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Original Article

The impact of obstructive sleep apnea on quality of life in children with asthma

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Abstract

Background In children with asthma, obstructive sleep apnea (OSA) is a comorbidity of concern. The presence of OSA has been associated with asthma exacerbations and decreased quality of life. Leukotriene played a role in tonsil hypertrophy which is one of the risk factors for OSA.

Objective To evaluate the influence of OSA on quality of life in children with asthma.

Methods This cross-sectional study in asthmatic children aged 7-15 years was conducted from August 2020 to June 2021 at government elementary and primary high schools in Bandung, West Java, Indonesia. Asthma was diagnosed by peak expiratory flow rate (PEFR) and OSA was diagnosed by polysomnography. Leukotriene was examined by an ELISA method and quality of life assessed by the *Pediatric Asthma Quality of Life Questionnaire* (PAQLQ).

Results Using the ISAAC questionnaire distributed through techers to parents, 206 (6.9%) of 2,964 children stated that they had been diagnosed with asthma, 80 of whom were included in our study. Subjects' mean age was 12 (SD 2) years and most were male. Intermittent asthma and history of allergy was dominant. Thirty-two children had OSA, mostly mild OSA. The mean level of leukotriene was not different between asthmatic children with and without OSA. The percentage of PEFR in asthmatic children with OSA was significantly lower than in those without OSA. The total PAQLQ score in asthmatic children with OSA and all PAQLQ domains were significantly lower than in those without OSA.

Conclusion Obstructive sleep apnea in children with asthma is significantly associated with decreased peak expiratory flow rate and lower quality of life. **[Paediatr Indones. 2022;62:166-73 DOI: 10.14238/pi62.1.2022.166-73**].

Keywords: *asthma; children; lung function; obstructive sleep apnea; quality of life*

Asthma is a chronic inflammatory airway disease with various comorbidities.[1] Obstructive sleep apnea (OSA) is one such comorbidity currently of concern[2] because it is a risk factor for asthma exacerbations[3] and is a potential factor for controlling asthma.[4] The incidence of OSA was reportedly 3.56 times higher in asthmatics than in non-asthmatics,[1] with a prevalence of 63.04% in children with asthma.[5]

Asthma accompanied by OSA have shared roles in the inflammatory pathway, often multiplying their effects in the pathophysiological process.[6] Lower airway inflammation in asthma can be triggered by tonsil-adenoid proliferation,[7] oxygen-free radicals from the airways in asthma regulate 5-lipoxygenase (5-LO) activity in pharyngeal lymphoid tissue that

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triggers leukotrienes synthesis and causes tonsil hypertrophy.[8] Tonsil hypertrophy is one of the pathogenic links between intermittent upper airway obstruction during sleep and repeated episodes of lower respiratory tract obstruction.[9] Decreased transverse diameter and patency, as well as increased upper airway collapse are causes of the high OSA incidence in asthmatic children.[10] The phase of immune acquisition continues until the age of six, the palatine tonsils are the physiologically hyperplastic, then is reflected mainly in an involution or regression until the age of twelve.[11]

A systemic inflammatory process in OSA was characterized by increased concentrations of leukotrienes, leukocytes (mainly neutrophils), and high-sensitivity C-reactive protein (hs-CRP). Comorbid OSA is more likely to trigger pathogenesis caused by neutrophils than eosinophils of the asthmatic type.[12] Increased circulating neutrophil count and degree of inflammation by neutrophils are significantly associated with leukotriene production in children with OSA.[13]

Obstructive sleep apnea can trigger lower airway inflammation mainly through intermittent hypoxia and oxidative stress,[14] associated with inflammatory changes in the respiratory tract with predominant neutrophil inflammation. Local inflammation of the respiratory tract and systemic inflammation can trigger non-eosinophilic types of asthma that are known to be associated with difficult asthma control.[15] Through one of the mechanisms of the non-eosinophilic inflammatory pathway, a previous study found a correlation between OSA symptoms and uncontrolled asthma, affecting their quality of life.[13]

Asthmatic patients with OSA had substantially greater declines in FEV1 than those without OSA. However, after multivariate stepwise linear regression analysis, only apnea-hypopnea index (AHI) remained an independent factor for FEV1 decline.[16] Children with OSA tend to have lower quality of life scores than healthy children. The presence of OSA can affect behavior, daily function, and family life.[17] Quality of life is also significantly decreased in asthmatic adults at risk of OSA.[18] If not properly monitored, OSA can contribute to the difficulty of asthma control.[19] The presence of OSA in asthma patients has been associated with asthma symptoms and exacerbations, as well as decreased quality of life.[16]

This study aims to evaluate the influence of OSA on the quality of life of children with asthma.

Methods

This observational study with comparative cross-sectional design in asthmatic children with and without OSA was conducted in Bandung, West Java, from August 2020 to June 2021. Asthma screening was conducted using the ISAAC questionnaire in children aged 7-15 years, with or without OSA, who were willing to participate by filling out parental informed consent. The G-form ISAAC questionnaire was distributed by teacher/school to parents, to be completed by the students of 1 government elementary school and 3 government primary schools (each school had 600-700 students). Children with asthma exacerbation, infection, taking steroids and/or controller at the time of the study, or unwilling to undergo peak flow meter (PFM), polysomnography (PSG), and laboratory examinations were excluded.

The total minimum required sample size was calculated to be 80 children using the mean difference test of two independent populations, with a standard deviation was 1.3.[20] Subjects were included by purposive sampling, resulting in 32 asthmatic children with OSA and 48 asthmatic children without OSA.

Children with suspected asthma and their parents were contacted by phone to ask if they were willing to join the study. Participants underwent PEFR exams using an *Ultechnovo*® peak flow meter administered by a pulmonary specialist in order to diagnose asthma. The reversibility test was performed with an increase in PEFR >15%[21] after 15 minutes of 200-400 mcg salbutamol administration. Pulmonary function based on the PEFR value was determined by 3 examinations with a maximum difference of 20 points; the highest value was taken. The PEFR percentage was also determined based on *Godfrey*'s normogram for boys and girls aged 5-18 years.[22] The severity of asthma is determined according to the *Pedoman Nasional Asma Anak* (National Guidelines for Paediatric Asthma) from the *Indonesian Paediatrics Association* (IPA) and PEFR persentage, divided into intermittent, mild persistent, moderate persistent, and severe persistent.[23]

The OSA screening in asthma was based on the presence of habitual/occasional snoring, tonsillar hypertrophy based on *Brodsky* criteria, and the *Pediatric Sleep Questionnaire* (PSQ). Subjects with suspected OSA underwent a home-based polysomnography examination. Subjects with apnea-hypopnea index

(AHI) ≥ 1 were diagnosed with OSA. Most sleep centers classify OSA as mild (AHI 1-4), moderate (AHI 5-10), and severe (AHI>10).[24, 25] Overnight polysomnography examination using the *ApneaLink*™ (*ResMed Corporation*, Poway, CA, USA) device at home with use under the direction of a certified expert.

Subjects underwent complete and differential blood counts. Leukotriene (LTB4 and LTE4) was examined using an enzyme-linked immunosorbent assay (ELISA) (*Elabscience®*, USA) at the Dr. Cipto Mangunkusumo Hospital Clinical Pathology Research Laboratory, Jakarta. Subjects' quality of life was assessed by the PAQLQ, consisting of 23 questions divided into 3 domains: symptoms, activity, and emotional. The scores ranged from 1-7, with 1 indicating severe impairment and 7 indicating no disturbance. Quality of life of asthmatic children were classified as no or minimal disturbance (≥ 6.0), moderate disturbance (3.0-5.9), and severe disturbance (< 3.0). All examination procedures were in accordance with health safety protocols during the Covid-19 pandemic.

Data analysis was done with *SPSS v.20* for the two-group difference test. Data normality was analyzed by Kolmogorov-Smirnov normality test. Normally distributed numerical data were presented as mean and standard deviation, while non-normally distributed data were presented as median (range). Numerical variables with non-normal data distributions were transformed using a logarithmic approach: if the data distribution became normal, then it was treated as a normally distributed variable; but if the variables could not be homogenized by the transformation process, then they were analyzed by a non-parametric ranking approach. Categorical data were presented as numbers and percentages.

Bivariate analysis of categorical data (differential test for two groups) was performed with unpaired T-test for normally distributed data and Mann Whitney-U test for non-normally distributed data. Further analyses were done with Pearson's test on normally distributed data and Spearman Rho test on non-normally distributed data. Results with P values <0.05 with 95% confidence intervals were considered to be statistically significant. This study was approved by the Ethics Committee of the Universitas Indonesia Faculty of Medicine.

Results

Based on the results of the ISAAC questionnaire in 3 elementary and 3 junior primary high schools (2,964 children), 206 children (6.9%) stated that they had been diagnosed with asthma. Of these, only 82 children were willing to be examined to confirm the diagnosis of asthma, based on the results of the PEFR from the reversibility test, but two children were not willing to undergo blood laboratory examinations.

Our 80 subjects were mostly male (60%) and aged > 12 years (54%), with mean age 12 (SD 2) years and mean neck circumference of 28 (SD 3) cm. The majority of subjects had tonsil hypertrophy +1 to +2, normal nutritional status, intermittent asthma, as well as predominant history of allergy, and PEFR 50 - <80%, with mean of PEFR of 73 (SD 12) % (**Table 1**).

Table 1. Characteristics of subjects

Characteristic	(N=80)
Gender, n (%)	
Male	48 (60)
Female	32 (40)
Age, n (%)	
≤12 years	37 (46)
>12 years	43 (54)
Tonsil hypertrophy, n (%)	
+1 to +2	70 (88)
+3 to +4	10 (12)
Nutritional status, n (%)	
Severely wasted	3 (4)
Wasted	4 (5)
Normal	49 (61)
Risk of overweight	15 (19)
Overweight	9 (11)
Severity of asthma, n (%)	
Intermittent	55 (69)
Mildly persistent	21 (26)
Moderately to severely persistent	4 (5)
History of allergy, n (%)	
No	21 (26)
Yes	59 (74)
History of rhinitis, n (%)	
No	42 (52)
Yes	38 (48)
Classification of PEFR, n (%)	
80 - 100%	26 (33)
50 - <80%	53 (66)
<50%	1 (1)
Classification of PAQLQ, n (%)	
No or minimal impairment	42 (52)
Moderate impairment	35 (44)
Severe impairment	3 (4)

In the 7-12 years age group, 35% of children had OSA, while the > 12-15 years group, 44% of children had OSA. The majority of all subjects had tonsil hypertrophy +1 (52% and 51%), as shown in **Table 2**.

Subjects with OSA were mostly male, with mean age 13 (SD 2) years, mean neck circumference 28 (SD 4) cm, and mean body mass index (BMI) 20.45. Their mean AHI was 2.9 TST/h, and distributed into mild OSA (31/32; 97%) or severe OSA (1/32; 3%). Tonsil hypertrophy +3 to +4 and a higher mean BMI was more dominant in asthmatic children with OSA than without OSA, and statistically significant. The characteristics and clinical features of subjects with and without OSA are shown in **Table 3**.

Subjects' complete blood count, differential lymphocyte count, and leukotriene measurements are shown in **Table 4**. The mean percentages of eosinophils were 6 (SD 3) in the OSA group and 7 (SD 4), indicating the presence of eosinophilia in both groups.

The PEFR % in asthmatic children with OSA was significantly lower than in those without OSA. The median PAQLQ scores (total and each domain) in asthmatic children with OSA were significantly lower than in subjects without OSA as shown in **Table 5**. According the PAQLQ scores, the majority of asthmatic children with OSA were considered to have moderate to severe disturbance (23/32), while most subjects without OSA had no or minimal disturbance (33/48). This difference was statistically significant (P<0.0001) (**Table 5**).

Table 2. Clinical signs based on age group

Variables	≤12 years (n=37)	>12 years (n=43)
Tonsil hypertrophy, n (%)		
0	2 (5)	0
+1	19 (52)	22 (51)
+2	9 (24)	18 (42)
+3	6 (16)	3 (7)
+4	1 (3)	0
Severity of asthma, n (%)		
Intermittent	27 (73)	28 (65)
Mildly persistent	9 (24)	12 (28)
Moderately persistent	1 (3)	3 (7)
Severely persistent	0	0
Comorbid OSA, n (%)		
No	24 (65)	24 (56)
Yes	13 (35)	19 (44)

Discussion

The PAQLQ values in all domains in asthmatic children with OSA were significantly lower than in asthma without OSA, indicating that the quality of life of asthmatic children with OSA was lower in all assessment domains. Previous studies found that the quality of life of asthmatic children with sleep-disordered breathing (SDB) was lower in all assessment domains than asthma without SDB.[26] The presence of OSA in asthma control is associated with the appearance of symptoms, exacerbations, and decreased quality of life.[16]

Intermittent hypoxia in OSA can modulate neutrophil chemotaxis and other inflammatory factors,[14] modulating the pathogenesis of asthma-

Table 3. Characteristics and clinical features in asthmatic children with and without OSA

Variables	Asthma		P value
	With OSA (n = 32)	Without OSA (n = 48)	
Median age (range), years ^	13 (7-14)	12.5 (7-15)	0.32
Gender, n (%)§			
Male	22 (69)	26 (54)	0.19
Female	10 (31)	22 (46)	
Mean BMI (SD), kg/m^2	20.81 (4.06)	18.25 (3.28)	0.01*
Median neck circumference (range), cm^	27 (22-39)	28 (20-37)	0.93
Tonsil hypertrophy, n (%)§			
0 to +1	12 (37)	31 (65)	0.009*
+2	12 (37)	15 (31)	
+3 to +4	8 (26)	2 (4)	

Normally distributed data are presented as mean (SD), unpaired T-test; §Chi-square test; ^Mann-Whitney U test; *P < 0.05 indicates statistical significance

Table 4. Complete blood count, differential lymphocyte count, and leukotriene level in asthmatic children with and without OSA

Variables	Asthma		P value
	With OSA (n=32)	Without OSA (n=48)	
Complete blood count			
Mean hemoglobin (SD), g/dL	14.3 (1.4)	13.9 (1.6)	0.23
Mean hematocrit (SD), g%	41.9 (2.9)	40.6 (3.8)	0.09
Median leukocyte (range), /mm^3	7,860 (4,420-12,330)	7,995 (4,680-17,040)	0.93
Mean platelet (SD), /mm^3	347,875 (80,070)	356,707 (87,785)	0.13
Differential blood count, %			
Median basophil (range)	0 (0-1)	0 (0-1)	0.86
Median eosinophil (range)	5 (1-14)	6 (0-16)	0.17
Neutrophil bands	0	0 (0-6)	0.15
Neutrophil segs	51 (8)	48 (10)	0.30
Lymphocyte	36 (7)	37 (8)	0.79
Median monocyte (range)	6 (5-10)	7 (3-10)	0.72
Median leukotriene (range), pg/mL			
LTE4^	334.6 (107.3-2,001)	428.8 (98.4-2,001)	0.17
LTB4^	45.2 (0.04-590.8)	73.7 (0.09-852.7)	0.18

Normally distributed data are presented as mean (SD), unpaired T-test; Mann-Whitney U test; *P < 0.05 indicates statistical significance

Table 5. Lung function and quality of life in asthmatic children with and without OSA

Variables	Asthma		P value
	With OSA (n=32)	Without OSA (n=48)	
Lung function			
Mean PEFR % (SD)	71 (13)	78 (12)	0.02*
Mean PEFR value (SD), L/min	254 (78)	243 (68)	0.50
Median PAQLQ domain scores (range)^			
Symptoms	5.5 (3.0-07.0)	6.9 (1.6-7)	0.004*
Activity	6.2 (2.6-7.0)	7.0 (2.4-7.0)	0.001*
Emotional	5.6 (2.8-7.0)	7.0 (1.4-7.0)	0.001*
Total	5.8 (3.1-7.0)	6.8 (2.1-7.0)	0.001*
PAQLQ classification§			
No to minimal disturbance	9 (21)	33 (79)	<0.0001*
Moderate to severe disturbance	23 (61)	15 (39)	

Normally distributed data are presented as mean (SD), unpaired T-test; ^Mann-Whitney U test; §Chi-square test; *P < 0.05 indicates statistical significance

type neutrophils,[13] and inflammation by neutrophils associated with leukotriene production.[12] Increased leukotrienes and oxidative stress can contribute to bronchoconstriction in asthma exacerbation.[8]

In our study, tonsillar hypertrophy was found in most asthmatic children with OSA. Tonsil hypertrophy of T3 and T4 was more frequent and significantly higher in asthmatic children with OSA and was more common in children ≤ 12 years of age than in those without OSA. Similarly, a previous study found that 392/495 (79%) subjects with OSA had tonsillar hypertrophy alone or adenoid hypertrophy alone or adeno-tonsillar hypertrophy (26%, 18%, 35%, respectively), and only 21% had T0. Tonsil hypertrophy was significantly increased the risk of OSA by 3.5 times.[27] Other study has shown that there is a significant correlation between adeno-tonsillar hypertrophy and OSA in pre-adolescents than in adolescents. Our results were in agreement with the statement that the upper respiratory tract area and the adenoidal-nasopharyngeal (A/N) ratio were not significantly different in the pre-adolescent group.[28] The correlation of tonsil size on OSA was the same in all age groups, indicating that it persisted in children and adolescents. Hence, the operative treatment for children with OSA is primarily tonsillectomy, sometimes accompanied by

adenoidectomy.[27]

Oxygen free radicals released from asthmatics' airways regulate 5-lipoxygenase activity in pharyngeal lymphoid tissue, triggering the synthesis of cysteinyl leukotriene, causing tonsilloadenoid hypertrophy.[8] Tonsil hypertrophy is one of the pathological links between intermittent upper airway obstruction during sleep and repeated episodes of lower airway obstruction.[9] Intermittent hypoxia can occur due to upper airway obstruction by reduced transverse diameter and patency, as well as increased upper airway collapse.[10,29] Permanent inflammation of the airway mucosa is common in asthmatics,[10] due to drainage into the cervical lymph nodes and proximal to the parapharyngeal area causing a tonsillitis infection that can progress to inflammation in the neck region.[30]

We found that mean BMI was significantly higher in the OSA group than in the non-OSA group. Previous studies reported that obesity was an independent risk factor for OSA, as adipose tissue surrounding the pharynx and neck along with adenoid and tonsil hypertrophy contribute to the occurrence of OSA in obese children. Commonly, clinicians conclude that obese children with similar adenotonsillar size with non-bese children, have a higher AHI than non-obese children.[27] Obesity affects breathing mechanically and physiologically. Fat deposition causes constriction of the upper respiratory tract, increases airway resistance, and causes airway collapse.[31]

Our subjects' AHI was mostly mild OSA (AHI 1-5 TST/h), while a multivariate analysis showed a correlation between persistent asthma and OSA. At age ≥ 60 years, persistent nighttime asthma symptoms were associated with OSA, whereas at a younger age (18-59 years), daytime persistent asthma symptoms were associated with OSA.[32] The AHI >5/h was noted in 50% of severe asthma, 23% of moderate, and 12% of controls.[33] Several studies have consistently found that asthma increased the prevalence of OSA by 70%, especially in severe asthma.[13,31,33] OSA correlates with persistent daily asthma symptoms, especially in difficult to manage cases. Thus, clinicians should pay attention to the presence of OSA comorbidities in asthma management in order to prevent persistent and nocturnal asthma.[31]

The PEFR % in asthmatic patients with OSA was significantly lower than those without OSA. Similarly, a previous study found that PEFR values measured by peak flow meter (PFM) in adolescents aged 13-14 years with OSA were significantly lower than those without OSA.[34] Asthmatic patients with OSA experienced a greater decrease in FEV1 than those without OSA. After analyzing for confounding factors, severity of OSA was the only independent factor that associated with decline in lung function.[16] However, another study found no association between asthmatics with and without OSA with regards to the percentage of predictive FEV.[5] Large prospective studies are still needed to ascertain the long-term effects on lung function.[31]

Children with OSA also have lower quality of life scores than healthy children. The presence of OSA can affect the child's behavior, daily functioning, and family life.[17] Quality of life was also significantly decreased in asthmatic adults at risk of OSA.[18] Clinically, it is important to control pediatric asthma, whether or not it is accompanied by OSA,[35] to prevent delays in diagnosis and avoid possible sequelae.[36] If not properly managed, OSA can contribute to the difficulty of asthma control.[19]

As our study had an observational case-control design, the correlations described do not confirm a cause-and-effect relationship. Examination of lung function and asthma severity should ideally include a spirometry test, but the Covid-19 pandemic constrained us, as we wanted to prevent aerosol spread. Other factors such as asthma control and treatment, diet, and environmental conditions should also be investigated. In conclusion, OSA comorbidity in children with asthma is significantly associated with decreased PEFR and lower quality of life.

Conflict of interest

None declared.

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