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Pediatric Obstructive Sleep Apnea: A Potential Late Consequence of Respiratory Syncitial Virus Bronchiolitis

Ayelet Snow, MD,[1] Ehab Dayyat, MD,[1] Hawley E. Montgomery-Downs, PhD,[2] Leila Kheirandish-Gozal, MD,[1] and David Gozal, MD[1]*

Summary. Study Objectives: To examine the hypothesis that children who suffered from severe respiratory syncitial virus (RSV) bronchiolitis during infancy may be at higher risk for obstructive sleep apnea (OSA) later in childhood. Methods: Survey of Kosair Children's Hospital medical records allowed for identification of potential candidates for the study. Twenty-one randomly selected children (mean age ± SD: 5.2 ± 1.5 years) with a history of verified RSV-induced bronchiolitis during their first year of life underwent overnight sleep study (NPSG). Children recruited from the general population with no history of RSV bronchiolitis served as a control group. After matching for age, gender, ethnicity, gestational age at birth, body mass index (BMI) z scores, household cigarette smoking, history of asthma and allergies, 63 control subjects (mean age ± SD: 5.1 ± 0.7 years) were also studied. Results: Children who had RSV bronchiolitis as infants had significantly higher obstructive apnea/hypopnea index compared to controls (2.3 ± 1.9 vs. 0.6 ± 0.8 / hr total sleep time (TST); $P < 0.05$). In addition, significantly higher respiratory arousal indices were apparent among children with previous RSV bronchiolitis compared to controls (1.3 ± 1.0 vs. 0.1 ± 0.2 /hr TST; $P < 0.05$). There were no significant differences between the groups in the lowest SpO_2, $ETCO_2$, and sleep indices. Conclusions: RSV bronchiolitis may contribute to the pathophysiology of OSA in vulnerable children. **Pediatr Pulmonol. 2009; 44:1186–1191.**

Key words: adenotonsillar hypertrophy; bronchiolitis; RSV; sleep apnea; sleep disordered breathing.

INTRODUCTION

Obstructive sleep apnea (OSA) is a relatively prevalent pediatric disorder, affecting 2–3% of all children. [1–4] OSA can lead to considerable cardiovascular, neurocognitive, and behavioral morbidities.[5–9] Adenotonsillar hypertrophy is presently considered as a significant factor contributing to OSA in children [10,11] with adenotonsillectomy therefore serving as the initial treatment of choice.[12]

Factors predicting adenotonsillar tissue (AT) hypertrophy are yet to be fully elucidated. However, smoking, intercurrent infections and allergies positively correlate to the increase in size of AT in snoring children, and such associations are therefore suggestive of activation of inflammatory pathways that will then induce and promote the proliferation of AT in the upper airways.[2,13–15] In a recent study, we found significantly higher expression rates of nerve growth factor (NGF) mRNA and its high affinity tyrosine kinase receptor (trkA) in AT harvested from 34 children with OSA when compared to AT harvested from 25 children with recurrent tonsillitis (RI). Furthermore, neurokinin 1 (NK1) receptor mRNA and protein expression along with substance P protein concentrations were also significantly enhanced in the OSA group.[16] The aforementioned changes most likely reflect underlying neuroimmunomodulatory responses that will predispose to enhanced inflammatory processes in the AT, and most likely promote hyperplasia. Of note, these findings are strikingly similar to the changes found in the lymphoid tissues obtained from the bronchial tree in the lungs of respiratory syncitial virus (RSV)- infected

Supporting information may be found in the online version of this article.

[1]Division of Pediatric Sleep Medicine, Department of Pediatrics, University of Louisville, and Kosair Children's Hospital Research Institute, Louisville, Kentucky 40202.

[2]Department of Psychology, West Virginia University, Morgantown, West Virginia 26506.

*Correspondence to: David Gozal, MD, Department of Pediatrics, Comer Children's Hospital, The University of Chicago, 5721 S. Maryland Avenue, MC 8000, Suite K-160, Chicago, IL 60637.
E-mail: dgozal@peds.bsd.uchicago.edu

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rats,[17–19] as well as in bronchoalveolar lavage specimens obtained from intubated children during RSV infection.[20]

It is estimated that 100% of children are infected with RSV during the first few years of life.[21,22] Since the 1950s, a number of studies have shown that RSV bronchiolitis is often followed by post-bronchiolitic wheezing, and with the diagnosis of asthma later in life.[23] These associations suggest that RSV infection in the lower respiratory tract induces priming of immune responses through neural networks that ultimately predispose toward an exaggerated inflammatory lung response to multiple environmental stimuli, both during and after the RSV infective process, and that such processes include immune tissues in the upper airway, such as adenoids and tonsils.[20,24,25] Based on the aforesaid considerations, we hypothesized that children undergoing a significant RSV infection early in life would be more likely to develop AT hyperplastic and hypertrophic changes that would subsequently contribute to and promote the occurrence of OSA later in life. As such, we further hypothesized that children with a history of severe RSV bronchiolitis would be prone to manifest obstructed breathing patterns during sleep.

METHODS

The study was approved by the institutional human study review committee. Parental consent and child assent for children ≥ 7 years of age, in the presence of a parent, were obtained.

Subjects

The population for the study was identified by screening charts from the medical records department at Kosair Children's Hospital in Louisville, Kentucky. The charts documenting hospitalizations of children aged 0–1 years of age between the years 1999–2005 (i.e., corresponding to ages of 2–8 years at the time of the study) were reviewed. Children who were diagnosed and admitted as RSV bronchiolitis, further confirmed by rapid Enzyme-Linked ImmunoSorbent Assay and/or RSV culture were identified. A previously validated sleep questionnaire was then mailed to each family to be filled out by one of each subject's parent/guardian (Appendix 1 in Supporting Information). The returned questionnaires were reviewed and subjects fulfilling the preset exclusion criteria were considered ineligible. Exclusion criteria were as follows: past adenotonsillectomy, obesity (see below), the presence of prematurity, admission to the pediatric intensive care unit, past intubation, chronic illnesses, genetic disorders, neuromuscular diseases, craniofacial abnormalities, the presence of an additional acute infection during the bronchiolitis episode (as adenovirus or Influenzavirus A or B), or current treatment with medications such as corticosteroids.

Eligible consecutive subjects were contacted by phone and invited to undergo overnight polysomnography at the Kosair Children's Hospital pediatric sleep laboratory. A control group of children was identified from several databases acquired during previous studies. After matching for age, gender, ethnicity, presence of asthma, cigarette smoking in the household, gestational age at birth, and history of environmental allergies between the two groups, the overnight polysomnographic studies of these children were used as comparison. Exclusion criteria for the control children were those used for the study group, and in addition required the absence of a previously diagnosed RSV infection. Tonsil size was examined and assigned a score of 0 (no tonsils present) to 4 (kissing tonsils).[26]

Sleep Questionnaire

A detailed sleep questionnaire consisting of 14 major categorical points regarding snoring and breathing patterns during sleep as well as potential indicators for daytime hypersomnolence and exclusion criteria was administered to the parents of all identified children to identify exclusionary criteria. (Appendix 1 in Supporting Information). This questionnaire is derived from one previously used in a prospective study of children attending first grade in public schools.[5] The questionnaire was modified to assign numerical scores to each of the answers ranging from 0 (never), 1 (rarely), 2 (occasionally), 3 (frequently) to 4 (almost always).

Overnight Polysomnography

A standard overnight multichannel polysomnographic evaluation was performed as previously described.[1,3] Children were studied for up to 12 hr in a quiet, darkened room with an ambient temperature of 24°C with a parent or guardian present. No drugs were used to induce sleep.

The following parameters were measured: chest and abdominal wall movements assessed by inductance plethysmography, heart rate assessed by electrocardiography, and air flow monitored by sidestream end-tidal capnography, which also provided breath-by-breath assessments of end-tidal carbon dioxide levels (BCI SC-300; Menomonee Falls, WI), nasal pressure, and an oronasal thermistor. Arterial oxygen saturation (SPO_2) was assessed by pulse oximetry (Nellcor N 100; Nellcor Inc, Hayward, CA), with simultaneous recording of the pulse waveform. Bilateral electroculograms, 8 channels of electroencephalogram, chin and anterior tibial electromyograms, and analog output from a body-position sensor (Braebon Medical Corp, Ogdensburg, NY) were also monitored. All measures were digitized with a commercially available polysomnographic system (Stellate, Montreal, Canada). Tracheal sounds were monitored with

a microphone sensor (Sleepmate, Midlothian, VA), and a digital, time-synchronized video recording was obtained.

Sleep architecture was assessed by standard techniques.[27] The proportion of time spent in each sleep stage was expressed as percentage of the total sleep time (TST). Awakenings were defined as sustained arousal lasting for $\geq$ 15 sec. The apnea index was defined as the number of episodes of apnea per hour of TST. Central, obstructive, and mixed apneic events were manually scored. Obstructive apnea was defined as the absence of airflow with continued chest wall and abdominal movements for the duration of at least 2 breaths.[28–30] Hypopnea was defined as a decrease in nasal flow of $\geq$ 50% with a corresponding decrease in SPO_2 of $\geq$ 4% and/or arousal.[28,30] The obstructive apnea/hypopnea index (AHI) was defined as the number of episodes of obstructive apnea and hypopnea per hour of TST. Children with AHI values of $\geq$1 episode per hour of TST but <5 episodes per hour of TST were considered to have mild OSA, children with AHI values of $\geq$5 episodes/hour of TST were considered to have OSA.The mean SPO_2, as measured by pulse oximetry in the presence of a pulse waveform signal void-of-motion artifact, and the SPO_2 nadir were recorded.

Arousals were expressed as the total number of arousals per hour of TST (arousal index), and were defined as recommended by the American Sleep Disorders Association Task Force report [31,32] and included respiratory-related (occurring immediately following an apnea, hypopnea, or snore), technician-induced, and spontaneous arousals.

BMI z Score Calculation

Height and weight were recorded for each child when arrived to night time polysomnography. Body mass index (BMI) z score was calculated using an online BMI z score calculator provided by the CDC (http://www.cdc.gov/epiinfo/). Children with BMI z score values greater than 1.67 were considered as being obese.[33]

Data Analysis

Data are presented as mean $\pm$ SD unless stated otherwise. Data were assessed for kurtosis and confirmed as being normally distributed. Statistical analyses were conducted using SPSS 14.0 (SPSS, Chicago, IL). A P value of < 0.05 was considered to achieve statistical significance.

RESULTS

Sleep questionnaires were mailed to 489 children admitted to Kosair Children's Hospital due to RSV infection before their first birthday and between the years 2000 and 2006. Two hundred eighty-three letters were returned because of wrong address, 121 were not returned or improperly completed, and 85 were returned completed.

From the valid 85 questionnaires, further review revealed that 42 subjects were ineligible for inclusion in the study: 19 underwent adenotonsillectomy/adenoidectomy, 8 were born prematurely (i.e., < 36 week gestation), 3 had Down syndrome, 9 were morbidly obese, 2 had neurodevelopmental abnormalities, 1 had other chronic medical conditions. Of the 19 who underwent adenotonsillectomy, habitual snoring and suspected OSA were reported by all as the main reason for the surgical extirpation of hypertrophic adenoids and tonsils. However, only 2 of the 19 children underwent a diagnostic NPSG, and in both moderate to severe OSA was present.

The remaining 43 who fulfilled inclusion criteria were contacted consecutively by phone and invited for an overnight polysomnography in Kosair Children's Hospital pediatric laboratory. Six declined to participate in the research because they had relocated and lived far away ($n = 4$) or were not interested in undergoing overnight polysomnography ($n = 2$); 3 children were excluded due to history of RSV infection that included hospitalization to the PICU and endotracheal intubation (which might cause anatomical changes to the upper airways not related to the adenotonsillar tissues and subsequent propensity to have OSA), 3 children who had a confirmed history of an additional viral infection (influenza virus) and 10 children ultimately could not be reached by phone. Thus, a total of 21 consecutive children with a confirmed history of RSV infection underwent NPSG, with 63 consecutive control subjects from the general population undergoing NPSG.

The demographic and polysomnographic characteristics of the 2 groups are shown in Table 1.

There were no significant differences on the matching criteria age, gender, and ethnicity, or on total sleep time and sleep efficiency between the two groups. Percentage time spent in stage 1 NREM sleep was significantly higher in the RSV group ($P < 0.05$). Otherwise, the distribution of sleep stages was similar between the two groups. The RSV group had significantly higher obstructive Apnea-Hypopnea index (2.3 ± 1.9 vs. 0.6 ± 0.8 events/hour sleep in the control group; $P < 0.05$) as well as significantly higher respiratory arousal index (1.3 ± 1 vs. 0.1 ± 0.2 events/hour sleep; $P < 0.05$). There were no significant differences in other respiratory or sleep-related measures. There was no significant correlation between the severity of OSA in the RSV group and the age at the time of polysomnography.

DISCUSSION

The present study shows that OSA is more likely to occur among children with a history of significant RSV bronchiolitis during infancy.

TABLE 1—Demographic and Polysomnographic Characteristics of Children with Previous RSV Infection and Matched Controls

	RSV (n = 21)	Control (n = 63)	*P* value
Age (months)	59.9 ± 17.7	59.5 ± 8.6	NS
Gender (% males)	50	44	NS
African American (%)	14	16	NS
BMI z score	0.08 ± 1.1	0.1 ± 1	NS
Tonsil size	2.5 + 0.9	1.2 + 0.3	<0.01
TST (min)	459 ± 43	488 ± 45	NS
Sleep efficiency (%)	90 ± 6	91 ± 7	NS
NREM sleep (%TST)			
Stage 1	7.9 ± 6.6	4.9 ± 2.7	<0.05
Stage 2	43.1 ± 6.2	46.1 ± 7.0	NS
Stage 3 + 4	30.3 ± 6.3	28.4 ± 6.4	NS
REM sleep (%TST)	18.6 ± 3.9	19.3 ± 4.2	NS
OAHI (/hrTST)	2.3 ± 1.9	0.6 ± 0.8	<0.05
SpO_2 nadir (%)	91.7 ± 4.2	93.6 ± 3.8	NS
RAI (/hrTST)	1.3 ± 1	0.1 ± 0.2	<0.05
% $PETCO_2$ > 55 mmHg	0	0	NS

BMI z, body mass index z score; NS, not significant; TST, total sleep time; NREM, non rapid eye movement; REM, rapid eye movement; OAHI, obstructive apnea hypopnea index; SpO_2, oxygen saturation measured by pulse oxymetry; RAI, respiratory arousal index; $PETCO_2$, end tidal carbon dioxide tension.

Although the pathophysiological mechanisms underlying the causal etiology of OSA in children are not yet fully understood, it has become clear that AT hypertrophy play a significant role in the occurrence of pediatric OSA.[10,11] However, the specific factors mediating the proliferation of AT are unclear. Increasing evidence suggestive of the presence of inflammation in the upper airway of children and adults with OSA has recently emerged, whereby increased levels of nitric oxide, cytokines, prostaglandins, and 8-isoprostane have been detected in exhaled condensates from the upper airway of pediatric and adult patients with OSA.[34–37] Moreover, increased numbers of neutrophils as well as of bradykinin and vasointestinal peptide have also been measured in nasal lavage fluid from OSA patients.[38] Similarly, AT tissues harvested from OSA children exhibited increased expression levels of leukotriene receptors along with increased concentrations of leukotrienes,[39,40] even in urine.[41] Taken together, these reports would strongly support the contention of recruitment of inflammatory pathways within upper airway tissues in the context of OSA. The presence of abnormal varicose nerves in the soft palate and altered innervation of the upper airways in pediatric OSA further provide support for recruitment of inflammatory processes. Since these neural pathways play a protective role and assist in the preservation of patent upper airways, particularly during sleep,[42–45] it is likely that damage to these structures via inflammatory processes may account for the relatively weak correlation between AT size and OSA, along with the relatively high frequency of residual OSA following adenotonsillectomy.[46–49]

Increased expression of nerve growth factor (NGF) mRNA and its cognate receptor TrkA along with elevated concentrations of substance P and increased expression of neurokinin 1 (NK1) receptor occur in AT samples obtained from children with polysomnographically defined OSA, but not in children with recurrent tonsillitis.[16] These findings are strikingly reminiscent of the changes previously described as late immunomodulatory responses in the lung and associated with RSV infection. Neurogenic inflammation was distinctly induced in the lower airways of RSV-infected rats, long after the virus had cleared from their airways.[25] This inflammatory process appeared to be mediated by the heightened expression of the high affinity receptor for substance P (NK1 receptor).[24] Furthermore, RSV-infected respiratory tract was shown to induce the release of NGF and to lead to short-term and long-term changes in the distribution and reactivity of sensory nerves across the respiratory tract acting as a significant factor in the exaggerated inflammatory reactions during and after the acute infection.[50] Indeed, human infants ventilated in the context of acute RSV infection were found to express increased levels of neurotrophic factors including NGF as well as NK1receptors in bronchoalveolar lavage specimens, suggesting that the RSV infection-induced inflammatory processes are perpetuated and amplified via the activity of neurotrophic factors.[20]

The similarity between findings in lung tissues infected with RSV and the findings in the AT tissues from OSA children raised the possibility that these are 2 pathophysiologically-related processes. The present study lends further credence to this assumption and suggests that early

life RSV infection may trigger long-term alterations in the neuroimmunomodulatory pathways within AT tissues. These RSV-associated long-term alterations may then allow for exaggerated proliferative responses in these tissues occurring even several years after the acute RSV infection, particularly in the context of exposures to stimuli such as respiratory viruses, allergens, cigarette smoke, and biomass air pollutants. We should also emphasize that NK1 receptors in AT tissues of children with OSA are mostly localized within the germinal centers of the tonsils, further reinforcing the concept that increased NK1 receptor expression via heightened NGF activity may have occurred during early life, perhaps during infancy, when the likelihood to acquire RSV infection is greatest. However, we should not exclude the potential role played by other viruses, such as rhinoviruses, which exhibit some trophism toward adenoid tissues.[51]

Some methodological limitations merit comment. The current study involved a relatively small number of subjects and those subjects represent only a small proportion of all those children who were hospitalized for severe RSV infection during infancy. The main obstacle to the gathering of larger numbers of subjects was the relocation of many of the families to unknown addresses since their babies were hospitalized for RSV infection. Therefore, we cannot be completely certain that the current cohort is indeed representative of the initial candidate cohort of children who suffered from severe bronchiolitis. As a corollary to such limitations, corroboration of current findings will require a multicenter prospective trial that should then allow for additional analyses regarding the potential connection between RSV infection severity spectrum of disease and the risk for developing OSA later in life. Additionally, this study was not designed to assess the contribution of other factors that may promote the susceptibility to develop OSA in the context of RSV infection. Considering the high prevalence of RSV infection in the first year of life, as well as the relatively high prevalence of OSA in children, and the potential connection between the 2 conditions, it is tempting to speculate on the effect of palivizumab passive vaccination against RSV on the prevalence of OSA in children. Indeed, Piedimonte et al. demonstrated in animals that passive prophylaxis against RSV, using palivizumab prevented abnormal neurogenic inflammatory responses when palivizumab was administrated 24 hr prior to virus inoculation.[25]

In summary, the occurrence of a significant RSV infection early in life appears to be associated with substantial increases in the risk for developing OSA later in life. Based upon previous evidence, we postulate that early RSV infection leads to long-term alterations in the neuroimmunomodulatory pathways of the upper airways, particularly in AT tissues, and thus predisposes AT tissues to enhanced proliferative responses, thereby increasing the prevalence of pediatric OSA.

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