

REGULAR ARTICLE

Atopy does not affect the frequency of adenotonsillar hypertrophy and sleep apnoea in children who snore

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Keywords

Adenotonsillar hypertrophy, Atopic dermatitis, Atopy, Eczema, Sleep-disordered breathing

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Received

9 July 2014; accepted 11 August 2014.

DOI:10.1111/apa.12774

None of the authors has any financial or other conflict of interests to disclose. No funding support for the present article.

ABSTRACT

Aim: Viral respiratory infections and atopy have been implicated in the pathogenesis of adenotonsillar hypertrophy and obstructive sleep apnoea (OSA), but the role of atopy is controversial. We aimed to test our hypothesis that atopy, expressed as physician-diagnosed eczema, was associated with adenotonsillar hypertrophy and OSA among children who snored.

Methods: Data on children who snored and were referred for polysomnography were reviewed. The primary outcome measures were adenotonsillar hypertrophy and OSA.

Results: We analysed data on 855 children with a mean age ($\pm$ standard deviation) of 6.3 ($\pm$ 2.5) years and median obstructive apnoea–hypopnea index of 2.1 episodes per hour. Of the 855 subjects, 133 (15.6%) had physician-diagnosed eczema, 591 (69.1%) had adenoidal hypertrophy, 605 (70.8%) had tonsillar hypertrophy, 219 (25.6%) were obese and 470 (55%) had OSA. Eczema was not related to adenoidal or tonsillar hypertrophy after adjustment for gender and age, with odds ratios (OR) of 1.00 (95% confidence interval 0.67–1.49; $p = 0.98$) and 0.88 (95% confidence interval 0.59–1.32; $p = 0.54$), respectively. Similarly, eczema did not affect OSA frequency after adjustment for adenoidal and tonsillar hypertrophy, obesity, gender and age, with an adjusted OR of 0.82 (0.56–1.21; $p = 0.32$).

Conclusion: Atopy was not related to adenotonsillar hypertrophy or OSA in children who snore.

INTRODUCTION

Increased upper airway resistance and, or, pharyngeal collapsibility predispose patients to intermittent pharyngeal airway narrowing during sleep and obstructive sleep-disordered breathing which presents as snoring and increased work of breathing (1). Children who snore are diagnosed with obstructive sleep apnoea (OSA) if they have detectable intermittent airflow cessation (apnoea) or airflow reduction (hypopnea), gas exchange abnormalities (hypoxaemia and hypercapnia) and arousals from sleep (2). OSA is the most severe form of obstructive sleep-disordered breathing (2).

Adenotonsillar hypertrophy and obesity are common clinical factors associated with increased upper airway resistance and, or, pharyngeal collapsibility, and for this reason, they predispose to OSA (1,2). Both OSA and allergic rhinitis are characterised by symptoms of sleep disturbance, such as frequent awakenings, daytime fatigue,

hypersomnolence, decreased cognitive functioning and impaired quality of life (3). This overlap in symptoms between the two disease entities has led to speculation that allergic rhinitis is implicated in the pathogenesis of OSA, by inducing nasal obstruction and enhancing nasal resistance (4). However, the association between the presence of allergic rhinitis or atopy and severity of sleep-disordered breathing has not been delineated due to the frequently

Abbreviations

AHI, Apnoea–hypopnea index; BMI, Body mass index; OSA, Obstructive sleep apnoea.

Key notes

- Atopy has been implicated in the pathogenesis of adenotonsillar hypertrophy and obstructive sleep apnoea (OSA), but its role is controversial.
- We tested the hypothesis that atopy, expressed as physician-diagnosed eczema, was associated with adenotonsillar hypertrophy and OSA among children who snored.
- Our study of 855 children who underwent polysomnography for suspected obstructive sleep-disordered breathing did not support the hypothesis.

coexisting adenoidal hypertrophy (5). Adenoidal hypertrophy develops in preschool years, persists into late childhood and adolescence and presents as nasal obstruction similar to allergic rhinitis (6).

Eczema is an atopic disease that frequently precedes the development of allergic rhinitis and asthma (7,8). In the current study, physician-diagnosed eczema was used as a surrogate measure of atopy, in an attempt to bypass difficulties with the diagnosis of allergic rhinitis in children who snore and have concurrent adenoidal hypertrophy. Therefore, we tested the hypothesis that children who are referred for polysomnography because of suspected obstructive sleep-disordered breathing, and also have physician-diagnosed eczema, face an increased risk of adenotonsillar hypertrophy and OSA. The effect of the interaction between physician-diagnosed eczema and age on frequency of OSA was also evaluated.

PATIENTS AND METHODS

Subjects and evaluation

We analysed data records of children who snored for at least one night per week and were referred to the sleep disorders laboratory of the Larissa University Hospital for polysomnography between January 2001 and June 2013. Data on subjects with craniofacial abnormalities and neuromuscular or genetic disorders were not included in the analysis.

Clinical information relevant to this study was extracted from the sleep laboratory database on each participant: (i) symptoms of obstructive sleep-disordered breathing; (ii) current or past physician-diagnosed eczema (atopic dermatitis); (iii) current or past physician-diagnosed allergic rhinitis; (iv) history of nasal congestion for at least 3 months over the 6-month period preceding polysomnography; and (v) body mass index (BMI) z score and tonsillar size (graded from 1+ to 4+) (9,10). Obesity was defined as a BMI z score of >1.645 and tonsillar hypertrophy as tonsillar size $>2+$. All children were evaluated by an ear, nose and throat surgeon for the presence of adenoidal hypertrophy, and the result of this assessment was included in the database.

Polysomnography

Overnight polysomnography was performed in the sleep disorders laboratory, and the following signals were recorded: electroencephalogram (C3/A2, C4/A1, O1/A2); right and left oculogram; submental and tibial electromyogram; body position; electrocardiogram; thoracic and abdominal wall motion (piezoelectric transducers); oronasal airflow (three-pronged thermistor and nasal pressure transducer); and oxygen saturation of haemoglobin.

Obstructive apnoea was scored when there was absence of airflow (at least 90% reduction in the airflow signal amplitude compared to baseline) for at least two respiratory cycles in the presence of chest or abdominal wall motion (11,12). Apnoea was characterised of mixed type when there was both an obstructive and a central component.

Hypopnea was defined as a decrease in the airflow signal amplitude of at least 50% compared to baseline associated with oxygen desaturation of haemoglobin equal to or $>4\%$ or with an arousal. Obstructive apnoea-hypopnea index (AHI) was the mean number of obstructive and mixed apnoeas and hypopneas per hour of total sleep time (13). Arousals and sleep stages were evaluated according to standard criteria (14,15).

Data analysis

Obstructive sleep apnoea was the main outcome measure of the study and was defined as an obstructive AHI of at least two episodes per hour or an obstructive apnoea index of at least one episode per hour (16). History of physician-diagnosed eczema was the primary explanatory variable, and age, adenoidal hypertrophy, tonsillar hypertrophy, obesity and gender were additional explanatory variables. Children with, and without, OSA were compared regarding age, frequency and other explanatory variables and polysomnography indices. The Student's *t*-test or Mann-Whitney *U*-test was used to compare continuous variables, and χ^2 was carried out for categorical variables.

Univariate logistic regression analysis was performed to calculate odds ratios and the corresponding 95% confidence intervals for the presence of adenoidal hypertrophy, tonsillar hypertrophy and OSA in children with and without eczema. Four multivariate logistic regression analysis models were tested as follows: model 1 included adenoidal hypertrophy as the outcome measure and eczema, age and gender as explanatory variables; model 2 incorporated tonsillar hypertrophy as the outcome measure and eczema, age and gender as explanatory variables; model 3 included OSA as the outcome measure and eczema, adenoidal hypertrophy, tonsillar hypertrophy, obesity, gender, age and the interaction between eczema and age as explanatory variables; and model 4 was similar to model 3, but without the interaction term. This retrospective research protocol was approved by the Larissa University Hospital Scientific Council.

RESULTS

Subjects' characteristics

A total of 1099 children who snored for at least one night per week were referred for polysomnography during the study period. We excluded 244 of the 1099 subjects from the analysis due to a history of craniofacial abnormalities ($n = 68$) or neuromuscular or genetic disorders ($n = 176$). This means that we analysed data on 855 children with a mean age ($\pm$ standard deviation) of 6.3 (± 2.5) years and a median obstructive AHI of 2.1 episodes per hour and an interquartile range of 1.1–4.5 episodes per hour. Of the 855 subjects, 133 (15.6%) had physician-diagnosed eczema, 219 (25.6%) were obese, 591 (69.1%) had adenoidal hypertrophy, 605 (70.8%) had tonsillar hypertrophy and 470 (55%) had OSA.

Children with OSA were younger in age, had a higher prevalence of adenoidal or tonsillar hypertrophy and worse

polysomnography indices than subjects without OSA ($p < 0.05$) (Table 1). However, the two groups of subjects did not differ significantly in prevalence of physician-diagnosed eczema, physician-diagnosed allergic rhinitis and history of nasal obstruction for at least 3 months in 6 months before polysomnography (Table 1).

Effects of physician-diagnosed eczema on frequency of adenoidal or tonsillar hypertrophy

Eczema was not significantly associated with the presence of adenoidal hypertrophy with odds ratio of 1.00 (95% confidence interval 0.67–1.50; $p = 0.99$), even after adjustment for age and gender [odds ratio of 1.00 (95% confidence interval 0.67–1.49); $p = 0.98$]. Similarly, there was no significant relationship between eczema and tonsillar hypertrophy before and after adjustment for age and gender with odds ratios of 0.91 (95% confidence interval

0.61–1.37; $p = 0.66$) and 0.88 (95% confidence interval 0.59–1.32; $p = 0.54$), respectively.

Effects of physician-diagnosed eczema and its interaction with age on frequency of OSA

Physician-diagnosed eczema was not associated significantly with OSA with an unadjusted odds ratio of 0.89 (95% confidence interval 0.62–1.30; $p = 0.56$). The interaction between physician-diagnosed eczema and age did not affect significantly the risk of OSA, with an odds ratio of 0.96 (95% confidence interval 0.81–1.14; $p = 0.64$). When the interaction term was removed from the multivariable logistic regression analysis model, the association of physician-diagnosed eczema with OSA, adjusted for the presence of adenoidal and tonsillar hypertrophy, obesity, gender and age, remained nonsignificant, with an odds ratio of 0.82 (95% confidence interval 0.56–1.21; $p = 0.32$) (Table 2).

Table 1 Subjects' characteristics and statistical comparisons of children without and with obstructive sleep apnoea

Variables	Children without OSA n = 385	Children with OSA n = 470	p value
Age, years	6.9 ± 2.7	5.8 ± 2.3	<0.01
Gender, male (%)	216 (56.1)	281 (59.8)	0.28
BMI z score	0.6 ± 1.4	0.7 ± 1.5	0.62
Obesity (%)	89 (23.1)	130 (27.7)	0.13
Adenoidal hypertrophy (%)	249 (64.7)	342 (72.8)	0.01
Tonsillar hypertrophy (%)	243 (63.1)	362 (77)	<0.01
Nasal obstruction for at least 3 months over the past 6 months	250 (64.9)	328 (69.8)	0.17
Physician-diagnosed allergic rhinitis (%)	136 (35.3)	156 (33.2)	0.51
Physician-diagnosed eczema (%)	63 (16.4)	70 (14.9)	0.56
Obstructive apnoea index, episodes per hour	0.3 (0.2, 0.6)	1.4 (0.8, 2.4)	<0.01
Obstructive apnoea-hypopnea index, episodes per hour	1 (0.5, 1.5)	4 (2.7, 7.3)	<0.01
Respiratory arousal index, episodes per hour	0.4 (0.2, 0.7)	1.7 (1, 3)	<0.01
Oxygen desaturation ($\geq 4\%$) of haemoglobin index, episodes per hour	1.2 (0.6, 2)	5.2 (3, 9.8)	<0.01
SpO ₂ nadir, %	92 (90, 93)	88 (84, 90)	<0.01

Continuous variables are expressed as mean ± standard deviation or median (interquartile range).

BMI = Body mass index; OSA = Obstructive sleep apnoea; SpO₂ = Oxygen saturation of haemoglobin.

Table 2 Associations of obstructive sleep apnoea with history of eczema and other explanatory variables

Variables	Outcome measure: OSA			
	Unadjusted odds ratio (95% confidence interval)	p value	Adjusted odds ratio (95% confidence interval)*	p value
Eczema	0.89 (0.62–1.30)	0.56	0.82 (0.56–1.21)	0.32
Adenoidal hypertrophy	1.46 (1.10–1.95)	0.01	1.52 (1.12–2.06)	<0.01
Tonsillar hypertrophy	1.96 (1.45–2.64)	<0.01	1.86 (1.37–2.54)	<0.01
Obesity	1.27 (0.93–1.74)	0.13	1.47 (1.06–2.03)	0.02
Male gender	1.16 (0.89–1.53)	0.28	1.11 (0.83–1.47)	0.49
Age	0.83 (0.78–0.88)	<0.01	0.84 (0.79–0.89)	<0.01

OSA = Obstructive sleep apnoea.

*Multivariate logistic regression analysis was applied to adjust OR of each independent variable by all other variables.

Adenoidal or tonsillar hypertrophy, obesity and young age were significant predictors of OSA (Table 2).

DISCUSSION

In the present series of children referred for polysomnography due to history of snoring, it was demonstrated that atopy expressed as physician-diagnosed eczema did not affect the risk of adenotonsillar hypertrophy and was not associated with increased risk of OSA, even when coexisting adenotonsillar hypertrophy was taken into consideration. No relationship between atopy and OSA was found for either younger or older children.

Allergic rhinitis has a negative impact on sleep quality in children, but it is unclear whether OSA is one of the pathophysiologic mechanisms that mediate this adverse effect (17). In a recent publication, 18 papers evaluating the association between allergic rhinitis and sleep-disordered breathing were systematically reviewed (5). Of these, 12 studies supported an association between allergic rhinitis and sleep-disordered breathing, but they were of low methodological quality. In seven studies, skin prick testing or *in vitro* measurement of specific IgE to common environmental allergens was carried out. However, in four of the seven studies, there was no report of nasal symptoms that would allow the diagnosis of allergic rhinitis and not just demonstration of allergic sensitisation. Seven studies used OSA diagnosed by polysomnography as an outcome measure, whereas in the remaining papers, only snoring, which is a symptom of sleep-disordered breathing, was recorded. Participants did not undergo complete evaluation for allergic rhinitis (allergy testing), adenotonsillar hypertrophy and OSA (polysomnography) in any of the studies. Furthermore, no criteria were applied to differentiate nasal symptoms that could be attributed to allergic rhinitis from those symptoms related to adenoidal hypertrophy.

It has been proposed that objective measures of increased nasal resistance, such as nasal peak inspiratory pressure, could facilitate delineation of the adverse effects that allergic rhinitis has on sleep quality (17). Nevertheless, many children with sleep-disordered breathing have concurrent adenoidal hypertrophy, and it is difficult to separate the component of increased upper airway resistance, which is due to allergic rhinitis, from the element related to adenoidal hypertrophy (6).

Allergic rhinitis, asthma and atopic dermatitis are different clinical expressions of atopy, and they frequently coexist in the same individual (7). The term 'atopic march' has been employed to describe the onset of eczema early in life, with later development of allergic rhinitis and asthma (8,18). In a retrospective report that was based on the Taiwan's National Health Insurance database, an increased propensity for developing atopic dermatitis was identified in 42 children and adolescents with an OSA diagnosis over a period of 5.5 years (19). In the present study, we have used physician-diagnosed eczema as a surrogate measure of atopy in a much larger cohort of children who snored, had a high prevalence of adenotonsillar hypertrophy and were

referred for polysomnography. Participants with, or without, adenotonsillar hypertrophy or OSA did not differ in the frequency of physician-diagnosed eczema. Moreover, adenoidal or tonsillar hypertrophy, obesity and young age were significant risk factors for OSA, but eczema was not.

A population-based study of 1-year-old infants born to atopic parents indicated that subjects with at least one positive skin prick test to aeroallergens or food allergens had increased risk of habitual snoring (20). Similarly, in a cross-sectional study of young children, allergic rhinitis and atopic dermatitis were significant risk factors for habitual snoring (21). However, the severity of sleep-disordered breathing was not evaluated by polysomnography in any of the population-based studies mentioned above. To interpret our findings in the context of the previous two studies, we speculate that allergic rhinitis and atopic predisposition do not determine the severity of intermittent upper airway obstruction during sleep in children who snore due to the profound effects of adenotonsillar hypertrophy on upper airway resistance.

Published evidence indicates that during the first 8 years of life, the pharyngeal lymphoid tissue is vulnerable to stimuli promoting cellular proliferation (3). Certain subgroups of subjects, such as children with parental history of adenotonsillectomy or physician-diagnosed wheezing, are more prone to the development of adenotonsillar hypertrophy and OSA during early childhood (22,23). Viral agents that may trigger wheezing at preschool age, such as respiratory syncytial virus, enhance the pathway of neurotrophins and the synthesis of cysteinyl leukotrienes (24,25). Both neurotrophins and cysteinyl leukotrienes have been implicated in the pathogenesis of adenotonsillar tissue hypertrophy. It should be mentioned that administration of montelukast, a type-1 cysteinyl leukotriene receptor, has been accompanied by a reduction in adenoid size (26–29).

Clinical studies support the dominant role of adenotonsillar hypertrophy, probably caused by viral respiratory infections, over atopy in the pathogenesis of OSA. In a large cohort from Israel, children and adolescents with suspected sleep-disordered breathing who underwent polysomnography in the winter had higher AHI than subjects who were studied in the summer (30). Seasonal variability was more apparent in children younger than 5 years of age and was not altered by the presence of atopy. Moreover, in a population-based study from the United States, which included young children, AHI was higher when polysomnography was performed in the winter and there was a downward trend in the spring when allergic rhinitis symptoms usually deteriorate (31).

We propose that the contribution of allergic rhinitis to the pathogenesis of sleep-disordered breathing can be quantitated more accurately in children who have already undergone adenotonsillectomy to treat OSA. It is interesting that combining oral montelukast and intranasal budesonide leads to improved respiratory and sleep parameters in children with residual OSA following adenotonsillectomy (32).

CONCLUSION

When we studied children who were referred for polysomnography due to a history of snoring, physician-diagnosed eczema was not associated with an increased risk of adenotonsillar hypertrophy or OSA. Adenotonsillar hypertrophy was the predominant risk factor for OSA in childhood when compared to atopic predisposition.

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