



Evaluation of Restless Legs Syndrome in Children with Allergic Rhinitis

Alerjik Rinit Tanılı Çocuklarda Huzursuz Bacak Sendromunun Değerlendirilmesi

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Abstract

Aim: It was aimed to evaluate the frequency of restless legs syndrome (RLS) in children with a diagnosis of allergic rhinitis (AR).

Material and Method: The study is case-control type. Age, gender, height, weight, Body Mass Index (BMI), allergic rhinitis symptom score, allergic rhinitis severity, allergy tests, total IgE, eosinophil values of the case group were examined. Gender, age, height, weight and BMI were also calculated in the control group. Patients in both groups were questioned using the International Restless Legs Syndrome Study Group's (IRLSSG) questionnaire containing the latest diagnostic criteria and severity scoring revised for the pediatric age group. Neurological examination, questionnaire and RLS severity scoring results of the patients were performed by a pediatric neurologist.

Results: In the study, the data of a total of 230 children, 115 AR cases and 115 control groups, were evaluated. The frequency of restless legs syndrome in children with allergic rhinitis was significantly higher than in the control group (15.7% and 5.2%, respectively; $p=0.010$). The clinical severity of RLS patients was mostly moderate in both the case and control groups [44.4% ($n=8$) and 50% ($n=3$), respectively].

Conclusion: According to the results of our study; restless legs syndrome was observed more frequently in patients with allergic rhinitis compared to the control group.

Keywords: Allergic rhinitis, allergy, restless legs, children

Öz

Amaç: Alerjik rinit (AR) tanılı çocuklarda huzursuz bacak sendromu (HBS) sıklığının değerlendirilmesi amaçlandı.

Gereç ve Yöntem: Çalışma vaka kontrol tipindedir. Olgu grubunun yaş, cinsiyet, boy, kilo, Vücut Kitle İndeksi (VKİ), alerjik rinit semptom skoru, alerjik rinit şiddeti, alerji testleri, total IgE, eozinofil değerleri incelendi. Kontrol grubunda da cinsiyet, yaş, boy, kilo ve VKİ incelendi. Her iki gruptaki hastalar, pediatrik yaş grubu için revize edilmiş en son tanı kriterlerini ve şiddet puanlamasını içeren Uluslararası Huzursuz Bacak Sendromu Çalışma Grubu anketi kullanılarak sorgulandı. Hastaların nörolojik muayeneleri, anket uygulanması ve huzursuz bacak sendromu şiddet skorlaması çocuk nöroloğu tarafından gerçekleştirildi.

Bulgular: Çalışmada 115 AR olgusu ve 115 kontrol grubu olmak üzere toplam 230 çocuğun verileri değerlendirildi. Alerjik rinitli çocuklarda huzursuz bacak sendromu sıklığı kontrol grubuna göre anlamlı olarak yüksekti (sırasıyla %15,7 ve %5,2; $p=0,010$). HBS hastalarının klinik şiddeti hem vaka hem de kontrol gruplarında çoğunlukla orta düzeydeydi [sırasıyla %44,4 ($n=8$) ve %50 ($n=3$)].

Sonuç: Çalışmamızın sonuçlarına göre, alerjik rinitli hastalarda kontrol grubuna göre huzursuz bacak sendromu daha sık gözlemlendi.

Anahtar Kelimeler: Alerjik rinit, alerji, huzursuz bacak, çocuklar



INTRODUCTION

The prevalence of allergic diseases is increasing, especially in middle- and low-income countries.^[1] Allergic rhinitis (AR) and asthma are among the most common allergic diseases.^[2] AR disease occurs as a result of the immunoglobulin E-mediated inflammatory response of the nasal mucosa against allergens.^[3,4] Common clinical findings of AR include some nasal symptoms like sneezing, itching and runny nose, nasal congestion. Besides the nasal symptoms, redness and tearing in the eyes can occur in patients with allergic rhinitis.^[5]

Clinical findings related to the disease can negatively affect the quality of life in children.^[6] There are also studies showing that school performance and sleep are adversely affected in children with allergic rhinitis.^[7-9] It has been shown that nasal congestion caused by AR contributes to sleep-disordered breathing.^[6,10] According to a study in the literature; in children with moderate and severe allergic rhinitis, the frequency of sleep disorders was reported to be higher than the control group, even when they continued the treatment regularly. Nighttime breathing disorders, sleepiness during the day, parasomnias are the sleep disorders that have been reported.^[11] Various studies have also shown that allergic rhinitis is associated with shorter sleep times, bruxism, night sweats, and nocturnal enuresis.^[12-15]

Restless legs syndrome (RLS) is a sleep-related periodic sensorimotor disorder. In RLS, people experience a feeling of discomfort, which creates the need to move their legs, especially at rest and/or before falling asleep.^[16] RLS is seen in approximately 2-4% of children and is not a rare disease for childhood.^[17,18] Symptoms related to RLS may negatively affect children's daily living activities, cognitive and behavioral characteristics by impairing their sleep quality.^[17] Studies have shown that RLS is associated with other sleep disorders, and people with RLS generally experience a delay in falling asleep, difficulty in maintenance of the sleep, and a reduction in total sleep time.^[19,20] Although the etiopathogenesis is not clearly known, iron depletion and dopaminergic dysfunction are thought to play a role in the central nervous system.^[21] Recent studies show that immune dysregulation and inflammation may also play a role in the pathogenesis of RLS.^[22,23] It has been shown that RLS is associated with many chronic diseases such as chronic respiratory diseases, diabetes, Parkinson's, cancer, osteoarthritis, anemia, and multiple sclerosis. Iron deficiency is the most common condition in the etiology.^[24-27]

In a study conducted among children aged 8-18 years, the incidence of restless legs syndrome in the patient group diagnosed with allergic rhinitis was found to be more than twice the frequency in the control group.^[28] Although there is no statistical significance, the frequency of restless legs syndrome in the patient group diagnosed with allergic rhinitis is higher than the control group, suggesting that these two diseases may be related to each other. In the

same study, the severity of restless legs syndrome in children found to be significantly higher in children with allergic rhinitis than in the control group. The fact that the frequency and severity of the diagnosis of restless legs syndrome is higher in children with a diagnosis of allergic rhinitis suggests that the relationship between these two diseases should be evaluated.

In this study, we aimed to evaluate the frequency of restless legs syndrome in children diagnosed with allergic rhinitis. We also aimed to evaluate the frequency of restless legs syndrome in the healthy control group in order to compare the frequency of co-occurrence of restless legs syndrome in patients with allergic rhinitis compared to the general pediatric group.

MATERIAL AND METHOD

The study was carried out with the permission of Health Sciences University Ümraniye Training and Research Hospital Ethics Committee (Date: 29/09/2022, Decision No: 315). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Informed consent was obtained from the participants.

Study Type and Sampling

The study is case-control type. The population of the study consists of children aged 10-18 years with a diagnosis of AR who applied to the pediatric allergy and immunology clinic for the case group. The population of the control group, on the other hand, consisted of children aged 10-18 years, who had no AR and any other chronic disease, applied to the pediatrics outpatients clinic of our hospital. In the sample size calculation, the incidence of restless legs syndrome in AR patients was accepted as 9.1%, the margin of error was 5%, and the confidence level was 95%, and it was calculated as 128. For the control group, the incidence of restless legs syndrome was accepted as 4.2%, the margin of error was 5%, and the confidence level was 95%, and it was calculated as 62.^[28] The study was conducted with children aged 10-18 years. Children younger than ten years of age were not included in the study. Since most of the children who applied to our clinic with the diagnosis of AR are over the age of 10 years, the study was planned to be conducted with children in this age group. Except this, patients with anemia, active cancer, peripheral vascular disease, polyneuropathy/myelopathy, and patients using neuroleptic/antiepileptic drugs were also excluded from the study.

Evaluations

In the study; age, gender, weight, height, Body Mass Index (BMI) z scores, allergic rhinitis symptom score and allergic rhinitis severity of the case group were evaluated. In addition, as laboratory data; specific IgE, total IgE and eosinophil values were evaluated. Gender, age, weight, height, BMI z-score values were also examined in the control group. Ferritin, vitamin B12, folic acid, thyroid stimulating

hormone (TSH), free T4 and vitamin D values of patients diagnosed with RLS in the case and control groups were also examined within the scope of the study. The diagnosis of restless legs syndrome for both groups was established by using the International Restless Legs Syndrome Study Group (IRLSSG) questionnaire containing the latest diagnostic criteria and severity scoring revised for the pediatric age group.^[29] Evaluation of the questionnaire and neurological examination were performed by a pediatric neurologist.

Rhino Conjunctivitis Scoring System (RCSS) was used for the investigation of the severity of AR symptoms. RCSS questions 6 symptoms including nasal itching, nasal congestion, rhinorrhea, sneezing, redness of the eye and watery eyes. Each symptom is scored by patients as 0 (none), 1 (mild), 2 (moderate), 3 (severe). The total RCSS is calculated by dividing the sum of the scores for each 6 symptoms into 6.

Patients with AR symptoms of less than 4 days in a week or less than 4 weeks are classified as intermittent AR; those with symptoms lasting more than 4 days per week and longer than 4 weeks were classified as persistent AR. AR patients presenting with at least one of the symptoms of sleep disturbance, impairment in daily activities, recreational and/or sports activities, deterioration in school or work performance, and disturbing symptoms were classified as moderate-severe AR. Mild AR patients are those in whom none of these findings are observed.^[30]

Statistics

SPSS (Statistical Package for Social Sciences) for Windows 25.0 program was used for the analysis of the data. Median, minimum, maximum values, numbers (n) and percentages (%) were used for the descriptive data. Conformity of continuous variables to normal distribution was evaluated with visual (histogram and probability charts) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). Mann Whitney U test was used for the non-normally distributed variables. Chi-square test was used for the categorical data. Logistic regression test was used as a multivariate analysis for the investigation of the factors associated with the presence of RLS in AR patients. p <0.05 was accepted as the statistical significance level.

RESULTS

Within the study, 115 children with allergic rhinitis were analyzed as the case group, and 115 children without allergic rhinitis or any other chronic disease were analyzed in the control group. Case and control groups were similar in terms of age and gender. While the percentage of girls in the control group was 51.3%, this rate was 42.6% in the case group. The median age was 13.0 years (10.0-18.0) in the case group, while it was 12.0 years (10.0-17.0) in the control group. Case and control groups were also statistically similar in terms of weight, height and BMI z-scores (**Table 1**).

Table 1. Gender, age and anthropometric measurements of the case and control groups

	Case (n=115)	Control (n=115)	P value	
Gender, n (%)	Female	49 (42.6)	59 (51.3)	0.186
	Male	66 (57.4)	56 (48.7)	
Age (years), median (min-max)	13.0 (10.0-18.0)	12.0 (10.0-17.0)	0.422	
Weight z scores, median (min-max)	0.66 (-2.27-3.00)	0.56 (-2.71-2.93)	0.871	
Height z scores, median (min-max)	0.12 (-2.56-4.48)	0.26 (-3.05-3.08)	0.531	
BMI* z scores, median (min-max)	0.67 (-2.53-2.51)	0.47 (-2.36-2.65)	0.773	

*BMI:Body Mass Index

When the laboratory and clinical features of allergic rhinitis patients are evaluated; absolute eosinophil, eosinophil (%), and total IgE median values were 260.0 103/uL (31.0-2930.0), 3.4% (0.17-24.1), 178.0 IU/mL (3.0-2472.0), respectively. The median RCSS-Nose and RCSS-Eye scores were 2.0 (0-3.0) and 1.0 (0-3.0), respectively. 67.0% (n=77) of the patients had positive blood specific IgE levels, and 40.3% (n=31) of them had specific IgE levels positive for more than one allergen. 67% (n=77) of the patients had persistent AR (**Table 2**).

Table 2. Laboratory and clinical features of the patients with allergic rhinitis

Laboratory parameters	Median (min-max)
Eosinophil (absolute)(103/uL)	260.0 (31.0-2930.0)
Eosinophil (%)	3.4 (0.17-24.1)
Total IgE (IU/mL)	178.0 (3.0-2472.0)
RCSS scores	Median (min-max)
RCSS-Nose	2.0 (0-3.0)
RCSS-Eye	1.0 (0-3.0)
Specific IgE Positivity	n (%)
No	38 (33.0)
Yes	77 (67.0)
Specific IgE* Positivity for house dust mite	76 (66.1)
Specific IgE Positivity for cat	26 (22.6)
Specific IgE Positivity for pollen	16 (13.9)
Specific IgE Positivity for peanut	3 (2.6)
Specific IgE Positivity for more than one allergen	n (%)
Positivity for one allergen	46 (59.7)
Positivity for more than one allergen	31 (40.3)
Clinical severity of AR*	n (%)
Intermittent	38 (33.0)
Mild	29 (25.2)
Moderate-Severe	9 (7.8)
Persistent	77 (67.0)
Mild	33 (28.7)
Moderate-Severe	44 (38.3)

IgE: Immunoglobulin E, AR:Allergic rhinitis

When the RLS frequency of the case and control group was compared; RLS was seen in 15.7% (n=18) of the case group and 5.2% (n=6) of the control group. The frequency of RLS in AR patients was significantly higher than the control group (p<0.05). The clinical severity of RLS patients was mostly moderate in both the case and control groups (44.4% [n=8] and 50% [n=3], respectively). RLS patients in the case and control groups were statistically similar in terms of clinical severity (p=1.000) (**Table 3**).

Table 3. Frequency of restless legs syndrome in case and control groups

Restless legs syndrome	Participants		P value
	Case group	Control group	
Yes	18 (15.7)	6 (5.2)	0.010
No	97 (84.3)	109 (94.8)	
Severity of RLS*			1.000
Mild	6 (33.3)	2 (33.3)	
Moderate	8 (44.4)	3 (50.0)	
Severe	4 (22.2)	1 (16.7)	
Very severe	0 (0)	0 (0)	

*RLS:Restless legs syndrome

When the presence of RLS was evaluated according to the clinical and demographic characteristics of AR patients; the presence of RLS was found to be higher in patients with persistent AR than in patients with intermittent AR (19.5% and 7.9%, respectively). But statistical significance was not observed (p=0.108). There was no statistical significance between gender, age, multiple allergen sensitivity, weight, height and BMI z scores and the presence of RLS (Table 4).

Table 4. Frequency of restless legs syndrome according to the clinical and demographic features of patients with allergic rhinitis

	Restless legs syndrome		P value
	No	Yes	
Gender, n (%)			0.864
Female	41 (83.7)	8 (16.3)	
Male	56 (84.8)	10 (15.2)	
Clinical presentation of AR*, n (%)			0.108
Intermittant	35 (92.1)	3 (7.9)	
Persistent	62 (80.5)	15 (19.5)	
Sensivity to multiple allergens, n (%)			0.605
No	33 (86.8)	5 (13.2)	
Yes	64 (83.1)	13 (16.9)	
Age, median (min.-max)	13.0 (10.0-18.0)	12.0 (10.0-17.0)	0.795
Weight z scores, median (min.-max)	0.67 (-2.35-2.93)	0.04 (-2.71-3.0)	0.125
Height z scores, median (min.-max)	0.20 (-3.05-3.08)	-0.09 (-2.65-4.48)	0.429
BMI* z score, median (min.-max)	0.75 (-2.31-2.51)	0.17 (-2.53-2.10)	0.108

*AR:Allergic rhinitis, BMI: Body Mass Index

The median values of ferritin, vitamin B12, folic acid, thyroid stimulating hormone (TSH), free T4 and vitamin D measurements of patients diagnosed with RLS in the case and control groups were compared. There was no significant difference between the laboratory parameters of RLS patients in both groups, except for folic acid (Table 5).

Table 5. Laboratory parameters of the patients diagnosed with RLS

	RLS* Patients		P value
	In AR Group	In Control Group	
	Median (min-max)	Median (min-max)	
Ferritin (ng/mL)	42.0 (6.0-80.0)	10.0 (9.0-36.0)	0.189
Vitamin B12 (ng/L)	342.0 (111.0-879.0)	233.0 (220.0-264.0)	0.180
Folic acid (µg/L)	6.8 (4.2-13.7)	3.7 (3.1-4.1)	0.009
TSH (mIU/L)	2.5 (0.8-5.2)	2.3 (1.5-4.7)	1.000
Free T4 (mg/dL)	1.2 (1.0-1.5)	1.1 (1.1-1.2)	0.233
25-OH vitamin D 7(ng/mL)	13.0 (4.7-32.0)	8.6 (7.8-14.0)	0.517

*RLS:Restless legs syndrome, TSH:Thyroid stimulating hormone

Variables that may be associated with RLS syndrome in AR patients were evaluated with logistic regression analysis. In the regression model, the presence of RLS was accepted as the dependent variable, while age, gender, BMI z score, persistent AR, and multiple allergen sensitivity were considered the independent variables. According to the logistic regression model, there was no statistical significance between the presence of RLS in AR patients and the variables of gender, age, BMI z score, persistent AR, multiple allergen sensitivity (Table 6).

Table 6. Logistic regression analysis for the restless legs syndrome diagnosis in AR patients

	P value	OR†	95% C.I. OR †	
			Lower	Upper
Gender*	0.787	1.178	0.360	3.848
Age	0.486	0.918	0.721	1.168
BMI z score	0.058	0.627	0.387	1.016
Persistent AR†	0.085	4.049	0.826	19.852
Sensivity to multiple allergens	0.575	1.410	0.424	4.688

*Female was the reference value for the gender, †AR:Allergic rhinitis, OR:Odds ratio, C.I.:Confidence Interval

DISCUSSION

Allergic rhinitis is a disease that is common in childhood and can negatively affect quality of life and sleep quality. Since chronic diseases may occur with similar pathophysiological mechanisms, some diseases can be seen together in childhood. In this context, we aimed to evaluate the frequency of restless legs syndrome in patients diagnosed with allergic rhinitis and to examine whether there was an increase in the frequency compared to the control group.

In a case-control type study conducted in children aged 8-18 years in our country, the frequency of restless legs syndrome in children with AR and in the control group was examined. While the frequency of RLS in children with AR was reported as 9.1%; the frequency of RLS in the control group was reported as 4.2%.^[28] Similarly, in our study, the presence of RLS in AR patients was higher than in the control group (15.7% vs 5.2%). According to the results of our study and the study in the literature; it can be thought that AR and RLS diseases can have co-existence. However, since the number of studies in this area is very limited, further studies are needed to explain the underlying pathophysiological mechanisms in the interrelated relationship between the two diseases.

In our study, factors related to the presence of RLS in AR patients were evaluated; the presence of RLS was found to be higher in patients with persistent AR than in patients with intermittent AR (19.5% and 7.9%, respectively). In the study in the literature, the frequency of RLS in patients with persistent AR is approximately 2 times that of patients with intermittent AR.^[28] Although there was no statistical significance in the study in the literature and in ours, the higher frequency of RLS in persistent AR suggests that the disease clinic and RLS may be associated. In addition, while 16.9% of AR patients with multiple allergen sensitivity were diagnosed with RLS in our study; 13.2% of those without multiple allergen sensitivities have RLS. In a study in the literature, the frequency of RLS was also found to be higher in patients with AR who had a higher number of allergens to which they were sensitive.^[28] This suggests that allergic mechanisms may play a role in the underlying pathophysiology of RLS. In a study in the literature; a relationship between mast cell activation syndrome, which is an allergic and inflammatory disorder, and RLS has been found.^[31] In another study, a higher rate of RLS was observed in patients with atopic dermatitis, which is one of the allergic diseases, compared to the control group. In addition, the rate of RLS was found to be higher in patients with active atopic dermatitis in the same study.^[32] According to the results of a different study in our country, the diagnosis of RLS is more common in people with asthma than in healthy individuals, and the frequency of RLS increases as asthma control decreases.^[33] In the literature, there is also a study showing that the frequency of RLS is higher in urticaria patients than in the control group.^[34] Since studies evaluating the relationship between allergic diseases and RLS are mostly conducted in adult patients, further studies are needed to evaluate the relationship between different allergic diseases and RLS, especially in the pediatric patient group.

In studies, an increased risk for the development of restless legs syndrome has been reported in many inflammatory diseases. However, the role of inflammatory factors in the pathogenesis of RLS is not fully understood, since there are very few studies evaluating serum/plasma levels of inflammatory factors.^[35] According to the results of a meta-analysis in the literature, serum/plasma C reactive protein (CRP) and NLR were reported to be higher in patients with RLS than in the control group.^[35] In a study conducted in pediatric allergic rhinitis patients, the NLR value of patients with a diagnosis of allergic rhinitis was found to be significantly higher than the control group.^[36] The fact that NLR, which is an important measure for systemic inflammation, was increased in both diseases suggests that there may be common inflammatory mechanisms in the development of the two diseases. Further studies are needed to explain the mechanism of the relationship between RLS and allergic rhinitis.

Strengths and Limitations

While investigating the frequency of RLS in allergic rhinitis patients in our study, the evaluation of the effects of disease severity and laboratory parameters on the frequency of RLS contributed to the literature in this area from a broad perspective. This is the strength of our study. As we know, there is only one study in the literature investigating the frequency of restless legs syndrome in children with allergic rhinitis, and this study was also conducted in our country. The limited number of studies in this area makes the results of the studies carried out on the subject valuable. This is another strength of our work. Besides the strengths of our study, there are also some limitations. The fact that our study was conducted in a clinic of a single hospital creates a limitation in terms of the generalizability of the research results. In our study, an increase in the frequency of restless legs syndrome was observed in children with a diagnosis of allergic rhinitis. Since the study was not conducted prospectively, the co-existence of two diseases in a single time frame was evaluated. For this reason, it is difficult to interpret the temporal relationship between the two diseases in the study. This is another limitation of the study. Further prospective studies can be planned for a better understanding of the subject.

CONCLUSIONS

According to the results of our study, restless legs syndrome was observed more frequently in patients with allergic rhinitis compared to the control group. Both diseases can be seen frequently in childhood and negatively affect quality of life and sleep. For this reason, the coexistence of some chronic diseases in childhood will increase the burden of disease in children. Thus, holistic approaches should be adopted in the diagnosis, treatment and management of childhood diseases. Additional diseases that may be associated with the child should be investigated with detailed system inquiries. As the results of our study emphasize that patients diagnosed with allergic rhinitis should also be evaluated in terms of restless legs syndrome when necessary. Further studies are needed to explain the underlying pathophysiological mechanisms between the two diseases.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Health Sciences University Ümraniye Training and Research Hospital Ethics Committee (Date: 29/09/2022, Decision No: 315).

Informed Consent: Informed consent was obtained for the study.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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