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Markers for severity of illness associated with decreased snoring in toddlers born ELGA

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Abstract

Aim—To describe the prevalence of paediatric sleep disordered breathing (SDB) symptoms in extremely low gestational age infants and identify neonatal risk factors, including early exposure to hypoxia and hyperoxia.

Methods—Patients <28 weeks gestation were monitored with high-resolution pulse oximetry. Hypoxia/hyperoxia variables were defined as percentage time of first 4 weeks of life that $\text{SaO}_2 < 80\%$ or $\text{SaO}_2 > 98\%$, respectively. Parents completed part of the OSA-18 questionnaire for symptoms of SDB at 18–22 months. Logistic regression was used to test the association between risk factors and sleep symptoms.

Results—Of 182 patients recruited, 138 (76%) completed the questionnaire. The mean gestation was 26 weeks, and mean birth weight 887 grams. Loud snoring (21%) and restless sleep (24%) were the most prevalent symptoms. Female sex was associated with an increased risk of loud snoring (OR, 2.7; CI, 1.13–6.5). Prolonged mechanical ventilation, necrotizing enterocolitis and prolonged caffeine use, however, were inversely correlated with loud snoring. Neither neonatal hypoxia nor hyperoxia were associated with sleep symptoms.

Conclusions—While the prevalence of sleep disordered breathing symptoms is similar to reported rates, we found a sex difference not previously reported. Interestingly, markers for severity of illness show a pattern of being protective against loud snoring.

Keywords

Snoring; Sleep disordered breathing; Prematurity

INTRODUCTION

Over the past decade, recognition of paediatric sleep disordered breathing (SDB) has increased with a current prevalence in the United States estimated to be 2–3% (1). Children with SDB have increased rates of apnoea, hypopnoea and hypoxia during sleep. Symptoms of SDB and its associated morbidities are thought to result from the prolonged repetition of these events (2). Complications of untreated paediatric SDB include poor neurocognitive development, cor pulmonale, failure to thrive, increased depressive symptoms and possibly cardiovascular disorders, such as hypertension, in adulthood (3,4).

Prematurity has consistently been demonstrated to be a risk factor for paediatric SDB. In 2003, a large U.S. cohort study, the Cleveland Children's Sleep and Health Study, found that at school age former preterm infants were found to be 3–5 times more likely to have SDB when compared to term born infants (5). Further, a Finnish cohort study found that in former low birth weight infants, this trend persisted into young adulthood (6). There is also evidence that indicates preterm infants are affected by the long-term neurocognitive effects of SDB to a greater degree than term children (7).

The aetiology of increased risk for SDB in preterm children remains unclear. Markers of severity of illness in the premature population have not been associated with risk for SDB (8, 9). One possible mechanism linking prematurity and SDB could be neonatal exposure to hypoxia or hyperoxia. Animal studies indicate that chronic intermittent hypoxia can influence or 'reset' the operation of peripheral chemoreceptors, such as carotid bodies, which mediate control of breathing (10). Evidence in human premature infants has also demonstrated an association between a history of bronchopulmonary dysplasia (BPD) and altered peripheral chemoreceptor activity (11).

This study aims to describe the prevalence of SDB symptoms at 18–22 months of age in a novel population of extremely low gestational age (ELGA) infants and to identify neonatal risk factors, including exposure to hypoxia or hyperoxia. We hypothesize that events from the newborn period have long-term effects on control of breathing which may be evident as early as late infancy.

PATIENTS AND METHODS

Study population

This is a prospective cohort study that recruited patients from Rainbow Babies and Children's Hospital NICU from June 2005 to April 2009. The major inclusion criteria were any inborn infant with GA 24–28 weeks. Any infants with a known congenital anomaly, airway anomaly or neuromuscular disorder were excluded.

There are two subcohorts in this study. The first is a group of patients recruited for the SUPPORT trial at Rainbow Babies and Children's Hospital (12). These infants were randomized to one of two arms: titration of inspired oxygen to a goal oxygen saturation (SaO_2) of either 85–89% or 91–95%. The second subcohort, recruited during the same period, consists of patients treated according to NICU guidelines at the time, a goal SaO_2 of 85–95%. Institutional IRB approval was obtained for the study, including a waiver of consent in regards to participation in the high-resolution pulse oximetry monitoring. Parents provided written consent prior to completing the questionnaire at the 18- to 22-month follow-up visit.

Pulse oximetry recording

All infants were monitored on a high-resolution pulse oximeter from birth to 8 weeks postnatal age or discharge. Pulse oximeters were set with a 2-sec sample rate and 2-sec averaging time (Radical; Masimo Corp., Irvine, CA, USA) to capture brief desaturation events because longer averaging rates may miss a good portion of volatility in saturations. For the SUPPORT subcohort, monitors were programmed so that caregivers remained blinded to goal SaO_2 range.

Hypoxia was defined as the total percentage time over the monitoring period that $\text{SaO}_2 < 80\%$. Hyperoxia was similarly defined with $\text{SaO}_2 > 98\%$. A parallel analysis was conducted to determine any association between symptoms of SDB and average number of desaturations per day. A single desaturation episode was defined as a period of ≥ 10 sec and

3min during which patient $\text{SaO}_2 < 80\%$. Analysis of saturation data was based on the first 4 weeks of life given the variation in quantity of data beyond 4 weeks due to varying lengths of hospital stay and an increasing attrition rate beyond this period. Only infants with $<10\%$ missing days of pulse oximetry monitoring during the first 4 weeks of life were included.

Neonatal characteristics

Baseline characteristics included birth weight, GA, race, sex and SNAPPE-II (Score for Neonatal Acute Physiology-Perinatal Extension-II) severity of illness score at 24 h of life (13). Neonatal characteristics were collected by chart review and included days and type of respiratory support and days of caffeine use. Number of days of each variable was converted into weeks by dividing by seven. Neonatal morbidities recorded included necrotizing enterocolitis (NEC) stage 2 by Bell's criteria, grade III–IV intraventricular haemorrhage (IVH), culture-proven sepsis and bronchopulmonary dysplasia (BPD) using the physiologic definition (14).

Sleep disordered breathing symptoms

To evaluate SDB symptoms in patients, parents were asked to complete a questionnaire at the 18-to 22-month follow-up visit. The questionnaire contained two domains (sleep disturbance and physical symptoms) of the *Obstructive Sleep Apnea Syndrome (OSAS) Quality of Life Survey* (OSA-18). The OSA-18 questionnaire has been validated in a group of 6-month-old to 12-year-old children (15). Each of the two domains consists of four questions. Question responses are based on a seven-point Likert scale which ranges from 'none of the time' to 'all of the time'. The two modules used include symptoms, such as snoring and physical activity during sleep, which are most highly associated with a diagnosis of SDB (9).

For analysis, we converted parent survey responses to a dichotomous variable. We designated a cut-point *a priori* with answers indicating a symptom at 'some of the time' or more frequently being positive and 'a little of the time' or less frequently being negative. Secondary sensitivity analyses using other cut-points were performed. Additionally, we assessed for differences in symptom distribution in SUPPORT and usual care subcohorts to test the appropriateness of pooling the subcohorts.

Statistics

The detectable difference calculation was based on a *t*-test using an estimated sample size of 63 per subcohort, an alpha of 0.05, and a power of 80%. This yielded a detectable difference of 0.7 of a standard deviation in percentage time spent in high or low oxygen saturation in children with and without dichotomized SDB symptoms.

Prevalence rates for the SDB symptoms queried were tabulated, and domain scores were determined. Logistic regression was used to test for the relationship between symptoms of SDB and candidate risk factors. Additional patient characteristics tested included length of hospital stay, smoking in the home and common morbidities. Fisher's exact test was used when an odds ratio could not be calculated by logistic regression. All analyses were performed using Stata, v.9.2 (College Station, TX, USA).

RESULTS

A total of 182 patients were initially recruited. Of 157 eligible survivors, 138 (87%) followed up and completed the questionnaire at 18–22 months (Fig. 1). Patient characteristics (Table 1) were notable for a median gestational age of 26 weeks and a

relatively high SNAPPE-II score. Of the symptoms of SDB queried, the most commonly reported were loud snoring and restless sleep (Table 1).

Female sex was the only candidate risk factor significantly positively associated with an increased risk of loud snoring. Caffeine weeks, ventilator weeks and length of hospital stay were inversely correlated with loud snoring (Table 2). Of the 14 patients with NEC, none reported loud snoring. None of the candidate risk factors were significantly associated with restless sleep.

When comparing the study population on the basis of sex, there was a statistically significant difference in gestational age ($p = 0.01$) with mean gestational age for females 26.4 weeks and 25.9 weeks for males. There was no difference in SNAPPE-II score or any of the neonatal characteristics based on sex.

There was no correlation between hypoxia and hyperoxia in the first 4 weeks of life and either snoring or restless sleep. Sensitivity analyses performed to determine the optimal cut-point for survey answers did not show a difference in results when a different cut-point was used. Additionally, there was no association with average number of desaturations per day (Table 2). *Post hoc* analyses showed there was no association between any candidate risk factors and SDB domain scores, nor any association between subcohort group and symptoms of SDB.

DISCUSSION

The prevalence of loud snoring (21%) in this novel population is commensurate with published estimates, while the rate of restless sleep is slightly higher (16). Our study corroborates the current literature that shows that traditional markers for severity of illness in the premature population are not risk factors for later SDB symptoms. Furthermore, our data suggest that greater severity of illness may be protective against SDB symptoms. Prolonged ventilation, caffeine use, NEC and length of hospital stay were all inversely associated with loud snoring. Interestingly, female sex was the only factor positively associated with an increased risk for symptoms of SDB.

Prior studies examining snoring in the prepubertal population demonstrate no sex differences (5, 6), while loud snoring in the postpubertal population has increased prevalence in males. One possible explanation is that socially, snoring in females tends to be less acceptable; therefore, parents may be more aware when it is present. However, this phenomenon has not been reported in other populations, and it is not clear why such a reporting bias would be specific to ELGA infants. Males in this population were 'sicker' with a mean SNAPPE-II score of 41, compared with 37 for females and, on average, had longer hospital stays (14.7 weeks for males, 13.5 weeks for females). These differences between sex groups suggest that the greater severity of illness maybe a contributing factor to the decreased rates of snoring in males, reinforcing the inverse relationship we see between severity of illness and loud snoring.

This is the first time that an inverse relationship between severity of illness markers and SDB symptoms has been seen. There is some evidence which allows us to speculate that a pathway mediated by peripheral chemoreceptors maybe implicated. A clinical study by Nock et al. (17) demonstrated an association between increased peripheral chemoreceptor activity and increased apnoeas in preterm infants. Studies by Katz–Salamon have shown that infants with BPD have decreased peripheral chemoreceptor activity (11). We hypothesize, therefore, that downregulation of excessive peripheral chemoreceptor activity could have a stabilizing effect resulting in fewer apnoeas and subsequently fewer symptoms of SDB, although the more recent data from this group do suggest delayed recovery of peripheral

chemosensitivity (18). Airway anatomy could possibly play a role as infants with prolonged intubation, common in ELGA infants, can develop a palatal groove or high-arched palate, which persists beyond childhood (19).

We also found an inverse association between length of caffeine exposure and loud snoring. A rat study by Montandon in 2009 demonstrated that neonatal exposure to caffeine resulted in altered respiratory control both while awake and during sleep which persisted into rat adulthood (20). Interestingly, caffeine-exposed rats demonstrated an increase in baseline ventilation during sleep and wake cycles, as well as a disturbed sleep structure. If we extrapolate to our population, this suggests that caffeine could be a potential mediator that decreases symptoms of SDB by increasing baseline ventilation. However, the Caffeine for Apnea of Prematurity Group demonstrated that premature infants who received caffeine therapy had lower rates of BPD and decreased duration of mechanical ventilation (21). Based on this, we would expect that these infants would be at increased risk of loud snoring and that caffeine should not be protective against loud snoring. Our study is too small to tease apart the inter-relationship among lung disease, caffeine use and subsequent loud snoring.

The primary limitation to this study is that it measures the symptoms of SDB and does not make a polysomnographic diagnosis of SDB. At the time of this study, the OSA-18 was gaining increasing acceptance as a diagnostic tool to identify patients with paediatric SDB. A study by Constantin et al. (22) suggests that it may have low diagnostic sensitivity when compared with a pulse oximetry study; however, it does not compare it to overnight polysomnography, the current gold standard. Unfortunately, the OSA-18 is the only survey that included the age of our target population in its validation study. As with any survey, there is the potential for reporter misclassification, and we had no way to account for accuracy of parental reporting. Given the severity of illness in this study population, we would expect parents to be more likely to report symptoms, but our prevalence rates are similar to current literature. While we have shown no relationship between early hypoxia/hyperoxia/desaturations and SDB symptoms, this does not exclude the possibility that certain patterns of desaturation and resaturation may be associated with SDB.

This is the first study to look at symptoms of SDB at 18–22 months specifically in the ELGA population. Our results confirmed previous findings that traditional markers of severity of illness are not risk factors for SDB. Furthermore, this study extends these findings by identifying an inverse association between these markers and SDB and by identifying female sex as a novel risk factor. The results underscore that clinical vigilance for SDB remains important in all preterm infants and not just the traditionally high risk population.

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Key notes

- Among infants born ELGA, loud snoring and restless sleep are the most commonly reported SDB symptoms.
- Neonatal markers for severity of illness are not risk factors for SDB symptoms and, actually, may confer a protective effect.
- Surprisingly, female sex is a risk factor in this population. While the mechanisms underlying these associations are unclear, clinicians should remain vigilant for SDB symptoms in all preterm infants, regardless of neonatal course.

Figure 1.
Diagram of patient flow.

Table 1

Patient Characteristics

	50th percentile	(25th, 75th percentiles)	Prevalence (%)
Demographics			
Gestational Age (weeks)	26	(25,27)	Black 57 White 43
Birth weight (gms)	16	(710, 950)	Female 50
Percentage time SaO ₂ < 80%	5	(3, 8)	BPD 33
Percentage time SaO ₂ > 98%	16	(9, 29)	NEC 10
SNAPPE-II score	41	(25, 51)	Grade III-IV IVH 8
Length of hospital stay (days)	89	(71, 115)	Culture-proven sepsis 25
Prevalence of SDB symptoms			
Sleep Disturbance			
Loud snoring		21%	
Breath holding spells		5%	
Choking/Gasping in sleep		5%	
Restless sleep		24%	
Physical Symptoms			
Mouth breathing		17%	
Frequent colds		13%	
Nasal discharge		28%	
Difficulty swallowing		7%	

Table 2

Candidate risk factors for loud snoring

Risk factor	Odds ratio	95% Confidence interval	p Value
Percentage time SaO ₂ < 80% in first 4 weeks of life	0.93	0.82–1.05	0.276
Percentage time SaO ₂ > 98% in first 4 weeks of life	1.01	0.99–1.04	0.171
Average no. of desaturations per day in first 4 weeks of life	0.99	0.97–1	0.058
Caffeine weeks	0.83	0.7–0.99	0.047
Hospital weeks	0.9	0.97–1	0.051
Female sex	2.7	1.13–6.5	0.025
Ventilator weeks	0.74	0.59–0.93	0.011
BPD	0.46	0.18–1.24	0.129