



Restless legs syndrome in children with allergic rhinitis: A comparative study on frequency, severity and sleep quality

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ABSTRACT

Objectives: This study aims to investigate the frequency and severity of restless legs syndrome (RLS) and its relationship with sleep quality in children with allergic rhinitis (AR) with the hypothesis that comorbid RLS may be an additional causative factor of sleep disturbances in pediatric AR.

Patients and methods: A total of 143 children with AR (aged 8-18 years) and 144 healthy control subjects (aged 8-18 years) were included. The diagnosis of AR was established on history, clinical examination and skin prick test according to the Allergic Rhinitis and its Impact on Asthma guidelines. Presence of RLS was determined using the International RLS study group (IRLSSG) criteria. The severity of RLS was assessed using the IRLSSG rating scale. Sleep quality was evaluated by Pittsburgh Sleep Quality Index (PSQI).

Results: Thirteen patients (9.1%) in AR group, and six children (4.2%) in control group had RLS ($p=0.159$). The frequency of RLS in AR group was higher than two folds when compared to the control group; however, the difference was not statistically significant. Restless legs syndrome severity score was significantly higher in AR group than control group (15.00 [11-20] and 11.00 [10-16] respectively, $p=0.046$). Total PSQI scores were similar between groups. Also, no significant differences were observed in total PSQI scores of AR patients with or without RLS.

Conclusion: Restless legs syndrome was not more common but was more severe in children with AR. There was no evidence that RLS has an obvious effect on sleep quality in children with AR.

Keywords: Allergic rhinitis; restless legs syndrome; sleep quality; Willis-Ekbom disease.

Allergic rhinitis (AR) is an inflammatory disease with symptoms including nasal congestion, rhinorrhea, sneezing, and pruritus of the eyes, nose and throat, and affects 20-40% of the general population in all over the world.^[1,2] Approximately 80% of patients are symptomatic before the age of 20 and the overall prevalence of AR in childhood has been reported to be 40%.^[2] Allergic rhinitis has negative effects on sleep and professional life and causes poor quality of life.^[2,3] Performance in daily life and work is affected by the

disease in approximately 75-80% of the patients with AR in Europe and USA.^[2-5]

Restless legs syndrome (RLS) is a chronic movement disorder, characterized by an urge to move legs usually accompanied by uncomfortable sensations and sleep disorders. The prevalence of the syndrome ranges from 1 to 15% in the general population, and about 2-4% of school-aged children and adolescents.^[6,7] The RLS symptoms which are worse at night and rest are partially or totally relieved by movements and may be

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associated with sleep disturbances and psychosocial distress.^[6,7] Diagnosis is based on clinical features and the diagnostic criteria suggested by International RLS Study group (IRLSSG).^[6] However, RLS still remains underdiagnosed probably due to lack of accurate information about the disease.^[8]

The etiology of pediatric RLS is poorly understood. The pathophysiology of RLS is focused on the dopaminergic system, reduced central nervous system iron and genetic linkages.^[8-12] Relationship between RLS and comorbid diseases such as iron deficiency, chronic renal failure and hyperactivity has been shown in pediatric age.^[12-15]

Allergic rhinitis is found to be one of the most common reasons for sleep disorders in childhood. The disease itself or the drugs given for treatment may both result in fatigue and difficulty in concentration during day time.^[16-18] There is a strong relationship between poor sleep quality and AR with impaired nasal function.^[2,16-18] Also, the addition of RLS to AR may cause poor sleep quality or RLS and AR may have a potentiating effect on sleep.

To the best of our knowledge, there have been no studies to date that evaluate the relationship between RLS and AR in children, and the effects of RLS on sleep quality in pediatric AR patients. Therefore in this study, we aimed to investigate the frequency and severity of RLS and its relationship with sleep quality in children with AR with the hypothesis that comorbid RLS may be an additional causative factor of sleep disturbances in pediatric AR.

PATIENTS AND METHODS

Study design and study population

This cross-sectional study was carried out in the Health Sciences University, Antalya Training and Research Hospital Pediatric Allergy and Physical Medicine and Rehabilitation Departments between January 2015 and December 2015. The study protocol was approved by the Health Sciences University, Antalya Training and Research Hospital Ethics Committee (approval number: 2014-246). A written informed consent was obtained from parents of all participants. The study was conducted in accordance with the principles of the Declaration of Helsinki. The diagnosis of AR was established on history, clinical examination, and skin prick test according to Allergic Rhinitis and its Impact on Asthma guidelines (2010 version).^[19] The patients with AR were classified as intermittent or persistent AR according to the duration of symptoms

and severity using the same guideline.^[19] All children with AR (aged 8-18 years), who applied consecutively to the outpatient clinics of Pediatric Allergy during the study period were evaluated. Patients with an underlying disease such as anemia, uremia, cancer, peripheral vascular disease, collagen tissue disease, endocrinopathy (hyper/hypothyroidism, diabetes mellitus), polyneuropathy or myelopathy were excluded. Patients using neuroleptic and antiepileptic drugs were also excluded. Ultimately, 143 children with AR were enrolled in the study and 144 age matched, healthy control subjects (aged 8-18 years) without allergy and chronic illnesses were recruited as controls.

Assessment parameters

Restless legs syndrome assessment: All participants were evaluated by a face-to-face interview to determine the presence of RLS according to the revised IRLSSG criteria.^[6] Subjects who fulfilled all five criteria were diagnosed as RLS. Updated integrated RLS diagnostic criteria were listed in Table 1.

Restless legs syndrome symptom severity assessment: To evaluate the symptom severity, IRLSSG rating scale was applied to the patients diagnosed to have RLS. This scale consists of ten questions regarding typical symptoms of the disease. Each question is rated between 0 and 4 points. Higher global score indicates more severe disease.^[20]

Skin prick test: A total of 18 allergen solutions, including the negative and positive controls, were employed. Saline and histamine were used as negative and positive controls, respectively. Allergens and

Table 1. International restless legs syndrome study group consensus diagnostic criteria for restless legs syndrome

1. An urge to move the legs usually but not always accompanied by, or felt to be caused by, uncomfortable and unpleasant sensations in the legs
2. The urge to move the legs and any accompanying unpleasant sensations begin or worsen during periods of rest or inactivity such as lying down or sitting
3. The urge to move the legs and any accompanying unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues
4. The urge to move the legs and any accompanying unpleasant sensations during rest or inactivity only occur or are worse in the evening or night than during the day
5. The occurrence of the above features is not solely accounted for as symptoms primary to another medical or a behavioral condition (e.g. myalgia, venous stasis, leg edema, arthritis, leg cramps, positional discomfort, habitual foot tapping)

Table 2. Demographic and clinical characteristics of allergic rhinitis patients and controls

	Allergic rhinitis patients (n=143)				Controls (n=144)				p
	n	%	Median	Min-Max	n	%	Median	Min-Max	
Age (year)			13	7-17			13	7-17	0.263*
Sex									0.236†
Female	71				81				
Male	72				63				
Hemoglobin			13.15	10.10-17.10			13.30	9.60-16.10	0.058*
Iron			73.00	10.00-361.00			63.00	15.00-194.00	0.135*
Total iron binding capacity			382.00	24.00-547.00			387.00	277.00-522.00	0.097*
Ferritine, mikro/mL			20.00	2.00-361.00			20.00	2.00-244.00	0.385*
Thyroid stimulation hormone			1.99	0.60-17.90			2.20	0.15-6.99	0.020*
Vitamin B12			208.00	9.62-1500.00			204.00	29.00-774.00	0.913*
Folic acid			8.88	4.30-149.00			9.31	1.42-112.86	0.993*
Vitamin D			15.55	4.00-42.60			12.80	4.62-38.80	0.004*
Presence of RLS	13	9.1			6	4.2			0.159†
The RLS severity score			15.00	11.00-20.00			11.00	10.00-16.00	0.046*

Min: Minimum; Max: Maximum; RLS: Restless legs syndrome; * Mann-Whitney U test; † Chi-square test.

positive/negative controls were applied to the volar surface of arm epidermally with commercially available prick test solutions (Allergopharma GmbH & CO KG, Reinbek, Germany). The allergens used included plants (trees, pine, verdure, grass, cereal, weed and olive), fungal spores (mixture of *Alternaria*, *Cladosporium*, *Penicillium*, *Aspergillus*), mites (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*), and animal epithelium (cat, dog, bird). When positive control's edema was above 3 mm while there was no reaction in the negative control, the result was considered as positive in epidermal skin prick test.

Sleep quality: Sleep quality was assessed by Pittsburgh Sleep Quality Index (PSQI). PSQI is a questionnaire assessing sleep quality as well as presence and severity of a sleep disorder. It includes seven components and 19 self-rated questions assessing subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medications and daytime dysfunction. All questions are rated between 0 and 3 points: 0, not during past month; 1, less than once a week; 2, once or twice a week; 3, three or more times a week. In addition, sleep quality is rated as follows: 0, very good; 1, fairly good; 2, fairly bad, 3 very bad. Component scores are summed to obtain a global score ranging between 0-21 points. Higher global scores indicate worse sleep quality. Its diagnostic sensitivity and specificity are 89.6% and 86.5%, respectively.^[21] Turkish validation and reliability study was performed by Agargun et al.^[22]

Laboratory: As impaired iron homeostasis plays an important role in the pathogenesis of RLS, all patients were tested for iron deficiency. A complete iron panel,

including serum hemoglobin, iron levels, ferritin, and total iron binding capacity were obtained. Also, thyroid-stimulating hormone, folic acid, vitamin B12 and vitamin D levels were analyzed.

Statistical analysis

Statistical analysis was performed using IBM SPSS version 20.0 software (IBM Corp., Armonk, NY, USA). Continuous variables were defined as median and range (minimum-maximum) with interquartile ranges for nonparametric tests. Although only nonparametric tests were used, mean±standard deviation values were given as well when necessary. Chi-square test was used for comparison of categorical variables. In the analysis of the difference between the values of the two groups, the normality hypothesis was tested with the Kolmogorov-Smirnov test, and as none of the parameters showed normal distribution, the Mann-Whitney U test was used. A *p* value <0.05 was considered as statistically significant.

A power analysis by Minitab 17 Statistical Software (Minitab, Ltd., Coventry, United Kingdom) according to the results of Tuna et al.^[23] revealed that 117 patients would be required in each group to detect significant differences with a power of 90% and a level of significance of $\alpha=0.05$.

RESULTS

There were no significant differences between AR patients and controls in terms of age or gender. Demographic and clinical characteristics of AR patients and controls were summarized in Table 2.

Table 3. Relationship of allergic rhinitis type and restless legs syndrome

	Restless legs syndrome (+) (n=13)		Restless legs syndrome (-) (n=130)		p*
	n	%	n	%	
Intermittent allergic rhinitis (n=77)	5	6.5	72	93.5	0.261
Persistent allergic rhinitis (n=66)	8	12.1	58	87.9	

* Chi-Square test.

Table 4. Relationship of sensitivity severity and restless legs syndrome

Number of sensitized allergens	Restless legs syndrome (+) (n=12)		Restless legs syndrome (-) (n=130)		p*
	n	%	n	%	
0-5 (n=122)	8	5.6	114	93.4	0.068
6-10 (n=20)	4	20	16	80	

* Chi-Square test.

Restless legs syndrome: Thirteen patients (9.1%) in AR group and six children (4.2%) in control group had RLS ($p=0.159$). The frequency of RLS in AR group was more than two folds when compared to the control group; however, the difference was not statistically significant (Table 2).

Restless legs syndrome symptom severity: Restless legs syndrome severity score was significantly higher in AR group than control group (15.00 [11-20] and 11.00 [10-16] respectively, $p=0.046$) (Table 2).

In AR group, 77 patients (53.8%) had intermittent, and 66 patients (46.2%) had persistent AR. Restless legs syndrome was two folds more frequent in persistent AR than intermittent form (12.1% vs. 6.5%), but the difference was not statistically significant ($p=0.261$) (Table 3).

Skin prick test: Patients were stratified according to the number of allergens they were sensitive to. One of the groups was composed of patients who had sensitivity to 0-5 allergens, and the other was composed of patients who had sensitivity to 6-10 allergens. Of the patients, 122 (85%) had sensitivity to 0-5 and 20 (15%) to 6-10 allergens. One patient refused to have

a pinprick test. The frequency of RLS was 5.6% and 20% in the less sensitive group and more sensitive group, respectively ($p=0.068$) (Table 4).

Sleep quality: There were no significant differences between AR patients and controls in terms of total PSQI scores ($p=0.730$). In the subgroups of PSQI regarding sleep latency and sleep disturbances, AR group had significantly worse scores ($p=0.002$ and $p=0.001$, respectively). In habitual sleep efficiency and use of sleep medications subgroups, control group had significantly worse scores than AR group ($p=0.022$ and $p=0.002$, respectively). No differences were observed between two groups in subjective sleep quality, sleep duration or daytime dysfunction ($p=0.913$, $p=0.093$, and $p=0.155$, respectively) (Table 5).

No significant difference was observed in total PSQI scores of AR patients with or without RLS ($p=0.538$). Only sleep disturbances subgroup score was significantly worse in RLS (+) group than RLS (-) group ($p=0.005$) (Table 6).

Persistent AR patients had slightly higher PSQI total and subgroup scores than intermittent AR patients, but this was not at a statistically significant level (Table 7).

Table 5. Mean and median Pittsburgh Sleep Quality Index scores of allergic rhinitis patients and controls

PSQI scores	Allergic rhinitis patients (n=143)			Controls (n=144)			p*
	Mean±SD	Median	Min-Max	Mean±SD	Median	Min-Max	
Subjective sleep quality	0.7±0.6	1.00	0.00-3.00	0.8±0.7	1.00	0.00-3.00	0.913
Sleep latency	1.0±0.7	1.00	0.00-3.00	0.7±0.7	1.00	0.00-3.00	0.002
Sleep duration	0.3±0.5	0.00	0.00-2.00	0.4±0.6	0.00	0.00-2.00	0.093
Habitual sleep efficiency	0.2±0.4	0.00	0.00-1.00	0.3±0.4	0.00	0.00-1.00	0.022
Sleep disturbances	1.0±0.3	0.00	0.00-2.00	0.8±0.4	0.00	0.00-2.00	0.001
Use of sleep medications	0.0±0.2	0.00	0.00-1.00	0.1±0.4	0.00	0.00-2.00	0.002
Daytime dysfunction	1.5±1.6	1.00	0.00-6.00	1.9±2.1	2.00	0.00-6.00	0.155
Total PSQI score	4.8±2.9	4.00	1.00-11.00	4.5±2.4	4.00	0.00-12.00	0.730

PSQI: Pittsburgh Sleep Quality Index; SD: Standard deviation; Min: Minimum; Max: Maximum; * Mann-Whitney U test.

Table 6. Mean and median Pittsburgh Sleep Quality Index scores of restless legs syndrome (+) or (-) patients in allergic rhinitis and persistent and intermittent allergic rhinitis

PSQI scores	Restless legs syndrome (n=13)			Restless legs syndrome (n=130)			p*
	Mean±SD	Median	Min-Max	Mean±SD	Median	Min-Max	
Subjective sleep quality	0.9±0.9	1.00	0.00-2.00	0.7±0.6	1.00	0.00-2.00	0.375
Sleep latency	1.3±0.5	1.00	1.00-2.00	0.9±0.7	1.00	0.00-3.00	0.115
Sleep duration	0.1±0.3	0.00	0.00-1.00	0.3±0.5	0.00	0.00-2.00	0.116
Habitual sleep efficiency	0.2±0.4	0.00	0.00-1.00	0.2±0.4	0.00	0.00-1.00	0.943
Sleep disturbances	1.2±0.4	1.00	1.00-2.00	1.0±0.3	1.00	0.00-2.00	0.005
Use of sleep medications	NA	0.00	0.00-0.00	0.0±1.27	0.00	0.00-1.00	0.578
Daytime dysfunction	1.3±1.5	1.00	0.00-4.00	1.5±1.6	1.00	0.00-6.00	0.880
Total PSQI score	5.0±2.6	4.00	3.00-10.00	4.5±2.5	4.00	0.00-11.00	0.538

PSQI: Pittsburgh Sleep Quality Index; SD: Standard deviation; Min: Minimum; Max: Maximum; * Mann-Whitney U test.

Table 7. Mean and median Pittsburgh Sleep Quality Index scores of persistent and intermittent allergic rhinitis

PSQI scores	Persistent AR (n=66)			Intermittent AR (n=77)			p*
	Mean±SD	Median	Min-Max	Mean±SD	Median	Min-Max	
Subjective sleep quality	0.8±0.7	1.00	0.00-2.00	0.6±0.6	1.00	0.00-3.00	0.182
Sleep latency	1.0±0.8	1.00	0.00-3.00	0.8±0.7	1.00	0.00-3.00	0.977
Sleep duration	0.2±0.5	0.00	0.00-2.00	0.3±0.5	0.00	0.00-2.00	0.278
Habitual sleep efficiency	0.2±0.3	0.00	0.00-1.00	0.2±0.4	0.00	0.00-1.00	0.462
Sleep disturbances	1.1±0.3	1.00	0.00-2.00	1.0±0.3	1.00	0.00-2.00	0.160
Use of sleep medications	0.01±0.1	0.00	0.00-1.00	0.01±0.2	0.00	0.00-1.00	0.391
Daytime dysfunction	1.6±1.7	1.00	0.00-6.00	1.3±1.5	1.00	0.00-5.00	0.248
Total PSQI score	4.8±2.7	4.00	1.00-11.00	4.4±2.4	4.00	0.00-10.00	0.554

AR: Allergic rhinitis; PSQI: Pittsburgh Sleep Quality Index; SD: Standard deviation; Min: Minimum; Max: Maximum; * Mann-Whitney U test.

Laboratory: Mean hemoglobin, iron, total iron binding capacity, ferritin, vitamin B12 and folic acid levels were normal or similar between AR and control groups ($p=0.058$, $p=0.135$, $p=0.097$, $p=0.385$, $p=0.913$, and $p=0.993$, respectively). Significant differences were observed in thyroid stimulation hormone (TSH) and vitamin D levels between groups. In both groups, vitamin D levels were under normal limits; however, in AR group, it was significantly higher than the control group ($p=0.004$). TSH levels were normal in both groups and significantly lower in AR group ($p=0.020$) (Table 2).

DISCUSSION

To the best of our knowledge, this is the first study that assessed the frequency of RLS in children with AR and its impact on sleep quality. Restless legs syndrome was two-fold more frequent in AR patients when compared to controls (9.1% vs. 4.2%); however, this difference did not reach a statistically significant level. On the other hand, symptom severity of RLS was found to be significantly worse in patients with AR, which gives the impression that AR mainly affects the severity of RLS, not the frequency. The ratio of RLS in control group was 4.2%, which was similar to

the previously reported ratios (2-4%).^[24,25] There was no evidence that RLS has an obvious effect on sleep quality in children with AR.

Various studies showed the increased frequency of RLS and its association with poor sleep quality in many diseases such as chronic renal failure,^[26] fibromyalgia,^[27] ankylosing spondylitis,^[28] lumbar radiculopathy,^[29] inflammatory bowel disease,^[30] or primary biliary cirrhosis.^[31] However, there exist only a small number of studies which investigate the relationship between RLS and allergic diseases in adults, but not in children. In these studies, a possible correlation has been reported between the two diseases.^[23,32] In atopic dermatitis patients, RLS was found to be more frequent and correlated with the disease severity compared with psoriasis and control groups.^[32] In another study, Tuna et al.^[23] showed that frequencies of RLS and sleep disturbances were higher in patients with chronic urticaria than the control group. Authors claimed that RLS and urticaria might share a common etiology and urticaria might trigger and worsen RLS. In the present study, RLS was more common in AR patients compared to control group, and in more sensitive AR patients compared to less sensitive ones; however, these differences were not

statistically significant. In this study, most of the children in AR group had sensitivity to fewer allergens (122 children were sensitive to 0-5 allergens, while 20 children were sensitive to 6-10 allergens). In other words, children with AR in the study group mostly had a mild form of the disease. This may be a reason for the nonsignificant differences.

The association between AR and RLS may be due to several reasons. Although the pathophysiology of RLS still remains unclear, dopamine dysfunction, genetic factors and iron deficiency are thought to be the leading causes of RLS.^[9-12,33] Also, recent studies suggest possible roles for inflammatory and/or immune mechanisms in the pathogenesis of RLS.^[27,29,33] Weinstock et al.^[33] reviewed the diseases and conditions associated with RLS and found that 42 of the 47 (89%) RLS-associated conditions were related with inflammatory and/or immune changes. Imbalances in innate and adaptive immunity together with environmental factors are likely to play major roles in AR.^[34] Inflammation and altered immunity in AR may contribute to iron deficiency and hypothetically cause central nervous system iron deficiency-induced RLS. Furthermore, antihistamines that are commonly used for the treatment of AR block dopamine receptors.^[6,7,31] Dopaminergic dysfunction caused by antihistamines may be a reason for increased severity of RLS symptoms.

Allergic rhinitis is a well-known and important risk factor for sleep disturbances.^[2,16-18] The reasons for poor sleep quality are not clearly defined, but nasal congestion and elevated inflammatory cytokines have been reported to be the likely causes of sleep impairment.^[2,16] Colás et al.^[35] reported that among 2,275 patients with AR, 52.8% had sleep disturbances and sleep quality was affected by severity of the disease. In the present study, sleep quality assessed by PSQI was similar in AR and control groups, and in contrast with our hypothesis, our results showed that presence of RLS did not seem to have any negative effect on sleep quality in AR.

This study has a number of limitations. The study group was composed of patients with sensitivity to fewer allergens; therefore, our results may not represent all patients with AR. Another limitation is that we did not perform polysomnography examination for the patients. The IRLSSG rating scale that was used to assess the severity of RLS had no Turkish validity and reliability study, which was another limitation of our study. However, in the literature, there are several manuscripts that have used IRLSSG rating scale in

Turkish population.^[36,37] Moreover, this scale was developed for adults, not for children. Nevertheless, due to the lack of a scale appropriate for children, it has been used in pediatric RLS studies as well.^[38] For all these reasons, despite its limitations, this scale was used in our study. Another limitation was PSQI having validation only for Turkish adults and not for Turkish children. Then again, as far as we know, there is no sleep quality index for which Turkish validity and reliability study has been conducted for children and this index has been used in several articles to assess sleep quality of Turkish children.^[39,40] Thus, PSQI was preferred in the current study.

In conclusion, our study showed that RLS may be more severe but is not associated with poor sleep quality in children with AR. Despite its high prevalence, RLS continues to be greatly underrecognized and undertreated in childhood. We advise clinicians to screen children with AR for comorbid diseases such as RLS to improve patients' quality of life. Additional studies are needed to confirm and expand upon our results.

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