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Obstructive Sleep Apnea in Poorly Controlled Asthmatic Children: Effect of Adenotonsillectomy

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Abstract

Background—Asthma and obstructive sleep apnea (OSA) in children share multiple epidemiological risk factors and the prevalence of snoring is higher in asthmatic children, suggesting that the latter may be at increased risk for OSA. Since both asthma and OSA are inflammatory disorders, we hypothesized that polysomnographically-demonstrated OSA would be more frequent among poorly controlled asthmatics (PCA), and that treatment of OSA, if present, would ameliorate the frequency of acute asthmatic exacerbations (AAE).

Methods—Children with PCA were referred for an overnight sleep study, and adenotonsillectomy (T&A) was performed if OSA was present. Frequency of asthma symptoms and exacerbations were compared.

Results—92 PCA children, ages 3-10 years, with a mean frequency of AAE of 3.4±0.4/year were prospectively referred for a sleep study. OSA (i.e., AHI>5/hrTST) was present in 58 patients (63.0%; OR: 40.9, 12.9-144.1, p<0.000001 compared to the prevalence of OSA in a non-asthmatic population). Information at 1-year follow-up was available for 35 PCA children after tonsillectomy and adenoidectomy (T&A). The annual frequency of AAE, rescue inhaled use, and asthma symptoms in this sub-group decreased compared to no changes in the group without OSA.

Conclusions—The prevalence of OSA is markedly increased among PCA children and treatment of OSA appears to be associated with substantial improvements in the severity of the underlying asthmatic condition.

Introduction

Obstructive sleep apnea (OSA) is a highly prevalent condition in children that leads to substantial cardiovascular and neurobehavioral morbidities. Increased proliferation of upper airway lymphoid tissue and obesity are the two major determinants of OSA in children. Recently, an association between asthma and OSA has been proposed. However, little information is available on whether such putative association is present, and whether the presence of OSA imposes adverse consequences on the severity of asthma symptoms in children.

Habitual snoring during sleep, the hallmark indicator of increased upper airway resistance, is a frequent occurrence during childhood, with up to 27% of children being affected.¹⁻⁹ OSA is most common in young children (pre-school and early school years) with a peak prevalence around 2-8 years, and subsequently declines in frequency. As noted above, the two major determinants of OSA are enlargement of tonsils and adenoids and obesity. The rather accelerated increase in the prevalence of pediatric obesity over the last 2 decades has led to substantial changes in the cross sectional demographic and anthropometric characteristics of the children being referred for evaluation of habitual snoring. For example, while <15% of all symptomatic habitually-snoring children were obese (body-mass index z score >1.57) in the early 1990's, >50% fulfilled such criteria among all clinical referrals for suspected OSA in the last 2-3 years at our Sleep Center.¹⁰ It is now apparent that OSA can lead to substantial morbidities affecting CNS, cardiovascular and metabolic systems, and somatic growth, ultimately leading to reduced quality of life.¹¹ The increasing prevalence of childhood asthma and the similar temporal trajectories of pediatric OSA have led to the hypothesis that the 2 conditions may be pathophysiologically related.

In the only published study in the US on the potential association between OSA and asthma (12), a parent/guardian report of asthma decreased the odds of having OSA by 34%, after controlling for individual and socioeconomic factors and assessment results. However, this study assessed a skewed population in that only children with habitual snoring referred to the sleep laboratory were examined.¹² Other studies have indicated that the risk for OSA is enhanced in the presence of asthma. For example, a random sample survey of 1234 children, aged 6-14 years in Belgium revealed a 2.0 fold increase in OSA symptoms among children with wheezing.¹³ Similar findings were reported in other countries.¹⁴⁻¹⁶ In addition, AHI was significantly higher in subjects with poorly controlled asthma in a cohort of African American children with asthma.¹⁷ Since both OSA and asthma share the presence of activated regional airway inflammatory pathways, the latter could contribute to mutually exacerbating each other.¹⁸⁻²⁰

Based on aforementioned considerations, we hypothesized that OSA would be frequently present among children with poorly controlled asthma, and that treatment of OSA with adenotonsillectomy would improve the severity of asthma symptoms.

Patients and Methods

From June 2004, we began to prospectively classify the level of asthma control among all children with the diagnosis of asthma being routinely followed at the Asthma Center at the University of Louisville and fulfilling the criteria for a clinician-confirmed diagnosis of asthma, as defined by the American Thoracic Society, with symptomatic improvement in response to use of short-acting β_2 -agonist bronchodilator, a history of documented reversible airway disease demonstrated by an increase of 12% or greater in FEV1 over baseline within 30 minutes of albuterol inhalation or after prednisone burst, or both. Similarly, due to empirical impression based on a series of cases in which OSA was diagnosed in children with unstable asthma, and treatment of OSA appeared to improve their clinical status, children fulfilling the criteria for poorly controlled asthma (PCA; see below) were referred for a sleep study as part of their routine clinical care, and subsequently treated accordingly based on their polysomnographic findings. A retrospective analysis of all the children with PCA was conducted after institutional review board approval by the local committee.

Asthma Control Selection Criteria

Routine clinical asthma control assessments were based on a daily diary that was collected for 30 days prior to clinic visits, in which patients scored the severity of day-time and night-

time asthma symptoms (0=none, 5=severe), amount of night-time awakenings, daily rescue β 2-agonist use, and the frequency of morning decreases in peak expiratory flow (PEF) rates from their personal best. Clinic nurses routinely contacted all patients weekly during the month before clinic to serve as reminders, conducted surveys for those days, and assisted in the completion of the asthma control assessments as needed. The clinic form was filled out during the clinic visit and recorded whether patients experienced treatment-related adverse events, exacerbations requiring oral corticosteroid, emergency department visits and hospitalization. Patients with > 2 days/week, symptom scores >2, >2 days/week use of β -agonist rescue inhaler, and >1 acute exacerbation/year were considered as poorly controlled and referred for overnight polysomnographic evaluation.

Anthropometry

Children were weighed using a calibrated scale to the nearest 0.1 kg and height (to 0.1cm) was measured with a stadiometer (Holtain, Crymmych, UK). Body mass index (BMI) was calculated and BMI z-score was computed using CDC 2000 growth standards (www.cdc.gov/growthcharts) and online software (www.cdc.gov/epiinfo). A BMI z score ≥ 1.65 was considered as fulfilling the criteria for obesity.

Overnight Polysomnography

Upon arrival to the University of Louisville Pediatric Sleep Research Laboratory, a questionnaire that included questions on snoring frequency (never, rarely, occasionally, frequently, almost always) and loudness (mildly quietly, medium loud, loud, very loud, extremely loud) was administered. Overnight polysomnography (NPSG) was then performed as previously described.²¹ Sleep architecture was evaluated by standard techniques and sleep parameters were scored as previously described.²² Briefly, chest and abdominal wall movement were monitored by respiratory impedance or inductance plethysmography, heart rate by ECG, air flow was assessed with a sidestream end-tidal capnograph which also provided breath-by-breath assessment of end-tidal carbon dioxide levels (PETCO₂; BCI SC-300, Menomonee Falls, WI), nasal pressure catheter, and an oronasal thermistor. Arterial oxygen saturation (SpO₂) was assessed by pulse oximetry (Nellcor N 100; Nellcor Inc., Hayward, CA), with simultaneous recording of the pulse waveform. The bilateral electro-oculogram (EOG), 8 channels of electroencephalogram (EEG), chin and anterior tibial electromyograms (EMG), and analog output from a body position sensor (Braebon Medical Corporation, NY) were also monitored. All measures were digitized using a commercially available polysomnography systems (Rembrandt, MedCare Diagnostics, Amsterdam, The Netherlands, or Stellate, Montreal, Canada). Tracheal sound was monitored with a microphone sensor (Sleepmate, VA) and a digital time-synchronized video recording was performed.

Sleep architecture was assessed by standard techniques.²³ The proportion of time spent in each sleep stage was expressed as percentage of total sleep time (%TST). Central, obstructive and mixed apneic events were counted. Obstructive apnea was defined as the absence of airflow with continued chest wall and abdominal movement for duration of at least two breaths.²² Hypopneas were defined as a decrease in oronasal flow of $\geq 50\%$ on either the thermistor or nasal pressure transducer signal with a corresponding decrease in SpO₂ of $\geq 3\%$ or arousal.^{22, 24} The obstructive apnea/hypopnea index (AHI) was defined as the number of apnea and hypopneas per hour of TST. Arousals were defined according to the American Academy of Sleep Medicine Scoring Manual.²⁴

OSA Criteria

The diagnostic criteria for OSA in this study consisted of an obstructive AHI $\geq 5/\text{hrTST}$ in the presence of snoring during the night, and a nadir oxyhemoglobin saturation $< 92\%$. If

OSA was present, subjects underwent a lateral film of the neck to assess for the presence of enlarged adenoids, and were then referred to an otolaryngologist for adenotonsillectomy (T&A), the standard first line of OSA treatment.²⁵

Data Analysis

All children enrolled in the study continued their regular asthma monitoring and treatment for a period of 1 year after their sleep study or after undergoing T&A. Data were expressed as mean $\pm$ SD. Significant differences in asthma control across groups (OSA and T&A or NPSG only) were analyzed using ANOVA for continuous variables and chi-square tests for categorical variables. Statistical analyses were performed using SPSS software (version 16.0; SPSS Inc., Chicago, Ill.). All p-values reported are 2-tailed with statistical significance set at <0.05 , and pairwise deletion of missing data was chosen.

Results

A total of 92 out of a total of 135 PCA children were identified during the period from June 2004 till October 2007 and agreed to undergo NPSG. Their demographic characteristics are shown in Table 1, and there were no differences between those who underwent NPSG and those children whose parents refused NPSG or did not show for the test. As a group, these children had 3.27 ± 1.13 acute asthmatic exacerbations (AAE) per year, and 36% were obese. NPSG revealed the presence of OSA (i.e., $AHI > 5/hrTST$) in 58 patients (63.0%; OR: 40.9, 12.9-144.1, $p < 0.000001$ compared to the maximal estimated prevalence of OSA in a non-asthmatic population, i.e., ~4%; Table 2). The frequency of habitual snoring among those whose NPSG revealed the presence of OSA was significantly higher than among those with normal NPSG (Table 2; $p < 0.00001$). Table 2 shows the differences between asthmatic children with OSA and those without OSA. Children with polysomnographic evidence of OSA were overall demographically similar to those without OSA, but had significantly worse asthma control scores ($p < 0.04$; Table 2). Of note, the overall compliance with asthma diaries was 66% for any given follow-up visit, and all children had at least one diary filled out during the 12 months follow-up period. The frequency of reported symptoms of allergic rhinitis did not differ between the PCA children with OSA and those without OSA. Similarly, there were no differences in medication use according to parents or according to medication refills. Information at 1-year follow-up was available for 35 PCA children with OSA after tonsillectomy and adenoidectomy (T&A), and for 24 PCA children without OSA. The annual frequency of AAE in the post T&A sub-group decreased from 4.1 ± 1.3 /year to 1.8 ± 1.4 /year ($p < 0.0001$), while no changes emerged in the non-OSA group (Table 3; $p < 0.0001$, 2-way ANOVA repeated measures). Similar favorable improvements occurred after T&A in the frequency of β -agonist rescue use or in asthma symptom scores (Table 3).

Discussion

This study shows that obstructive sleep apnea is highly prevalent among children with moderate to severe asthma, compare to the anticipated frequency in the general pediatric population. Furthermore, treatment of OSA with T&A appears to reduce the frequency of asthmatic symptoms and β -agonist inhaler rescue use, as well as result in declines in the number of acute asthmatic exacerbations requiring either systemic steroid use or emergency room visits. Thus, upper airway inflammatory processes may play a role in lower airway inflammation and asthma, and conversely lower airway inflammatory disease may promote adenotonsillar proliferation, and therefore increase the propensity for OSA.

Before we discuss the potential implications of the present study, several methodological issues deserve comment. First, the cohort was prospectively assigned to undergo sleep studies as part of their routine clinical care, but this was not a randomized cohort of

asthmatic children, and as such, it was purposefully limited to those children with known poor control of their asthma, and the data were retrospectively analyzed in an unblinded fashion. Therefore, we can not extrapolate current findings on the prevalence of OSA to asthmatic children with varying degrees of disease severity. We should denote however, that the association between asthma and OSA is not novel, and has prompted a comprehensive review of potential mechanistic links in adult patients.²⁶ Some of such putative mechanisms could be operational in children as well. Indeed, Kaditis and colleagues have recently reported on the more frequent history of wheezing among children developing tonsillar hypertrophy,²⁷ suggesting that the inflammatory processes in the lower airways may promote the proliferation of lymphadenoid tissues in the upper airway. Similarly, an estimated prevalence of up to 33% sleep-disordered breathing was suggested among 194 inner city 4-10 year old children who were enrolled in a school-based asthma intervention program, particularly among those with persistent asthma,²⁸ suggesting that asthma severity is associated with dose-dependent increases in the prevalence of OSA. Second, we did not conduct follow-up NPSG after T&A in those subjects who required the surgery to ascertain that there was complete resolution of sleep-disordered breathing. We should emphasize that based on recent evidence on the putative efficacy of T&A in children with OSA, such assumption would be highly unlikely, considering the <30% rate of normalization of sleep breathing patterns achieved in a recent multicenter study.²⁵ Therefore, if residual OSA was indeed present in a substantial proportion of the children undergoing T&A in the current study, it is likely that further efforts to address this issue may have resulted in even more significant improvements in asthma control. Conversely, we can not be certain that OSA did not develop over time in a subset of the children without OSA in the initial NPSG, since habitual snoring was frequent in this group, albeit significantly less frequent than in the group with OSA (Table 1). Thirdly, we did not assess the frequency of asthma and its severity among children being evaluated for OSA in the pediatric sleep clinic. The latter assessment should clearly be conducted to confirm the initial validity of the putative interaction between OSA and asthma in children. Fourthly, we did not assess specific responses to allergens, nor did we consistently measure lung volumes and other pulmonary function measures in our cohort. In addition, we did not measure the concentrations of inflammatory mediators in exhaled breath in all children before and after T&A or NPSG only, and as such further strengthen the reciprocal contribution of inflammatory processes in one site of the airway continuum to the other. Nowadays, there is little doubt that asthma is an inflammatory disease,^{19, 20, 29-33} and conversely, evidence has emerged implicating OSA and airway inflammation.^{18, 34}

Although we anticipated increases in the frequency of OSA, the extremely high prevalence of OSA in this cohort was somewhat unexpected, and could be due not only to the underlying asthmatic condition, but also to the relatively high proportion of obese children. Indeed, obesity has emerged as an important risk factor for OSA in children,^{35, 36} and similarly, obesity and asthma are also epidemiologically linked,³⁷⁻³⁹ thereby suggesting that the 3 conditions may contribute to each other. However, this study was not designed to assess such interactions, and such assessment will require a larger prospective cohort and different study design. Notwithstanding, T&A treatment of OSA, whether resulting in either partial or complete normalization of the respiratory disturbances during sleep, led to significant ameliorations in the severity of asthma without any concomitant changes in BMI z score (data not shown). Thus, the present study provides highly suggestive initial evidence on the potential benefits of recognizing and treating OSA in asthmatic patients, and therefore warrants future studies aiming to replicate the high prevalence and inherent benefits of addressing OSA in poorly controlled asthmatic children. Additionally, the published evidence and the current study certainly lay the foundations for further exploring the epidemiological interactions between asthma, obesity and OSA, and their respective contributions to morbidity and reduced quality of life.

In summary, we present preliminary observations that the prevalence of OSA is exceedingly high in poorly controlled asthmatic children, and that treatment of the latter may ameliorate the former.

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Table 1

Demographic and asthma control characteristics in 92 children with poorly controlled asthma.

N	92
Age (range, years)	6.58 ± 1.8 (3-10)
Gender (% male)	49 (53%)
Ethnicity (%African American)	23 (25%)
BMI z score (%obese)	1.40 ± 1.21 (36.9%)
Acute Asthma Exacerbations (/year)	3.27 ± 1.13
Weekly β-agonist rescue use (/week)	4.1 ± 2.43
Asthma Symptom Score	2.7 ± 1.76
FEV₁ (n=48)(%predicted)	84.7 ± 6.3
Allergic Rhinitis (n)	72

Table 2

Demographic and asthma severity characteristics in 58 asthmatic patients with OSA and 34 patients without OSA.

	OSA (+)	(OSA (-)	P value
N	58	34	NS
Age (range, years)	5.8 ± 1.8 (3-10)	6.9±2.3 (4-10)	NS
Gender (% male)	51.7	55.8	NS
Ethnicity (%African American)	32.0	14.7	NS
BMI z score (%obese)	1.46 ± 1.32 (38.2%)	1.38 ± 1.24 (35.1%)	NS
Habitual Snoring (>3 nights/week)	49	14	<0.0001
Acute Asthma Exacerbations (/year)	3.57 ± 1.37	3.12 ± 1.40	<0.05
Weekly β -agonist rescue use (/week)	4.7 ± 2.9	3.6 ± 2.1	<0.04
Asthma Symptom Score	2.93 ± 1.93	2.1 ± 1.65	<0.04
FEV ₁ (%predicted)	82.1 ± 7.1 *	87.9 ± 6.4 **	NS
Allergic Rhinitis (n)	46	26	NS
TST (min)	476.4 ± 25.2	472.8 ± 32.3	NS
REM (%TST)	21.1 ± 6.3	23.8 ± 7.1	NS
Stage 1 (%TST)	16.4 ± 5.2	11.0 ± 4.4	<0.05
Stage 2 (%TST)	47.7 ± 15.1	44.3 ± 14.7	NS
SWS (%TST)	15.2 ± 9.4	21.8 ± 25	<0.01
OAHI (hr TST)	14.6 ± 8.2	0.8 ± 0.2	<0.0001
Nadir SaO ₂ (%)	84.5 ± 2.7	91.5 ± 1.4	<0.0001
Arousal Index (/hrTST)	18.7 ± 7.3	11.3 ± 6.2	<0.0001

* - n=28;

** - n=17

SWS – slow wave sleep; REM – rapid eye movement sleep; TST – total sleep time; OAHI – obstructive apnea hypopnea index,

Table 3

Changes in asthma symptoms and control in poorly controlled asthmatic children with OSA before and after T&A, and in those without OSA before and after sleep studies.

	OSA (+) N=35		P value	OSA (-) N=24		P value	P value OSA(+) vs. OSA (-)
	Pre T&A	Post T&A		Pre NPSG	Post NPSG		
Acute Asthma Exacerbations (year)	4.1±1.3	1.8±1.4	<0.0001	3.5±1.5	3.7±1.7	NS	<0.0001
Weekly β -agonist rescue use (/week)	4.3±1.8	2.1±1.5	<0.001	4.2±1.9	3.9±2.2	NS	<0.001
Asthma Symptom Score	3.1±1.9	1.9±1.7	<0.0001	3.2±2.0	3.1±2.1	NS	<0.001
FEV ₁ (%predicted)	80.1±8.7*	86.5±8.4	<0.04	82.5±9.1**	83.1±9.7	NS	0.05

* - n=18;

* - n=12