–6] Although the pathogenesis of RLS has not yet been fully clarified, disorders of iron metabolism and the dopaminergic system have been cited.[7,8]

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Conflict of interest: none declared.

Accepted for publication 16 December 2011

RLS can generally be divided into primary and secondary forms. The primary (idiopathic) form occurs in most cases, and up to half of these patients have a positive family history.[3–5] RLS may also develop secondary to a variety of conditions, such as pregnancy, iron-deficiency anaemia, peripheral polyneuropathy, diabetes, multiple sclerosis (MS), rheumatoid arthritis (RA), Parkinson disease (PD), end-stage renal disease, fibromyalgia syndrome and chronic obstructive pulmonary disease (COPD).[3,6,9–17] Nicotine, caffeine, alcohol, many antidepressants and antihistamines, and most anti-nausea and antipsychotic agents have the potential to increase RLS symptoms.[2]

There are no studies in the literature investigating the presence of RLS in patients with atopic dermatitis (AD) or psoriasis. In the present study, we aimed to investigate the prevalence and severity of RLS in patients with plaque-type psoriasis and in patients with AD, and to assess the effect on RLS of drugs (such as antihistaminics) used to treat AD or psoriasis.

Methods

The study was approved by the local ethics committee, and all patients provided informed consent.

Study design and classification

This was a prospective clinical study. The allocation method for the groups was simple randomization.

Detailed medical history was taken from all patients, including personal and family history of atopy, personal history of RLS, frequency of symptom occurrence (times per week), and history of previous use of antihistamines, alcohol, antidepressants, anti nausea agents and antipsychotics, together with any increase in RLS symptoms noticed during their use.

Physical and dermatological examinations were conducted, and the AD group was divided into active and inactive subgroups according to the presence or not of active dermatitis. Patients with active AD had dry, scaling erythematous papules/plaques and lichenified plaques, and weeping, crusting and exudative lesions in the flexural areas.[18]

Because psoriatic lesions were present in all patients with psoriasis, we were not able to classify the disease as active and inactive. However, we determined disease severity based on the Psoriasis Area and Severity Index (PASI), and calculated the body surface area (BSA) involvement and Dermatology Life Quality Index (DLQI).[19–21]

Assessment of restless legs syndrome

All participants were asked to complete an RLS symptom questionnaire, specifically addressing the four cardinal clinical diagnostic features of RLS as defined by the International RLS Study Group (IRLSSG) consensus:[4] (i) a desire to move the limbs, usually associated with some definable discomfort; (ii) motor restlessness (moving the body or providing a counterstimulus to relieve discomfort, for example, by walking, or rubbing the legs, respectively); (iii) symptoms worse at rest with temporary relief provided by activity; and (iv) symptoms worse later in the day or at night.

RLS symptoms were further quantified by the 10-point RLS questionnaire, with each item scoring up to four points for a maximum of 40 points.[22] The quantified symptoms were further classified as (i) mild (1–10 points); (ii) moderate (11–20); (ii) severe RLS (21–30); and (iv) very severe (31–40).

Exclusion of other disorders

To exclude other underlying causes, any subjects determined as having RLS signs underwent further investigations. Those with normal values for serum iron, ferritin and calcium, iron-binding capacity, white cell count, haemoglobin, erythrocyte sedimentation rate, electrolytes, blood urea nitrogen, creatinine and liver enzymes, rheumatoid factor, and thyroid function tests were included in the study. Exclusion criteria included pregnancy or presence of diabetes, MS, RA, PD, end-stage renal disease or anaemia (defined as haemoglobin < 12 mg/dL for women and < 13.5 mg/dL for men). Any patient with anaemia who had a serum ferritin level of < 5 ng/mL (women) or < 28 ng/mL (men) were considered to have iron-deficiency anaemia.

All patients and controls were examined by the same neurologist for polyneuropathy. Nerve-conduction studies were carried out on all subjects with signs of RLS in the patient and control groups, in accordance with the standard neuropathy protocol (in both legs and one arm) to exclude polyneuropathy, although none had any symptoms that suggested peripheral neuropathy. Those in whom marked pathology was found were excluded from the study.

Any patients reporting use, in the 2-month period before the study, of alcohol, antihistamines, antidepressants, anti-nausea agents or antipsychotics, which might have led to an increase in RLS symptoms, were excluded. However, these patients were questioned about any

noted increases in RLS symptoms during the period of use.

Study population

The demographic distribution of patients with AD, patients with psoriasis and the control group is presented in Table 1. In total, 120 patients (68 women, 52 men; mean ± SD age 32.10 ± 8.7 and 30.65 ± 8.8, years, range 19–52) who were diagnosed with AD in accordance with the Hanifin and Rajka classification were included in the study.[23] Of these 120 patients, 65 had active and 55 inactive AD (mean ± SD age 33.33 ± 8.4 and 30.65 ± 8.8, respectively). The psoriasis group comprised 50 patients with psoriasis (29 women, 21 men; 35.10 ± 12.8 years, range 18–69). Mean duration of disease (AD or psoriasis) was 11.12 ± 10.71 years (range 1–40).

The control group was composed of 83 healthy volunteers (51 women, 32 men; 34.36 ± 11.1 years; range 19–65). There was no significant difference in age, gender or AD duration between the three groups.

Statistical analyses

The sample sizes of patients and controls in this study were calculated by considering the 80% power. Values obtained in the study are presented as mean ± SD for continuous variables or numbers and percentages for categorical variables. chi-square test, Student *t*-test for independent samples and ANOVA test were used in the comparison of groups. Tukey test was carried out for multiple comparisons. Values of $P < 0.05$ were accepted as statistically significant. SPSS (version 12.0; SPSS Inc., Chicago, IL, USA) was used in the statistical analyses.

Results

Of the 120 patients with AD, 65 had active and 55 had inactive AD. Of the 50 patients with psoriasis, 13 (26%) had mild, 28 (56%) moderate and 9 (18%) severe involvement. Mean BSA was 19.52 ± 17.56, mean PASI was 6.17 ± 4.20, and mean DLQI was 7.44 ± 5.44. When the relationship between PASI and DLQI was evaluated, DLQI was calculated as 8.66 ± 5.74 for severe psoriasis, 7.60 ± 5.51 in those for moderate psoriasis and 6.23 ± 5.29 for mild psoriasis according to PASI. The increase in DLQI values in patients with severe psoriasis compared with patients with moderate psoriasis was significant ($P = 0.02$).

RLS was significantly more common in patients with AD (40.8%) than in patients with psoriasis (18.0%) or controls (10.8%) ($P = 0.004$ and $P < 0.001$, respectively). Prevalence of RLS was higher in patients with active (55.3%) than in those with inactive AD (23.6%) or controls (10.8%). There was a significant difference in RLS prevalence between patients with active and those with inactive AD; patients with active AD and patients with psoriasis; patients with active AD and healthy controls; and patients with inactive AD and healthy controls ($P < 0.001$, $P < 0.001$, $P < 0.001$, $P = 0.04$, respectively). There was no significant difference between patients with inactive AD and patients with psoriasis, or between patients with psoriasis and healthy controls in terms of RLS prevalence ($P > 0.05$) (Tables 1 and 2).

When RLS was categorized as mild, moderate, severe and very severe, the mild-severity disease was most common, but a significant difference was found between the groups ($P > 0.05$). However, when RLS scores were compared between the different disease groups, the mean RLS score was found to be considerably higher in patients with psoriasis (15.11 ± 9.87) than in patients with AD (8.97 ± 6.05) or controls (5.00 ± 2.09), and the difference was significant ($P = 0.01$ and $P = 0.03$, respectively). Interestingly, even though RLS was quite common in patients with AD, the RLS severity score was not significantly different from that in the healthy controls ($P > 0.05$). Table 2 demonstrates the distribution of patient and control groups according to RLS severity.

When frequency of symptom occurrence (times per week) of RLS-positive patients was investigated, no significant difference was detected between the three groups ($P > 0.05$) (Table 3).

When patients and controls were questioned in terms of previous drug use and increase in RLS symptoms, no significant difference between the three groups was found in terms of drugs used and increase in symptoms ($P > 0.05$) (Table 3).

Family history of RLS was positive in 24.2% of patients with AD, 4% of patients with psoriasis and 7.2% of the control group. Of the 67 RLS-positive participants, 27 (40.3%) had a family history of RLS, and there was a significant relationship between the presence of RLS and a positive family history of RLS ($P < 0.001$) (Table 4). A family history of atopy was present in 33 (56.9%) of the RLS-positive patients, and there was a significant relationship between the presence of RLS and positive family history of atopy ($P < 0.001$). However, we found no significant association between positive family history of atopy and RLS severity or score ($P > 0.05$) (Table 4).

Table 1 Demographic distribution and clinical characteristics of patients and control subjects.

	Patients with AD				
	Active disease (n = 65)	Inactive disease (n = 55)	Patients with psoriasis (n = 50)	Controls (n = 83)	P
n	65	55	50	83	> 0.05
Gender, F/M	36/29	32/23	29/21	51/32	> 0.05
Age, years	33.33 ± 8.4	30.65 ± 8.8	35.10 ± 12.8	34.36 ± 11.1	> 0.05
Disease duration, years	10.43 ± 8.38	10.18 ± 7.36	11.12 ± 10.71		> 0.05
Mean PASI	–	–	6.17 ± 4.20	–	–
Mean DLQI	–	–	7.44 ± 5.44	–	–
BSA, %	–	–	19.52 ± 17.56	–	–
Nail involvement, %			29 (58)		
Positive RLS, %	55.3*†‡	23.6*§	18.0‡	10.8†§	< 0.05
Mean severity score	8.94 ± 5.51¶	9.07 ± 7.58	15.11 ± 9.87¶**	5.00 ± 2.09**	< 0.05

DLQI, Dermatology Life Quality Index; PASI, Psoriasis Area and Severity Index. Data are mean ± SD unless otherwise stated. *P < 0.001, active AD vs. inactive AD; †P < 0.001, active AD vs. healthy controls; ‡P < 0.001, active AD vs. psoriasis; §P = 0.04, inactive AD vs. healthy controls; ¶P = 0.01, active AD vs. psoriasis; **P = 0.03, psoriasis vs. healthy controls.

Table 2 Positivity for restless legs syndrome (RLS) and the distribution of patient and control groups according to the RLS category.

	Patients with AD	Patients with psoriasis (n = 50)	Controls (n = 83)
RLS			
Positive	49 (40.8)	9 (18.0)	9 (10.8)
Negative	71 (59.2)	41 (82.0)	74 (89.2)
Severity			
Mild	36 (30.0)	4 (8.0)	6 (7.2)
Moderate	9 (7.5)	2 (4.0)	0
Severe	4 (3.3)	2 (4.0)	0
Very severe	0	1 (2.0)	0

Data are n (%).

Table 3 Weekly frequency of restless legs syndrome (RLS) symptoms and the relationship between previous drug use and RLS symptoms according to group.

	Patients with AD			
	Active disease (n = 65)	Inactive disease (n = 55)	Patients with psoriasis (n = 50)	Controls (n = 83)
Frequency, times/week				
1–2	12 (18.4)	2 (3.6)	4 (8.0)	6 (7.2)
3–4	14 (21.5)	8 (14.5)	2 (4.0)	2 (2.4)
5–6	6 (9.2)	2 (3.6)	0	1 (1.2)
7–10	4 (6.1)	1 (1.8)	2 (4.0)	0
Increase with drug use				
Present	14 (21.5)	5 (9.0)	1 (2.0)	2 (2.4)
Absent	4 (6.1)	4 (7.2)	1 (2.0)	2 (2.4)
Unclear	18 (27.6)	4 (7.2)	6 (12.0)	5 (6.0)

AD, atopic dermatitis. Data are n (%).

Table 4 The relationship between restless legs syndrome (RLS) positivity and positive family history for RLS* or atopy.

	Family history of RLS		Family history of atopy	
Presence of RLS*	Positive	Negative	Positive	Negative
Positive (n = 67)	27 (40.2)	40 (59.7)	33 (49.2)	25 (37.3)
Negative (n = 186)	10 (5.3)	176 (94.6)	40 (21.5)	105 (56.4)

Data are n (%). *Includes the whole population registered in the study (disease and control groups).

Possible relationships between PASI, DLQI, BSA, and positive RLS or RLS severity and score were also investigated. Mean PASI was 4.73 ± 2.39 in RLS-positive patients and 6.49 ± 4.47 in RLS-negative patients, which was not significant (P > 0.05). There was a strong relationship between RLS positivity and BSA, which is an important indicator of psoriasis involvement (η coefficient = 0.82); however, no significant relationship was detected between BSA and RLS severity (correlation coefficient = 0.37, P = 0.32).

In patients with psoriasis, a moderate relationship was seen between DLQI and RLS positivity (η coefficient = 0.47), and a strong relationship between RLS severity category and DLQI (η coefficient = 0.84). No significant relationship was detected between RLS and DLQI (P > 0.05).

Discussion

RLS was first defined in 1685 by Thomas Willis in patients with 'anxietas tibiarum' who reported lack of sleep and restlessness in their legs. In 1945, Karl-Axem

Ekbom used the descriptions 'irritable legs' and 'restless legs', and the condition was termed 'Ekbom syndrome'.[2]

The most evident consistency in the presentation of RLS is that symptoms are exacerbated at night before sleep, continue well into sleep, disappear later in the day, and can be alleviated by shaking the legs or by walking. It is claimed that the major factor maintaining this circadian rhythm is the circulation of dopamine in the central nervous system (CNS). Although the improvement brought about by dopaminergic treatment suggests a dysfunction of central origin in the dopamine system, the aetiopathogenesis of the disease remains to be fully explained.[2,3,6,7]

Most cases of RLS cases are the primary (idiopathic) form and show autosomal dominant transmission. Susceptibility loci have been described on chromosomes 9p, 12q and 14q.[2] Secondary causes of RLS are more common, occurring in > 70% of those with onset at 65 years or later, although a positive family history seems to be most common in those with early-onset RLS.[24,25]

The leading secondary causes of RLS are iron-deficiency anaemia and PD.[3,6,24] O'Keeffe *et al.*[24] found RLS in 15 (5%) of 307 patients who presented to acute-care geriatric medical services. Iron deficiency was found in 31% of patients with RLS, but in only 5% of patients without RLS, with a significant difference between the two groups. The authors emphasized that iron-deficiency anaemia was a treatable disease. O'Keeffe *et al.*[26] also stated that in addition to serum iron, vitamin B12, folate and haemoglobin levels, serum ferritin levels were correlated with the severity of RLS symptoms in patients with RLS, and they stressed that serum ferritin was accepted as the best screening test for iron deficiency. The literature contains numerous studies indicating that RLS is seen significantly more commonly in patients with PD relative to healthy controls, and that this condition lowers the patients' sleep quality and quality of life.[2,7,25,27]

In the ensuing publications, autoimmune diseases (ADs) such as diabetes, fibromyalgia syndrome MS, RA, ESRD, and COPD were cited in the aetiology of RLS.[3,6,9–17] RLS was noted in a mean of 30% (8% to 52%) of patients with ESRD, and was found to be particularly prominent in patients on haemodialysis, possibly because of the enforced rest.[15,28] Enomoto *et al.*[15] evaluated the clinical features and the required dose of treatment medication in patients with uraemic and idiopathic RLS, and reported that the Pittsburgh Sleep Quality Index, International Restless Legs Syndrome Severity Scale, Periodic Leg Movement Index, Polysomnographic Index and Suggested Immobilization Test all gave higher scores before treatment in the uraemic group. In their conclusion, the authors stressed that RLS would quickly develop in patients with uraemia shortly after haemodialysis, that RLS had a more severe course in patients with uraemia, and that the response to dopaminergic agonists in patients with uraemic RLS was not as good as that in patients with idiopathic RLS.[15,28] It was reported that renal transplantation in patients on haemodialysis markedly reduced RLS signs, and that the improvement in RLS after renal transplantation was associated with lower serum iron and phosphorus levels.[14] Interestingly, no correlation was seen in that study between RLS and haemoglobin levels, age, gender, dialysis duration or time after transplantation.[14]

It has been noted in a population of patients with MS that RLS coexisted in 32.7% (three times the rate in the normal population), that the primary progressive MS course was more common in patients with RLS, and that the same group had a high rate of disability.[12] Reynolds *et al.*[13] reported that RLS was present in 30% of patients with RA, and that all of these patients were women. By contrast, Yunus *et al.*[16] found the prevalence of RLS to be significantly higher in fibromyalgia than in RA (31% vs. 15%).

RLS symptoms have not been found to correlate with age, pain severity, number of tender points, fatigue, poor sleep, global anxiety, stress or depression, but have been found to correlate with paraesthesia and leg cramps. There are two studies in the literature reporting cases of arborizing telangiectasia in the leg, and it was thought that vascular disturbances might have a part in the disease aetiology.[29] In a study on 174 patients with chronic venous failure, the prevalence of RLS in these patients was found to be significantly higher than the rate in patients without chronic venous failure (36% vs. 19%).[30] It was emphasized in that study that RLS was markedly more prevalent in women and the elderly, and that there was an evident relation between leg cramps, one of the signs of both chronic venous failure and RLS.[30] In a study on 9100 patients, Kröger *et al.*[31] classified small cutaneous veins into four groups according to their severity. They reported that night cramps and RLS were among the most common problems patients reported, and they found that RLS was significantly correlated with the severity of varicose veins. Lo Coco *et al.*[17] stated that prevalence of RLS was significantly higher (36.8%) in patients with COPD compared with controls. They found that RLS symptoms had a more severe course, that daytime somnolence and daytime sleepiness were higher in patients with COPD, and that RLS decreased sleep quality and quality of life.

AD is a chronic dermatitis characterized by intense itching and excessive dryness of the skin.[32] The itching increases during rest and thus is analogous to RLS.[32] Recently, autonomic dysfunction has been held responsible for the dryness and itching seen in AD.[33] Zakrzewska-Pniewska *et al.*[34] found a correlation between skin dryness/itching and autonomous function in patients with uraemia, and reported a significant correlation between severity of itching/paraesthesia and RLS.

In the present study, we investigated rates and severity of RLS in patients with psoriasis and AD, two different diseases that present with dryness and itching. We found the prevalence of RLS to be 40.8% in patients with AD, 18% in patients with psoriasis and 10.8% in the control group. The rate in the control group was much higher than the mean value reported for Turkey (3.19%).[35] In patients with AD, positive RLS was also consistent with the AD disease activity.

Interestingly, RLS presented with mild severity in most of our groups. However, the RLS severity score was considerably higher in patients with psoriasis, even though the incidence of RLS was lower. When the relationship between psoriasis severity and RLS positivity was investigated, there was a particularly striking relationship of RLS with BSA. However, the most important relationship was seen between DLQI and both RLS positivity and RLS score, which is probably because both psoriasis and RLS considerably reduce the quality of life.

Furthermore, we found that 24.2% of the families of patients with AD had a positive RLS history, and there was a significant relationship between familial atopy history and the presence of RLS. This may be because both disease are present concomitantly or they run in families.

Additionally, we established that a significant proportion of our patients with AD experienced worsening of RLS symptoms when they took antihistamines. Some of our patients could not discern this relation clearly, but the vast majority of the patients stated clearly that their RLS was worse in the winter months. We think that this increase in severity may be secondary to worsening of AD due to a decrease in skin moisture and/or more common use of antihistamines in winter.

We cannot precisely explain the reason for the high rate of RLS seen in patients with AD. However, although the exact aetiopathogenesis of these disorders remains unknown, the current literature hints at a possible association with a disruption in the balance between the dopaminergic and noradrenergic systems in the CNS.[36,37] Thus, it has been reported in the literature that bupropion, a dopamine reuptake inhibitor, brought about a marked recovery in a significant proportion of lesions in patients with severe and resistant AD and psoriasis, independent of emotional factors (without depression). The precise effect of bupropion in this recovery has not yet been fully elucidated, but it has been theorized that the concerned effect may be associated with the ability of bupropion to restore an imbalance in dopamine in the neurotransmitter system of the CNS.[36–38] By contrast, other antidepressants [the selective serotonin reuptake inhibitor (SSRI) group in particular] may worsen RLS symptoms by making the serotonergic activity in the CNS more marked. Nevertheless, although the lesion-healing action of bupropion applies to psoriasis, we cannot explain why there was no significant increase in the coexistence of RLS in our patients with psoriasis as opposed to those with AD.

We determined that there was a significant increase in the frequency of RLS in patients with active AD. It is possible that patients may confuse the symptom of itching caused by dermatitis with the symptoms of RLS, but this can be clarified easily on a clinical basis. The itching in patients with AD leads to a scratch reflex, and patients relax after the scratching, whereas RLS symptoms are more difficult to describe, and itching is present in a minority of patients. Generally a feeling of unrest or some sort of pain is described in RLS, and is a condition that forces the patient to move, not scratch.[1,3,19] The itching in AD can increase minimally in the evening at rest, but it can also continue throughout the day, whereas symptoms of RLS do not usually occur while patients are awake and active during the day. Complaints generally begin when the patient is seated, typically at rest or before sleep, and are more frequent at night. Additionally, the lesions in AD may be widespread or localized on the body, and in adults, the lesions tend to be localized to flexural areas, whereas RLS symptoms are usually limited to the legs.[1,3,19]

Conclusion

In conclusion, RLS is more common in patients with AD compared with controls or patients with psoriasis. Concomitant RLS, in addition to the dryness and itching experienced by patients with AD, lowers their quality of life. We believe that consideration of this fact during treatment of patients with AD should facilitate an improvement in their quality of life.

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