

Associations of Tonsillar Hypertrophy and Snoring With History of Wheezing in Childhood

Athanasios G. Kaditis, MD,^{1*} Efthimia Kalampouka, MD,¹ Souzana Hatzinikolaou, MD,¹ Loukia Lianou, MD,¹ Maria Papaefthimiou, MD,¹ Polytimi Gartagani-Panagiotopoulou, MD,¹ Elias Zintzaras, MSc, PhD,² and George Chrousos, MD¹

Summary. Background: Reports in adults and children have correlated history of wheezing or asthma with the presence of obstructive sleep-disordered breathing but the mechanism of this epidemiologic association is unknown. The goal of the present study was to examine whether tonsillar hypertrophy can explain this association. Methods: Children were recruited from the Emergency Department and the Pediatric Pulmonology Clinic. History of wheezing requiring treatment (explanatory variable) and snoring ≥ 1 night/week (outcome) were recorded and presence of tonsillar hypertrophy (outcome) was assessed. Results: Four hundred forty-two children were recruited (mean age: 7.6 ± 3.6 years) and 210 of them had history of wheezing. History of wheezing was significantly associated with the presence of tonsillar hypertrophy and snoring even after adjustment for age, gender, obesity, and passive smoking [odds ratio (95% confidence interval): 2.23 (1.37–3.63); $P = 0.001$ and 1.73 (1.12–2.67); $P = 0.013$, respectively]. When only children with tonsillar hypertrophy were considered ($n = 92$), history of wheezing was significantly related to the presence of snoring, whereas in subjects without tonsillar hypertrophy ($n = 350$) wheezing did not affect snoring [odds ratio: 2.76 (1.10–6.93); $P = 0.031$ and 1.49 (0.92–2.43); $P = 0.107$, respectively]. Conclusions: Children with history of wheezing have more frequently tonsillar hypertrophy than those without wheezing. Tonsillar hypertrophy may mediate at least in part the reported association between asthma and obstructive sleep-disordered breathing in childhood. **Pediatr Pulmonol.** © 2010 Wiley-Liss, Inc.

Key words: asthma; obstructive sleep apnea; snoring; wheezing.

INTRODUCTION

Snoring is the most common clinical manifestation of obstructive sleep-disordered breathing (SDB).¹ Increased upper airway resistance and excessive pharyngeal collapsibility are important factors contributing to intermittent upper airway obstruction during sleep in both adults and children.¹ Moreover, wheezing is the most characteristic symptom of lower airway obstruction, a disorder that is frequently virus-induced and with or without an asthmatic component.² A number of reports in adults and children have correlated history of wheezing and/or a diagnosis of asthma with the presence of obstructive sleep apnea, and airway inflammation has been proposed as the pathogenic link connecting these disease entities.^{3–10}

Lower and upper airway inflammation is related to atopy and enhanced cysteinyl leukotriene (CysLT) activity, and can lead to decreased lower airway caliber and increased nasal resistance and pharyngeal collapsibility.^{11–16} These airway changes predispose to episodes of wheezing and snoring during sleep. In addition to airway inflammation, adenotonsillar hypertrophy is another well-described factor that can increase upper airway resistance and predispose to SDB in childhood.¹ Early infection with respiratory syncytial

virus (RSV), increased CysLTs synthesis and possibly atopy accentuate adenotonsillar tissue proliferation.^{17–19} Not surprisingly, children with history of hospitalization for RSV bronchiolitis in infancy have larger tonsils and higher obstructive apnea–hypopnea index than controls.²⁰

¹First University Department of Pediatrics, Pediatric Pulmonology Clinic, University of Athens School of Medicine, Aghia Sophia Children's Hospital, Athens, Greece.

²Department of Biomathematics, University of Thessaly School of Medicine, Larissa, Greece.

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*Correspondence to: Athanasios G. Kaditis, MD, First University Department of Pediatrics, Aghia Sophia Children's Hospital, Thivon and Papadiamantopoulou St., Athens 11527, Greece.
E-mail: kaditia@hotmail.com

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Since both viral upper respiratory infections and atopy during childhood are also implicated in the pathophysiology of wheezing disorders, it is conceivable that children with history of wheezing are at increased risk for snoring because of pharyngeal lymphoid tissue enlargement. Therefore, in the current investigation it was hypothesized that: (i) children with history of wheezing have more frequently tonsillar hypertrophy than subjects without wheezing; (ii) enlarged tonsils mediate at least in part the association between wheeze and snoring, and (iii) among subjects with history of wheezing, children with allergic sensitization are at increased risk for tonsillar hypertrophy. To explore these hypotheses, we analyzed data from an existing cohort of children who have been recruited for the assessment of risk factors and complications of SDB.²¹

PATIENTS AND METHODS

Participants

Children were recruited in the Emergency Department and the Pediatric Pulmonology Clinic of a major pediatric medical center in Athens (Greece) that accepts patients with diverse socioeconomic status. We have recruited children (≥ 2 years old) who: (i) presented to the Emergency Department for minor problems or were referred to the Pediatric Pulmonology Clinic for recurrent wheezing by their pediatrician and (ii) did not have history of tonsillectomy, neuromuscular disorders, craniofacial abnormalities, or genetic syndromes.

In the current study, we have analyzed data of 378 subjects who were included in a previous publication from the same cohort²¹ and of 64 additional children who were recruited subsequently. The study protocol was approved by the Aghia Sophia Children's Hospital Ethics Committee and parental informed consent was obtained for participation in the study.

Clinical Evaluation

Parents were approached at the completion of the health visit and those who agreed to participate responded to a questionnaire administered by the investigators.^{22–24} Information was collected on: (i) symptoms of SDB; (ii) symptoms of lower airway obstruction; (iii) use of inhaled bronchodilators or corticosteroids; (iv) history of tonsillectomy; and (iv) history of any chronic disease.

All subjects underwent a physical examination and somatometrics were determined. Body mass index (BMI) z-score was calculated.²⁵ The size of tonsils was evaluated by inspection of the oropharynx and was described using a score ranging from 1+ to 4+.²⁶ Several children who attended the Pediatric Pulmonology Clinic underwent venipuncture for the measurement of total serum IgE and

specific IgE levels related to a panel of 10 aeroallergens (RAST) as part of their routine evaluation.

Explanatory Variables of Interest and Outcome Variables

History of physician-diagnosed wheezing that was treated with inhaled bronchodilators or inhaled corticosteroids over the past year was considered clinically significant and was the main explanatory variable in the current report. Additional explanatory variables were: (i) high total serum IgE level defined as $>$ predicted mean value for age $+1$ standard deviation; and (ii) positive specific IgE (class $\geq$ II) to at least one of the aeroallergens in the panel. Tonsillar hypertrophy and snoring ≥ 1 night/week over the last 6 months were the primary outcome variables. Tonsillar hypertrophy was defined as grade $>2+$.

Data Analysis

Children with and without history of wheezing were compared in terms of subjects' characteristics, frequency of tonsillar hypertrophy, and snoring using Student's *t*-test for continuous variables and χ^2 for categorical variables. Odds ratio (OR) and the corresponding 95% confidence intervals (CI) for tonsillar hypertrophy or snoring in children with versus without history of wheezing were calculated using univariate logistic regression analysis. Multivariate logistic regression analysis was carried out to adjust OR for age, gender, obesity, and passive smoking.

To assess whether the effect of wheezing on snoring (outcome) is mediated at least in part by tonsillar size two different analyzes were carried out: (i) tonsillar hypertrophy was included in a logistic regression analysis model as independent variable along with history of wheezing; and (ii) the association of wheezing with snoring was assessed in subjects with and without tonsillar hypertrophy using logistic regression analysis.

High total IgE and positive specific IgE were introduced as independent variables in two separate multivariate logistic regression analysis models in order to examine their effect on presence of tonsillar hypertrophy (outcome) among children with history of wheezing. Age, gender, obesity, and passive smoking were included as covariates in the same models.

RESULTS

Subjects' Characteristics

A total of 458 children were recruited in the study. Sixteen of 458 participants had a history of tonsillectomy and were excluded from further analysis. History of wheezing was reported in 210 out of 442 remaining participants. Subjects with history of wheezing did not differ from those without wheezing in terms of

TABLE 1—Subjects' Characteristics, Outcome Measures and Statistical Comparisons of Children With and Without Wheezing

Variables	Children with wheezing (n = 210)	Children without wheezing (n = 232)	P value
Age, years	6.8 ± 3.4	8.4 ± 3.6	<0.001
Gender, female (%)	92 (43.8)	109 (47.0)	0.566
BMI z-score	0.5 ± 1.4	0.6 ± 1.4	0.362
Obese (%)	50 (23.8)	52 (22.4)	0.736
Passive smoking (%)	97 (46.2)	113 (48.7)	0.634
Tonsillar hypertrophy (%)	59 (28.1)	33 (14.2)	<0.001
Habitual snoring (%)	74 (35.2)	52 (22.4)	0.002

BMI, body mass index.

female-to-male ratio, frequency of obesity or passive smoking ($P > 0.05$) (Table 1). In contrast, children with wheezing had higher frequency of tonsillar hypertrophy or snoring compared to participants without wheezing ($P < 0.05$) (Table 1).

Association of History of Wheezing With Tonsillar Hypertrophy and Snoring

History of wheezing was significantly associated with the presence of tonsillar hypertrophy and snoring: OR (95% CI) = 2.36 (1.46–3.79); $P < 0.001$ and OR = 1.88 (1.24–2.86); $P = 0.003$, respectively. These associations persisted even after adjustment for age, gender, obesity, and passive smoking (Table 2).

When both history of wheezing and tonsillar hypertrophy were entered in the same multivariate logistic regression model, the latter was more strongly associated with snoring than the former: OR = 2.08 (1.27–3.43) versus OR = 1.58 (1.01–2.45) (Table 3). Additionally, wheezing had a significant effect on snoring in children with hypertrophic tonsils ($n = 92$), but not in subjects without tonsillar hypertrophy ($n = 350$): OR = 2.76 (1.10–6.93); $P = 0.031$ and OR = 1.49 (0.92–2.43); $P = 0.107$. After adjustment by age, gender, obesity, and passive smoking, OR in subjects with tonsillar hypertrophy was marginally significant [2.55 (0.95–6.83); $P = 0.064$], whereas OR in children with tonsils

of normal size became non-significant [1.38 (0.83–2.27); $P = 0.220$].

Association of High IgE Level or Positive Specific IgE With Tonsillar Hypertrophy in Children With Wheezing

Measurements of total IgE and specific IgE levels for the aeroallergen panel were available in 127 of 210 children with wheezing. Neither high total IgE nor positive specific IgE for one of the aeroallergens were significantly associated with tonsillar hypertrophy [OR = 0.85 (0.37–1.96); $P = 0.705$ and OR = 1.19 (0.52–2.71); $P = 0.687$] even after adjustment for other risk factors (Table 4).

DISCUSSION

In the present investigation, it was confirmed that history of wheezing affects the presence of habitual snoring significantly. Furthermore, it was demonstrated that children with history of wheezing have more frequently hypertrophic tonsils compared to subjects without such a history. When both wheezing and tonsillar hypertrophy were introduced as independent variables in the same multivariate analysis model, the latter was stronger predictor of snoring than the former. Of note, wheezing was related to presence of snoring only in children with large tonsils but not in those with tonsils of

TABLE 2—Associations of History of Wheezing With Tonsillar Hypertrophy or With Presence of Snoring, Adjusted for Other Potential Risk Factors

Risk factors	Dependent variable: tonsillar hypertrophy OR (95% CI)	P value	Dependent variable: snoring OR (95% CI)	P value
Age	0.97 (0.90–1.04)	0.321	0.95 (0.90–1.01)	0.125
Gender	1.03 (0.64–1.65)	0.906	1.67 (1.08–2.58)	0.020
Obesity	0.69 (0.38–1.25)	0.219	1.65 (1.02–2.66)	0.041
Passive smoking	0.96 (0.60–1.53)	0.851	0.88 (0.58–1.35)	0.565
History of wheezing	2.23 (1.37–3.63)	0.001	1.73 (1.12–2.67)	0.013

All factors and history of wheezing were included in the multivariate logistic regression models simultaneously. OR, odds ratio; CI, confidence interval.

TABLE 3—Associations of History of Wheezing and Tonsillar Hypertrophy With Snoring, Adjusted for Other Potential Risk Factors

Risk factors	Dependent variable: snoring OR (95% CI)	<i>P</i> value
Age	0.95(0.89–1.02)	0.153
Gender	1.68 (1.08–2.61)	0.021
Obesity	1.75 (0.98–2.66)	0.024
Passive smoking	0.89 (0.58–1.37)	0.593
History of wheezing	1.58 (1.01–2.45)	0.044
Tonsillar hypertrophy	2.08 (1.27–3.43)	0.004

All factors, history of wheezing and tonsillar hypertrophy were included in the multivariate logistic regression model simultaneously.

OR, odds ratio; CI, confidence interval.

normal size. Hence, pharyngeal lymphoid tissue enlargement should mediate at least in part the previously reported association between wheezing and snoring in children.

The association of habitual snoring with wheezing persisted even after adjustment for age, gender, obesity, and passive smoking. It is known that boys are more frequently snorers than girls, obese subjects are at higher risk for SDB than non-obese individuals and children of parents who smoke are more likely to snore and to have episodes of wheezing.^{7,9,22,27}

Previous pediatric investigations have shown significant correlations between snoring or obstructive sleep apnea and wheezing or asthma.^{6–10} In a population-based study, Corbo et al.⁷ found that asthmatic children were more frequently snorers relative to non-asthmatic controls and this finding was reproduced by two other studies.^{9,10} In addition, Teculescu et al.⁸ documented an association of exercise-induced asthma with habitual snoring in pre-school children. Finally, Redline et al.⁶ reported that usual cough, occasional wheeze, persistent wheeze, and doctor-diagnosed asthma were significant risk factors for an apnea–hypopnea index >10 episodes/h.

The epidemiologic association of wheezing with habitual snoring could be the result of one or more of

the following mechanisms: (i) lower airway obstruction promoting SDB; (ii) SDB exacerbating wheezing; and (iii) both conditions sharing common pathogenetic pathways.⁶ Poorly controlled asthma might accentuate the degree of hypoxemia accompanying apneas and hypopneas. The inverse relationship may also be active, that is, systemic low-grade inflammation related to intermittent nocturnal hypoxemia and oxidative stress in children with sleep apnea could initiate and maintain upper and lower airway inflammation.^{28,29} Of interest, increased percentage of neutrophils has been detected in induced sputum collected from children with SDB and treatment of sleep apnea with nCPAP in asthmatic adults improved control of their asthma.^{30,31}

Atopic predisposition, increased CysLTs synthesis and the related airway inflammation may be common pathways in the pathogenesis of SDB and recurrent wheezing and/or asthma.^{11,13–16,32} They all possibly contribute to increased airway resistance and pharyngeal collapsibility. Moreover, viral respiratory tract infections such as those caused by RSV or rhinoviruses can predispose to recurrent wheezing and SDB.^{20,33}

Data of the present study suggest that tonsillar hypertrophy could be another pathogenetic link between intermittent upper airway obstruction during sleep and recurrent episodes of lower airway obstruction. Pharyngeal lymphoid tissue is the primary site for proliferation of viruses, like rhinoviruses, that are associated with wheezing.^{34,35} Subjects with asthma have similar frequency of rhinovirus infections to that in healthy controls but delayed clearance of the virus due to an inadequate immune response.^{35–37} Persistent rhinovirus infection is accompanied by release of multiple pro-inflammatory cytokines that could induce proliferation of tonsillar lymphocytes.³⁸

A recent investigation revealed that adenotonsillar tissue from children with sleep apnea is characterized by increased expression of nerve growth factor, substance P and their respective receptors, a response that has been attributed to past RSV infection.¹⁸ In accordance with this finding, children hospitalized for RSV bronchiolitis as

TABLE 4—Associations of High Total IgE or Positive Specific IgE With Tonsillar Hypertrophy in Children With Wheezing, Adjusted for Other Potential Risk Factors

Risk factors	Dependent variable: tonsillar size OR (95% CI)		Dependent variable: tonsillar size OR (95% CI)	
		<i>P</i> value		<i>P</i> value
Age	1.07 (0.94–1.23)	0.325	1.07 (0.92–1.23)	0.379
Gender	0.54 (0.24–1.22)	0.138	0.55 (0.24–1.27)	0.159
Obesity	0.77 (0.27–2.19)	0.617	0.74 (0.26–2.10)	0.569
Passive smoking	0.71 (0.30–1.67)	0.436	0.71 (0.30–1.68)	0.440
High IgE level	0.75 (0.31–1.81)	0.523	—	—
Positive specific IgE	—	—	0.92 (0.36–2.34)	0.853

All Factors and High IgE or Positive Specific IgE Were Included in the Multivariate Logistic Regression Models Simultaneously.

OR, odds ratio; CI, confidence interval.

infants, have higher obstructive apnea–hypopnea index and larger tonsils than controls.²⁰ Last but not least, increased CysLTs activity has not only been associated with recurrent wheezing but it has also been detected in tonsils excised from children with sleep apnea and this activity seems to promote tonsillar cell proliferation.^{17,19,39} However, in the present study we could not document a positive correlation between atopy and tonsillar hypertrophy in children with wheezing.

Some methodological issues of the current report should be briefly discussed. Since making the diagnosis of asthma in young children is difficult, especially in those of preschool age, history of clinically significant wheeze that required treatment was selected as the main explanatory variable in this study.² Only children with wheezing recruited from the Pediatric Pulmonology Clinic had measurements of total and specific IgE levels as part of their routine clinical evaluation. Therefore, the absence of a significant correlation between high IgE level or allergic sensitization and tonsillar hypertrophy in children with wheezing does not necessarily exclude a potential role of atopy in the pathogenesis of tonsillar enlargement. In addition, this report does not clarify whether tonsillar hypertrophy contributes to upper airway inflammation.

Finally, a positive association between history of wheezing and presence of adenoidal hypertrophy would strengthen the conclusions of this study. Nevertheless, there are apparent ethical concerns for radiation exposure of asymptomatic, non-snoring children. For this reason, assessment of adenoidal size by lateral neck radiograms was not included in the aims of the current study.

In conclusion, children with history of wheezing have larger tonsils than subjects without wheezing. Hypertrophic tonsils could mediate at least in part the known association between asthma and obstructive SDB in childhood. Children with wheezing and allergic sensitization do not differ in the frequency of tonsillar hypertrophy when compared to subjects with wheezing but without sensitivity to aeroallergens.

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