Sleep-related Breathing Disorders in Children with Asthma: Impact on Asthma Control

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ABSTRACT

Objective: To investigate the frequency of sleep-related breathing disorder and the relationship between asthma control and sleep-related breathing disorder in children with persistent asthma.

Study Design: Comparative cross-sectional study.

Place and Duration of Study: University of Health Sciences, Hamidiye Etfal Training and Research Hospital, Istanbul/-Turkey, from January 2019 to June 2019.

Methodology: Children aged 4-11 years with persistent asthma were included. At enrollment, socio-demographic and asthmatic characteristics were investigated, and pediatric sleep questionnaire and childhood asthma control tests were administered.

Results: Out of 120 patients, 75 (62.5%) were males and 45 (37%) females. According to GINA guidelines, asthma was well controlled in 23.3% children, partially controlled in 50.8% children and uncontrolled in 25.8% children. The frequency of habitual snoring was reported as 20.8% and the frequency of sleep-related breathing disorder was 29.2%. The prevalence of sleep-related breathing disorders was significantly higher in the uncontrolled asthma group ($p < 0.001$). Significant-independent efficacy of physician-diagnosed allergic rhinitis, habitual snoring, and low asthma control test scores was observed in predicting sleep-related breathing disorders in multivariate logistic regression model ($p < 0.001$).

Conclusion: Uncontrolled asthma is associated with sleep-related disordered breathing. The authors suggest that allergic rhinitis, habitual snoring, and low asthma control test scores are important risk factors for sleep-related breathing disorders in children with persistent asthma.

Key Words: *Asthma, Asthma control test, Allergic rhinitis, Habitual snoring, Pediatric sleep questionnaire, Sleep-related breathing disorder.*

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INTRODUCTION

There are significant overlaps between asthma and sleep-related breathing disorder (SRBD) in terms of symptomatology and pathophysiology.[1] The vibration in the upper respiratory tract and airway collapse, associated with obstructive sleep apnea (OSA), are suggested to lead to bronchoconstriction by increasing the vagal tone.[2] Increased vagal tone is known to increase the severity of nocturnal asthma exacerbations.[2]

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The vibration and collapse in the upper airways are thought to lead to inflammation in the upper airways and to trigger an increase in neutrophils in the lower airways.[1,2] It is thought that leukotriene concentrations increase in the adenotonsillar tissue and leukotrienes play a role also in persistent asthma in children with OSA; and as a result, it is recommended to use leukotriene receptor antagonist therapy in the treatment of some asthma phenotypes and children with OSA.[3] There are other studies suggesting that OSA therapy reduces asthma symptoms and nocturnal asthma attacks.[4]

On the other hand, according to the studies suggesting that asthma increases the development and severity of OSA; nocturnal hypoxemia associated with asthma increases the severity of OSA.[1,5] Asthma is suggested to cause contraction of the respiratory muscles due to systemic inflammation, and negatively affects the upper airway patency, leading to sleep disorder and interruption.[6]

In this study, the aim was to investigate the prevalence of SRBD in children with asthma and evaluate the effects of SRBD on asthma control and the risk factors associated with the presence of SRBD.

METHODOLOGY

The study was conducted at the University of Health Sciences, Hamidiye Etfal Training and Research Hospital, Istanbul, Turkey. One hundred and twenty patients, between 4 and 11 years of age, who were being followed up with the diagnosis of persistent asthma, were included in the study.

Patients who had not received regular inhaled corticosteroid treatment for at least three months and had history of asthma exacerbations during the last month were excluded from the study. The pediatric sleep questionnaire, asthma control test, and study questionnaire to evaluate the demographics and the clinical characteristics of asthma were obtained. According to the GINA guidelines, asthma control levels are classified into three classes: controlled, partly controlled, and uncontrolled asthma.[7] The childhood asthma control test (C-ACT), performed in children to evaluate asthma control levels, is an easily applicable questionnaire of which the Turkish reliability and validity were established.[8] Asthma is considered uncontrolled, partly controlled, and well-controlled for scores of ≤19, 20 to 24 and ≥25, respectively.

Pediatric sleep questionnaire (PSQ) is applicable to parents of children aged between 2 and 18 years, of which the Turkish reliability and validity were established by Yilmaz *et al*.[9] It consists of 22 items that contain questions such as those about frequency and severity of snoring during sleep, nocturnal apnea during sleep, breathing difficulty during sleep, daytime sleepiness, hyperactivity, other pediatric obstructive sleep apnea symptoms and attention deficit. Answers to the questions were "yes", "no" or "I don't know". The total mean point is the average of all points, excluding missing numbers. The most effective cutoff value for pediatric obstructive sleep apnea was defined as 0.33.[10]

Mean, standard deviation, median, range, frequency and ratio values were used in the descriptive statistics of the data. Categorical variables were expressed as counts and percentages, and the Chi-square test or Fisher's Exact test was used to perform group comparisons. Kolmogorov-Smirnov test was used for the valuation of the normality of continuous variables. Variables with normal distribution were expressed as mean ± SD; and group comparisons were performed using Student t-test. Variables with non-normal distribution were expressed as median (IQR) and analysed by using Mann-Whitney U-test.

The effect level was investigated using the univariate and multivariate logistic regression analyses. The SPSS version 22.0 software was used for the analyses. A p-value <0.05 was considered statistically significant.

RESULTS

One hundred and twenty patients, who were included in the study, were examined as two separate groups, *i.e* 35 patients (29.2%) with SRBD and 85 patients (70.8%) without SRBD, according to the results of the pediatric sleep questionnaire. Table I presents the comparison of the demographics and the clinical characteristics of the patients with and without SRBD. No significant difference was found between the groups in terms of demographics and clinical characteristics except physician-diagnosed AR, family history of AR, SRBD and habitual snoring (all $p < 0.05$).

In the SRBD group, the prevalence of physician-diagnosed AR, family history of AR, SRBD, and habitual snoring were high and considered statistically significant ($p = 0.001$, $p = 0.02$, $p = 0.017$, and $p < 0.001$, respectively).

The comparison of the ACT scores and asthma control levels of the groups with and without SRBD is presented in Table II. The mean ACT score of the patients with SRBD was significantly lower than the mean score of the group without SRRD ($p < 0.001$). Of the patients with SRBD, one (2.9%), 15 (42.9%), and 19 (54.3%) were considered well controlled, partly controlled and uncontrolled asthma, respectively. The rate of poorly controlled patients was significantly higher in the group with SRBD ($p < 0.001$).

The evaluation of the risk factors affecting the relationship between SRBD and asthma control level is presented in Table III. In the univariate model, a significant effectiveness of physician--diagnosed allergic rhinitis, habitual snoring, ACT score was observed in the prediction of SRBD (all $p < 0.001$). In the multivariate reduced model, a significant-independent effectiveness of presence of physician-diagnosed allergic rhinitis, habitual snoring, and ACT score was observed in the prediction of SRBD (all $p < 0.001$).

DISCUSSION

Previous studies have suggested a two-way relationship between asthma and SRBD.[1,2,6,11] It is suggested that asthma seen in patients with SRBD increases the severity of SRBD as well as SRBD seen in children with asthma increases the severity and impairs the control of asthma.[12]. SRBD is thought to be an independent risk factor for partly controlled or uncontrolled asthma.[13-15] Changes in the intrathoracic pressure, frequent awakening and intermittent hypoxemia increase inflammation in the airways. During obstructive episodes, increased vagal tone, increased non-specific bronchial reactivity, airway dryness associated with sleeping with open mouth, negatively affect asthma control by increasing airway broncho-constriction.[1,14] In this study, the relationship between asthma control level and SRBD was investigated in patients with the diagnosis of persistent asthma. There was a significant effectiveness of physician-diagnosed allergic rhinitis, habitual snoring, asthma control test score, family history of AR and presence of SRBD, which were observed in the prediction of SRBD. In the multivariate reduced model, the authors suggest a significant-independent effectiveness of physician-diagnosed AR, habitual snoring, and ACT scores.

Table I: The comparison of the demographics and asthma clinical characteristics of the patients with and without sleep-related breathing disorder (SRBD).

	SRBD (-)		SRBD (+)		P
	1.Q-3.Q/ n (%)	Median	1.Q-3.Q/ n (%)	Median	
Age (month)	73.5-110.0	89.0	75.0-102.0	85.0	0.722[m]
Gender					
Male	51 (60)		24 (68.6)		0.378[x2]
Female	34 (40)		11 (31.4)		
Weight (kg)	22.2 - 35.1	28.0	21.0 - 36.5	29.0	0.933[m]
Height (cm)	119.0 - 136.5 11.5	127.0	120.0 - 142.0	123.0	0.585[m]
BMI	15.4 – 19.8	17.0	15.0 – 21.1	17.9	0.856[m]
Smoking exposure	50 (58.8)		23 (65.7)		0.482[x2]
Skin prick test (pos.)	47 (55.3)		17 (48.6)		0.502[x2]
IgE levels (high)	55 (64.7)		20 (57.1)		0.437[x2]
Inhaled allergen (high)	46 (54.1)		18 (51.4)		0.788[x2]
Physician diagnosed AD	17 (20)		7 (20)		1.000[x2]
Physician diagnosed AR	32 (37.6)		28 (80.0)		<0.001[x2]
Pets at home	11 (12.9)		2 (5.7)		0.247[x2]
Nasal steroid	35 (41.2)		21 (60)		0.060[x2]
Montelukast	63 (74.1)		29 (82.9)		0.304[x2]
Habitual snoring	7 (8.2)		18 (51.4)		< 0.001[x2]
PFT	47 (55.3)		20 (57.1)		0.893[x2]
FEV1	91.0 – 106.0	98.0	88.0 – 111.5	97.0	0.884[m]
FEV1/FVC	97.5 – 105.0	102.0	96.0 – 103.5	100.0	0.428[m]
PFT interpretation					
Normal	45 (95.7)		19 (95.0)		1.000[x2]
Obstructive	2 (4.3)		1 (5.0)		
Family hx of asthma	44 (51.8)		23 (65.7)		0.162[x2]
Family hx of AR	29 (34.1)		20 (57.1)		0.020[x2]
Family hx of SRRD	11 (12.9)		11 (31.4)		0.017[x2]

BMI: Body mass index, ER: Emergency room, PICU: Pediatric intensive care unit, GER: Gastroesophageal reflux, AD: Allergic dermatitis, AR: Allergic rhinitis, PFT: Pulmonary function test, FEV1: Forced expiratory volume at 1 second, FVC: Forced vital capacity. [m]Mann-Whitney U-test/ [x2]Chi-square test.

Table II: The comparison of the asthma control test (ACT) scores and asthma control levels of the groups with and without sleep-related breathing disorder (SRBD).

	SRBD (-)		SRBD (+)		p
	1.Q-3.Q/ n (%)	Median	1.Q-3.Q/ n (%)	Median	
ACT scores	21.0 – 25.0	23.0	17.0 – 21.0	19.0	0.001[m]
Asthma control level					
Well controlled	27 (31.8)		1 (2.9)		0.001[x2]
Partly controlled	46 (54.1)		15(42.9)		
Uncontrolled	12 (14.1)		19 (54.3)		

[m]Mann-Whitney U-test / [x2]Chi square test.

Table III: The evaluation of the risk factors affecting the relationship between sleep-related breathing disorder (SRBD) and asthma control level.

	Univariate model			Multivariate model		
	OR	CI 95%	P	OR	CI 95%	P
Family hx of AR	2.57	1.15-5.76	0.021			
Family hx of SRRB	3.08	1.19-8.01	0.021			
Physician diagnosed AR	7.73	2.89-20.69	<0.001	6.8	1.9-25.1	<0.001
Habitual snoring	11.8	4.26-32.67	<0.001	11.4	3.4- 38.1	<0.001
ACT score	5.58	2.63-11.80	<0.001	5.3	2.2- 12.5	<0.001

AR: Allergic rhinitis, ACT: Asthma control test. OR: Odds ratio, CI: Confidence interval, Logistic regression.

Snoring is an important symptom and a major risk factor for SRBD. In a limited number of studies, the prevalence of snoring in children with asthma has been reported between 17.2% and 58%.[2,12,13,16,17] There was a prevalence rate of 20.8% for habitual snoring in children, which is consistent with the literature. On the other hand, the prevalence of snoring in children with concurrent asthma and SRBD has been reported as 48.2% and 79.1%.[2,13,14,17,18] Similarly in this study, there was a prevalence rate of 51.4 for habitual snoring in the group with SRBD. In the studies, where questionnaires were used similarly to this study, the prevalence of SRBD in children with asthma has been reported as being

between 19.6% and 47.5%.[12] Similarly, the frequency of SRBD was as 29.2% in children with persistent asthma. The relationship between asthma and sleep-related respiratory disorder is a two-way relationship due to the common risk factors that trigger airway inflammation. Recent studies have demonstrated the negative effect of sleep-related respiratory disorder on the childhood asthma control levels and the severity of asthma.[12-15] There are limited number of studies in the literature that investigated the relationship between asthma control level and SRBD, using the ACT and PSQ questionnaire, similar to this study. In a study conducted on children with asthma, Sheen *et al*. have reported a significantly higher prevalence for SRBD in the uncontrolled and partly controlled asthma groups.[14] Ginis *et al*. suggested that the prevalence of SRBD is high in the uncontrolled asthma group.[13] In a similar study conducted by Perikleous *et al*., it is suggested that the C-ACT scores in patients with asthma and SRBD are statistically significantly lower.[18] In this study, a significantly higher prevalence for SRBD in the uncontrolled asthma group was found, which is consistent with the literature.

AR is an important risk factor for the development of asthma. In a study conducted on children with asthma using the PSQ questionnaire, while the prevalence of AR was significantly higher in the group with SRBD, the presence of AR was not defined as an independent risk factor in terms of SRBD.[18] In the present study, the physician-diagnosed allergic rhinitis is significantly effective in the prediction of SRBD in the multivariate model.

Familial predisposition is an important factor that should be questioned in the diagnosis of SRBD. In a study conducted by Li *et al*. on children with asthma, it was suggested that the prevalence of habitual snoring in the parents of children with habitual snoring is significantly higher.[19] Similarly, in the present study, presence of SRBD in first-degree relatives in the group with SRBD was not considered to be an independent risk factor in the multivariate analysis despite being found to be significantly higher.

The limitations of this study include the fact that the diagnosis of sleep-related respiratory disorder in the patients was not confirmed by polysomnography, which is the gold standard test, lack of the control group, the adenoid and tonsil sizes were not evaluated by an ENT specialist, and pulmonary function tests were not available in the files of some patients due to their ages.

CONCLUSION

Uncontrolled asthma is associated with SRBD in children. The presence of an allergic rhinitis, habitual snoring, and low asthma control test scores are important risk factors for SRBD in children with asthma.

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ETHICAL APPROVAL:

Ethics Committee approval was received for this study from the Ethics Committee of Sisli Hamidiye Etfal Training and Research Hospital, Istanbul, Turkey.

PATIENTS' CONSENT:

Written consents of the patients and their parents were obtained, who participated in this study.

CONFLICT OF INTEREST:

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

NB, SO: Conceived, designed and did editing of the manuscript and critical review.
NB, AK: Data collection, analysis and manuscript writing.
YY: Manuscript review.
All authors read and approved the final manuscript.

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