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The frequency of sleep-disordered breathing in preschool children with asthma and its effects on control of asthma

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Abstract
Sleep-disordered breathing (SDB) is more common in asthmatic patients than in non-asthmatic persons, and SDB affects negatively to control asthma. A limited number of studies are discovered on the effect of SDB in preschool asthmatic children. In this study, we aimed to investigate the prevalence of SDB and its effect on control and severity of asthma in preschool children. A pediatric sleep questionnaire was completed by parents of asthmatic children. Patients who received a score of 0.33 or higher were diagnosed with SDB. Control and severity of asthma was assessed by a pediatric allergy specialist based on the Global Initiative for Asthma (GINA) criteria. The study included 249 patients, with a mean±SD age of 4.37±1.04 (range: 2-5.9) years; 69% were boys; 56.6% children had uncontrolled asthma and 28.7% had SDB. The SDB score was significantly different between controlled and uncontrolled asthma (0.19 vs 0.28; $P < 0.001$). The frequency of uncontrolled asthma in patients with and without SDB was 74.3% and 49.4%, respectively ($P < 0.010$). Based on the severity of asthma, the frequency of SDB among patients with mild, moderate, and severe asthma was 23.4%, 35.2%, and 47.4%, respectively ($P = 0.010$).
Conclusion: The frequency and score of SDB were higher in patients with uncontrolled asthma. Frequency and score of SDB were significantly affected by the severity of asthma. SDB must be evaluated in preschool children with uncontrolled asthma.

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Introduction

Asthma is the most common chronic disease of childhood, and the aim of disease management is to achieve and maintain control. Therefore, conditions that disrupt control of asthma and trigger an attack must be assessed cautiously. Exercise, allergens, cold and flu, and air-pollution as well as comorbid conditions frequently trigger symptoms and worsen control of asthma. Among these comorbid conditions, sleep-disordered breathing (SDB) was reported as an important risk factor for control and severity of asthma.[1]

The prevalence of SDB ranges between 1% and 7% in normal population. However, it is reported more commonly in asthmatic children.[2–4] Both diseases involve airway obstruction and widespread inflammation of the airways, and similar diurnal and nocturnal symptoms.[4,5] The prevalence of uncontrolled asthma was significantly higher in SDB patients, and treatment of SDB led to the lessening of symptoms in patients with uncontrolled asthma.[2,6]

Evaluation of asthmatic patients for sleep disorders and providing them an appropriate treatment are important for disease control.[7] The National Asthma Education and Prevention Program (NAEPP) also recommends investigating the presence of SDB in patients with uncontrolled asthma.[5,8] A limited number of studies are observed in the literature on the effect of SDB in asthmatic patients aged less than 5 years.[3,9,10] Hence, we aimed to determine the risk factors that may affect the development and control of asthma and to investigate the prevalence of SDB and its effect on control and severity of asthma in children aged less than 5 years.

Material and Methods

Asthmatic patients aged less than 6 years that visited our Pediatric Allergy Outpatient Clinic between June 2013 and December 2014 were included in this cross-sectional study.

Inclusion criteria for the study were as follows: regular follow up at our clinic between June 2013 and December 2014 for recurrent wheezing; diagnosis of asthma at <6 years of age; at least three scheduled visits during 1 year period; and using inhaler steroid or having montelukast therapy. Exclusion criteria were as follows: patient aged >6 years; patient having been followed for less than 1 year at our clinic; and patient not using inhaler steroid or montelukast therapy.

A questionnaire about asthma risk factors and demographic and clinical features of asthma as well as pediatric sleep questionnaire (PSQ) was filled by a physician.[11,12]

Asthma diagnosis and control assesment

Patients were diagnosed with asthma based on Global Initiative for Asthma (GINA) criteria;[12] and had used controller drug correctly and regularly. Inhaler corticosteroids or leukotriene receptor antagonists were routinely used for 2–3 months in patients with consistent asthma manifestations and a history of recurring wheezing (three or more times). Patients who responded to treatment but their symptoms recurred after cesation of treatment; the symptoms lessened after resumption of treatment; were asymptomatic between attacks; and for whom other causes of wheezing were ruled out were diagnosed as asthmatic. Response to treatment was assessed based on symptom management and frequency of attacks. Disease control was assessed based on GINA criteria by a pediatric allergy specialist. Severity and control situation of the disease were determined according to the dosage of drugs used by patients and frequency of manifestations in patients.

Pediatric Sleep Questionnaire: Sleep Disordered Breathing Subscale (PSQ-SDB)

Patients were diagnosed with SDB based on the PSQ filled by a pediatric allergy specialist. The PSQ consists of 22 questions. Patients respond to question in the form of "Yes," "No," or leave it blank, while "Yes" is rated as 1 point, "No" is rated as zero (0) point. The total score of each patient was calculated and divided by 22. Patients receiving a score of 0.33 or higher are considered as having SDB. The Turkish version of PSQ was reported by Yüksel et al.[13] as a reliable and valid scale used in the initial assessment of SDB symptoms in Turkish children in a study comprising 111 children, aged 2–17 years.[14,15]

Atopy test

Skin prick tests for allergens, such as *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Alternaria alternata*, cat and dog fur, mixed tree pollens, mixed grass pollens, and *Parietaria officinalis* (Stallergenes, SA Antony, France), were performed in case of all patients. Positive control used was 10% histamine phosphate and 0.9% physiological saline solution was used as a negative control. Atopy was defined as having at least one positive skin test response.

Total serum immunoglobulin E (IgE) levels of the patients were measured by nephelometry (Beckman Coulter Immage 800, CA, USA).

Risk factors of uncontrolled asthma

Risk factors that trigger symptoms and worsen asthma control are smoking at least one cigarette in the house (passive smoking), living with five or more people in the house (crowded home environment), and being exposed to truck exhaust fumes once or more daily in the living environment (exposure to exhaust fumes).[16,17] Height (in cm) and weight (in kg) of all the patients were measured during the period of the study. Patient was considered obese according to body mass index (BMI) value.[18]

The local ethics committee approved the study, and informed consent was obtained from parents of all the participants.

Statistical Analyses

Statistical analyses were performed by using Statistical Package for Social Sciences (SPSS) 21.0 for Windows (IBM

Corporation, Armonk, New York, USA). Mann-Whitney U test was used for the binary comparison of numerical data; Kruskal-Wallis test was used for the comparison of multiple numerical data; Chi-square test was used for the comparison of categorical data; and Spearman's correlation test was used for correlation analyses. $P < 0.05$ was considered statistically significant.

Results

A total of 249 children with a mean age of 4.37±1.04 (2-5.9) years were included in the study and 69.1% (n = 172) of them were males. The mean age at the onset of symptoms was 20.7±14.7 (1-54) months, and the mean age at diagnosis was 33.7±16.1 (range: 6-60) months. Of all the patients, 54.2% (n = 135) were taking anti-inflammatory treatment (inhaled corticosteroids [ICS] and/or leukotriene receptor antagonists [LTRA]), 56.6% (n = 141) had uncontrolled disease according to the GINA criteria, 34.8% (n = 54) had used systemic steroids for at least one attack within the past 1 year, and 15.3% (n = 54) had no attack during the past 1 year (Table 1).

Patients were questioned about risk factors that may affect asthma control. Of the most common risk factors, passive smoking was present in 38.1% of the patients, 34.4% of the patients were living in a crowded home environment, and rhinitis manifestations were present in 22.8% of the patients. When the patients were classified as having controlled and uncontrolled disease, the frequency of risk factors for uncontrolled asthma was similar between the groups (Table 2).

In all patients, 28.7% (n = 70) were diagnosed with SDB, 16.5% had snoring, 29.7% had mouth breathing, and 11.3% had throat clearing. In all patients, mean of SDB score was 0.24±0.18 (0-0.86). The SDB score was significantly different between controlled and uncontrolled asthma (0.19 vs 0.28; $P < 0.001$).

The frequency of uncontrolled disease was significantly higher in asthmatic patients with SDB (74.3% vs 49.4%; $P < 0.001$; Table 3). The frequency of steroid use and hospitalization of the patients within the past 1 year was not statistically different. However, the number of attacks and emergency room admissions within the past 1 year was significantly higher in the group with SDB ($P = 0.035$ and 0.004, respectively). When the patients were classified according to the severity of their asthma as having mild, moderate, and severe asthma, the prevalance of SDB was

Table 1 Demographic and clinical characteristics of patients.

Characteristics	Results
Age (year), mean ± SD	4.37 ± 1.04 (2-5.9)
Gender (male), n (%)	172 (69.1)
Age at onset of complaints (month), mean±SD	20.7 ± 14.7 (1-54)
Age of diagnosis (month), mean ± SD	33.7 ± 16.1 (6-60)
Patient using anti-inflammatory treatment (ICS and/or LTRA), n (%)	135 (54.2)
Patient with uncontrolled asthma (according to GINA), n (%)	141 (56.6)
Patient with symptoms of rhinitis, n (%)	48 (22.3)
Atopy, n (%)	33 (13.6)
Eosinophilia (≥4%), n (%)	50 (25.8)
Presence of SDB, n (%)	70 (28.7)
Score of SDB, mean ± SD	0.24 ± 0.18 (0-0.86)
Level of IgE (IU/mL), median (IQR)	22.0 (8.9-92.7)
Asthma severity, n (%)	
Mild	159 (63.9)
Moderate	71 (28.5)
Severe	19 (7.6)
Number of emergency admissions during last year, n (%)	141 (56.6)
Number of steroids used during last year, n (%)	54 (21.7)
Number of hospitalizations during last year, n (%)	34 (13.7)

SDB: Sleep-disordered breathing; ICS: inhaled corticosteroids; LTRA: leukotriene receptor antagonists; IQR: interquartile range; IgE: Immunoglobulin E.

Table 2 Effect of risk factors to control asthma.

Risk Factors	Total N (%)	Controlled asthma n (%)	Uncontrolled asthma n (%)	P
Passive smoking exposure	93 (38.1)	45 (43.7)	48 (34.0)	0.125
Presence of rhinitis symptom	48 (22.3)	22 (23.4)	26 (21.5)	0.738
Atopy	33 (13.6)	15 (14.0)	18 (13.2)	0.860
Living in a crowded home environment	75 (34.4)	36 (39.6)	39 (30.7)	0.175
Obesity	24 (11.8)	9 (10.3)	15 (12.9)	0.572
Presence of mold and moisture at home	22 (15.4)	8 (15.1)	14 (15.6)	0.941
Wood stove heating	34 (15.2)	15 (15.8)	19 (14.8)	0.846
Exposure to diesel exhaust füme	31 (24)	14 (28.6)	17 (21.3)	0.345
Attending nursery	24 (17.9)	8 (15.4)	16 (19.5)	0.544
Pets at home	14 (6.2)	5 (5.2)	9 (7.0)	0.574
Eosinophilia (≥4%)	50 (25.8)	17 (21.0)	33 (29.2)	0.197
SDB score, mean±SD	0.24 ± 0.18 (0-0.86)	0.19 ± 0.14 (0-0.63)	0.28 ± 0.19 (0-0.86)	<0.001

SDB: Sleep-disordered breathing.

Table 3 Characteristics of patients with and without SDB.

Characteristics	SDB patients	Non-SDB patients	P
Patients with uncontrolled asthma (GINA), n (%)	52 (74.3)	86 (49,4)	<0.001
Number of attacks during the past year[a]	4.6 ± 4.1 (0-15)	3.4 ± 3.3 (0-15)	0.035
Number of emergency admissions during the past year[a]	3.6 ± 3.0 (0-10)	2.3 ± 2.7 (0-10)	0.004
Number of steroids used during the past year[a]	0.710 ± 1.39 (0-5)	0.756 ± 1.31 (0-6)	0.862
Number of hospitalizations during the past year[a]	0.435 ± 1.44 (0-10)	0.151±0.41 (0-2)	0.114
Presence of emergency admissions during the past year[a]	47 (67.1)	92 (52.9)	0.042
Presence of steroids used during the past year[a]	10 (14.3)	43 (24.7)	0.074
Presence of hospitalization during the past year[a]	12 (17.1)	22 (12.6)	0.359
Asthma severity			
Mild, n(%)	36 (51.4)	118 (67.8)	
Moderate, n (%)	25 (35.7)	46 (26.5)	0,010
Severe, n (%)	9 (12.9)	10 (5.7)	

[a]Mean±SD.
SDB: Sleep-disordered breathing.

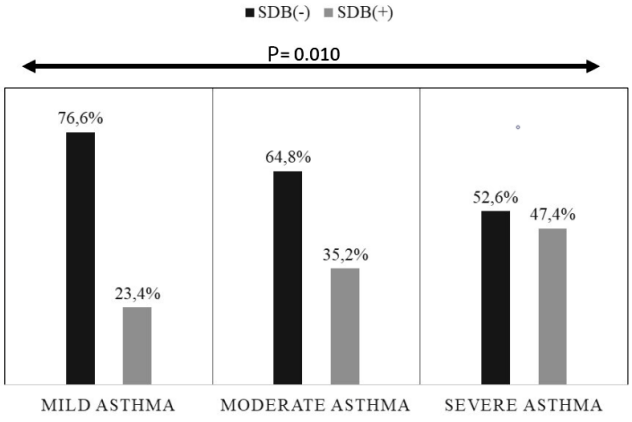

Figure 1 Frequency of patients with/without SDB according to asthma severity.

23.4%, 35.2%, and 47.4%, respectively (P = 0.010; Table 3 and Figure 1).

Discussion

In this study, we observed that of the 249 children, followed for the diagnosis of preschool asthma, 56.6% had uncontrolled disease, and 28.7% had SDB. The prevalence of uncontrolled asthma in patients with and without SDB was 74.3% and 49.4%, respectively. The frequency of SDB increased with increase in the severity of asthma; also, SDB was more common among uncontrolled asthmatic pediatric patients aged less than 5 years.

One of the most important issues observed in asthmatic patients is the control of asthma. Despite all improvements in treatment and all published guidelines, the rate of controlled asthma is around 50%. In the two studies conducted in Turkey, the rate of controlled asthma according to the GINA criteria among pediatric patients aged 5 years was 55%.[11,19] In a meta-analysis comprising 988 asthmatic patients aged <16 years from 12 countries of Asia, the prevalence of uncontrolled disease according to the GINA criteria was 53.4%.[20] In our study, the frequency of uncontrolled asthma was found to be 56.6%, consistent with the literature.

Sleep-disordered breathing can have a clinical manifestation ranging from a simple snore to apnea. Snoring has been found in 3.2-12.1% of healthy children and 6.2-35.5% of asthmatic patients. In this study, the prevalence of snoring in asthmatics was found as 16.5%, which is consistent with previous studies.[21,22] The prevalence of SDB is reported in 1-7% of pediatric patients.

Studies have shown that the rate of SDB was higher among asthmatic patients. In a study using PSQ, the frequency of SDB was 25.9% in asthmatic children and 10.6% in healthy controls.[3] In another meta-analysis, 45,155 children, with a mean age of 8.6 years from 17 separate studies, were evaluated. SDB was reported in 23.9% of asthmatic children and 16.7% of non-asthmatic children.[4] In another study comprising 194 asthmatic children aged 4-10 years, the frequency of SDB was found as 33%.[23] Ginis et al. found the frequency of SDB as 34.6% in 408 asthmatic patients aged 4-18 years.[2] Similarly, Rivera et al. found the frequency of SDB as 40.8% in 70 asthmatic patients aged 2-5 years.[24] However, in our study, the prevalence of SDB was as 28.7%.

Asthma treatment is directed toward achieving and maintaining control on the disease. Some factors, such as allergen exposure in sensitized patients, severe allergic rhinitis, passive smoking, living in a crowded family, and obesity, are reported to have negative effect on asthma control. However, in the present study, no difference was found between controlled and uncontrolled patients in terms of passive smoking, crowded living conditions, and the presence of atopy. These results suggested that there could be additional factors that may affect disease control in preschool asthmatic children. Among these factors, presence of SDB has been suggested as a risk factor for uncontrolled disease.[31-35] In our study, the frequency of SDB in uncontrolled patients was higher than in controlled patients (37.7% and 17.0%, respectively; P < 0.001).

Sleep-disordered breathing plays an important role in the development of attacks in asthmatic patients, and SDB patients require higher doses of preventer inhalers.[36,37] In a study comprising 102 asthmatic children aged 3-10 years,

asthmatic manifestations, the annual number of attacks, and the weekly requirement of beta-agonists were found to be significantly higher in SDB patients, compared to the non-SDB group.[6] It has been also reported that the use of continuous positive airway pressure (CPAP) therapy for sleep-related obstructive apnea and snoring facilitate the management of asthmatic patients.[38]

In our study, the frequency of uncontrolled disease according to the GINA criteria was significantly higher in the SDB group, compared with the non-SDB group (74.3% and 49.4%, respectively; $P < 0.001$). The number of attacks and emergency admissions in the SDB group within the past 1 year was found to be higher, compared to the non-SDB group ($P = 0.035$ and $P = 0.004$, respectively). In addition, the presence of SDB was found to be different in patients with controlled and uncontrolled asthma (37.7% and 17.0%, respectively; $P < 0.001$).

Limited studies have been observed concerning SDB and the severity of asthma. The current study investigated the relationship between SDB and severity of asthma in children aged 2–15 years. In the group with severe persistent asthma, significantly higher presence of SDB was observed.[3,6] Similarly, in our study, the frequency of SDB was higher in severe asthmatic patients.

A few mechanisms have been suggested to explain the association between SDB and severe asthma. TNF-alpha levels are higher in asthmatic patients than in healthy controls.[39] It has also been found high in sleep disorders. These results suggest that proinflammatory TNF-alpha could have a role in the relationship between severity of asthma and presence of SDB. Another mechanism that suggested the relationship between SDB and severity of asthma was neutrophilic inflammation, which affected the control of asthma in the airways, as also observed in SDB patients.[35,39,40] It is known that as the severity of asthma increases, inflammation in the airways shifts toward the neutrophilic side. Neutrophilic inflammation has also been shown in the respiratory tract of SDB patients. This could be another mechanism to explain the relationship between the severity of asthma and the presence of SDB. In our study, the prevalence of SDB increased with increase in the severity of asthma in asthmatic patients aged <5 years.

In the present study, the relationship between severity and asthma control and the presence of SDB was studied at a single center and cannot be generalized for the whole population; however, it was conducted with a larger number of patients than the numbers reported in other studies. The inability to perform polysomnography on patients was a limitation of the present study. The gold standard for the diagnosis of SDB in children is execution of polysomnography in a sleep laboratory.[41] However, this technique cannot be executed easily in daily clinical practice. The PSQ developed for this reason has 81% sensitivity and 87% specificity, hence used in the present analysis. In addition, a number of studies have demonstrated that PSQ could be used instead of polysomnography for diagnosis of SDB.[14,42,43]

Conclusion

In the present study, it was shown that the frequency and score of SDB were higher in patients with uncontrolled asthma, and the same were significantly affected by the severity of asthma. Evaluating of SDB in asthmatic patients and recommending appropriate therapy could increase the rate of control of asthma.

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