Symptoms of Sleep Disordered Breathing in Children with Craniofacial Malformations

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Study Objective: The purpose of this study was to investigate the frequency of sleep disordered breathing (SDB) symptoms in a clinical sample of children with congenital craniofacial malformations (CFM) followed at a tertiary medical center and non-selected for sleep problems.

Methods: Cross-sectional study of 575 children aged 2-18 years followed at the Craniofacial Anomalies Program between March 2007 and May 2011. The Sleep-Related Breathing Disturbance scale of the Pediatric Sleep Questionnaire was used to screen for SDB, snoring, and sleepiness. A cutoff value ≥ 0.33 of the total answered questions identified children with positive screening for SDB symptoms.

Results: Overall, 25% of children screened positive for SDB, 28% for snoring, and 20% for sleepiness. In children with non-syndromic CFM, those with Robin sequence had the highest frequency of SDB, snoring, and sleepiness (43%, 44%, and 38%, respectively). In children with syndromic CFM, velocardiofacial/DiGeorge syndrome had the highest frequency of SDB and

sleepiness (48% and 43%, respectively). Children with Treacher Collins had the highest frequency of snoring (83%). The presence of cleft palate was not associated with an increased frequency of SDB symptoms. Nevertheless, children with syndromic CFM, compared to those with non-syndromic CFM, had a higher SDB score (0.27 ± 0.21 vs. 0.21 ± 0.19 , $p = 0.003$) and were more likely to have sleepiness (26% vs. 18%, $p = 0.05$).

Conclusions: Congenital craniofacial malformations in children are associated with high risk for SDB symptoms. Our findings should encourage a high index of suspicion for SDB in children with CFM, with a low threshold for further testing and close follow-up.

Keywords: Snoring, sleepiness, sleep-disordered breathing, cleft, craniofacial anomalies

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Sleep disordered breathing (SDB), a common condition in childhood, encompasses a range of breathing disorders during sleep, from habitual snoring at one end of the spectrum to obstructive sleep apnea at the other. The latter is characterized by recurrent episodes of upper airway obstruction during sleep that causes arousals, intermittent hypoxemia, and disruption of normal ventilation. In typically developing children, up to 4% have obstructive sleep apnea based on polysomnography and a much larger proportion—approximately 11%—have habitual snoring based on parental report,¹ with obesity being a major risk factor.² However, the prevalence of SDB varies widely depending on the severity and diagnostic method employed. Moreover, it is well known that untreated SDB of even mild forms is associated with significant comorbidity, such as neurobehavioral problems and cardiovascular dysfunction.³⁻⁶

Craniofacial malformations (CFM) include a heterogeneous but highly prevalent group of congenital anomalies. It is estimated that 1 in 700 newborns in the United States has cleft palate (CP), while 1 in every 1,600 have other CFM.⁷ Data from small clinical studies of children with specific syndromes or retrospective reviews of clinical data suggest that children with cleft palate and other CFM have increased risk for SDB.⁸⁻¹¹ The obstruction of the upper airway during sleep in children with CFM is likely multifactorial.¹² The reduced dimensions of the

BRIEF SUMMARY

Current Knowledge/Study Rationale: It is suspected that children with congenital craniofacial malformations (CFM) are at high risk for sleep disordered breathing (SDB) compared to typically developing children. However there is a lack of data regarding the frequency of SDB symptoms across different types of CFM. Thus this study investigated the pattern of SDB symptoms in a large sample of children with CFM who were unselected for sleep problems.

Study Impact: The frequency of SDB symptoms in all children with CFM was found to be high but varied widely depending on the craniofacial anomaly; notably almost half of children with Robin sequence and velocardiofacial/DiGeorge syndrome screened positive for SDB. The presence of obesity or cleft palate repair did not appear to affect the frequency of SDB symptoms. Clinical sleep evaluation should be considered in all children with craniofacial anomalies, particularly in those children with conditions such as Robin sequence or velocardiofacial syndrome.

airway¹³ and some anatomical features such as macroglossia, mandibular hypoplasia, or oropharyngeal hypotonia contribute to increased upper airway resistance.^{12,14} Furthermore, concern has been raised that palatal operations may lead to obstruction of the airway.¹⁵⁻¹⁷ Nevertheless, a recent study found that infants with CP have a high prevalence of SDB even before repair surgery.¹⁸ Despite small objective studies in children with CFM referred for sleep evaluation, there is a lack of data regarding

the frequency of SDB symptoms in a general population of children with CFM. Therefore, the purpose of this study was to investigate the frequency of SDB symptoms, using a validated screening tool, in a large pediatric population with a range of congenital CFM followed at a tertiary medical center.

METHODS

Participants

All children with craniofacial anomalies referred to the Craniofacial Anomalies Program at the University of Michigan since March 2007 have been routinely screened for SDB symptoms. Children aged between 2-18 years with congenital syndromic and non-syndromic CFM who attended the Craniofacial Anomalies Program between March 2007 and May 2011 were included in this study. Children younger than 2 or older than 18 years old, with acquired craniofacial anomalies due to traumatic events, or with other major medical problems were excluded. Since families follow up on an annual basis, in cases of duplicated screening, the first visit with completed data was selected. In order to avoid selection and spectrum bias, all the children with congenital CFM follow during this period and non-selected by sleep problems were included. This study was approved by the University of Michigan Institutional Review Board.

Measurements

As part of routine clinical care, parents complete the sleep-related breathing disturbance scale of the Pediatric Sleep Questionnaire,¹⁹ a widely used tool to screen for SDB in children aged 2-18 years. The sleep-related breathing disturbance scale contains 22 items that ask about symptoms of SDB, such as snoring, apneas, nocturnal breathing, daytime sleepiness, or inattention/hyperactivity. This scale includes a 4-item snoring subscale and a 4-item sleepiness subscale. Choices for each response are “yes,” “no,” or “don’t know.” A threshold score ≥ 0.33 identifies children with a positive screening for SDB, snoring and/or sleepiness.

Data extracted from medical records included gender, age, ethnic background, weight, height, and diagnosis. Body mass index ($\text{BMI} = \text{weight (kg)} / \text{height (m)}^2$) was calculated, and BMI percentile adjusted for age and gender was used to define BMI status. The study population was divided into 3 weight groups according to the cutoff points recommended by the American Academy of Pediatrics and the Center for Disease Control and prevention²⁰: underweight ($\text{BMI} < 5\text{th percentile}$), normal weight ($\text{BMI} \geq 5\text{th percentile}$ and $< 85\text{th percentile}$), and overweight/obese ($\text{BMI} \geq 85\text{th percentile}$). The study population was also categorized into 3 age groups: toddlers/preschoolers (2.0-4.9 years), school-aged (5.0-11.9 years), and adolescents (12.0-18.9 years).

In addition to the craniofacial anomaly diagnosis, the presence or absence of CP was also recorded in each case. The study population was divided into 2 main groups according to the characteristics of the congenital anomaly: syndromic or non-syndromic CFM. The term “syndromic” was restricted to those cases with orofacial anomalies that occur with other non-orofacial anomalies, and the term “non-syndromic” was used to define isolated orofacial anomalies. The non-syndromic

orofacial cleft is the most common CFM. Children with Robin sequence are typically considered in the non-syndromic group.

Statistical Analysis

The frequency of demographic and anthropometric characteristics of the study population was examined for outliers. Data were summarized using means ($\pm$ standard deviation) for continuous variables and counts and percentages for categorical variables. T-tests were conducted on continuous variables, and χ^2 analyses were used to examine bivariate differences in frequency of SDB symptoms for categorical variables such as gender (males vs. females), BMI groups (normal weight vs. overweight/obese), and type of craniofacial anomalies (syndromic vs. non-syndromic and CP vs. no CP). All analyses were conducted using SPSS 19.0 (IBM, Armonk, NY), and differences were considered statistically significant with a $p\text{-value} < 0.05$.

RESULTS

In total, 1,116 parent-reported questionnaires were completed, comprising 650 children, but only 575 met inclusion criteria. Therefore, the final sample size was $n = 575$. The mean age was 8.25 ± 4.64 years, 57% were boys, 24% were overweight/obese, and 82% were Caucasian. Four hundred thirty-six children (76%) had non-syndromic CFM. Of these, 76% had CP compared to only 23% in the subgroup of children with syndromic CFM ($p = 0.001$). **Table 1** summarizes characteristics of the study population.

Sleep-Related Breathing Disturbance Scale

Overall, 25% of children screened positive for SDB. More boys screened positive for SDB than did girls, however this did not quite reach statistical significance (28% vs. 21%, $p = 0.06$). School age children were more likely to screen positive for SDB than toddlers/preschoolers (29% vs. 18%, $p = 0.02$). Adolescents appeared more likely to screen positive for SDB than toddlers/preschoolers, but this did not reach significance (27% vs. 18%, $p = 0.08$). Interestingly, there were no differences in the frequency of positive screening for SDB among the BMI groups (22% of underweight children, 25% of normal weight, and 25% of overweight/obese, $p = 0.91$). African American and Caucasian children were equally likely to screen positive for SDB (29% vs. 25%, $p = 0.80$), and Asian children were least likely to screen positive (15%). However, these differences were not significant (29% in African-American vs. 15% in Asian [$p = 0.21$] and 25% in Caucasian vs. 15% in Asian [$p = 0.13$], respectively).

Neither syndromes nor CP were associated with an increased frequency of SDB (30% vs. 23% [$p = 0.12$] and 25% vs. 24%, [$p = 0.76$], respectively; **Figure 1**). Nevertheless, the mean SDB score was higher in children with syndromic CFM than children with non-syndromic CFM (0.27 ± 0.21 vs. 0.21 ± 0.19 , $p = 0.003$). Of the 436 children with non-syndromic CFM, those who had Robin sequence had the highest frequency of positive screening for SDB (43%), while those with isolated cleft lip had the lowest (17%). In the subgroup of children with syndromic CFM ($n = 139$), the highest risk for SDB was found in children with velocardiofacial/DiGeorge syndrome

Table 1—Characteristics of the study population

	All (n = 575)	Positive screening for SDB (n = 144)	Negative screening for SDB (n = 431)
Age (mean $\pm$ SD)	8.25 $\pm$ 4.64	8.66 $\pm$ 4.56	8.12 $\pm$ 4.67
BMI percentile	54.17 $\pm$ 32.01	56.05 $\pm$ 31.81	53.54 $\pm$ 32.09
Boys	57%	64%	55%
Race			
Caucasian	471 (82%)	120 (25%)	351 (75%)
African American	21 (4%)	6 (29%)	15 (71%)
Asian	52 (9%)	8 (15%)	44 (85%)
Other	31 (5%)	10 (32%)	21 (68%)
Non-syndromic CFM	(N = 436)	(N = 102)	(N = 334)
CL	77 (18%)	13 (17%)	64 (83%)
CLP	223 (51%)	47 (21%)	176 (79%)
CP	73 (17%)	17 (23%)	56 (77%)
Robin sequence	37 (8%)	16 (43%)	21 (57%)
Craniosynostosis	20 (5%)	7 (35%)	13 (65%)
Others (n < 6 for any non-syndromic CFM)	6 (1%)	2 (68%)	4 (32%)
Syndromic CFM	(N = 139)	(N = 42)	(N = 97)
VCF/DiGeorge syndrome	21 (15%)	10 (48%)	11 (52%)
Hemifacial microsomia	18 (13%)	5 (28%)	13 (72%)
Goldenhar	18 (13%)	4 (22%)	14 (78%)
Treacher Collins	6 (4%)	2 (33%)	4 (67%)
CHARGE	6 (4%)	1 (17%)	5 (83%)
Syndromic craniosynostosis	28 (20%)	9 (32%)	19 (68%)
Crouzon	8 (6%)	2 (25%)	6 (75%)
Apert	7 (5%)	3 (43%)	4 (57%)
Pfeiffer	6 (4%)	1 (17%)	5 (83%)
Other syndromic craniosynostosis	7 (5%)	3 (43%)	4 (57%)
n < 6 (Saethre-Chotzen n = 4; Kleeblattschädel, n = 1; Muenke, n = 1; Sphrintzen-Goldberg, n = 1)			
Others (n < 6 for any syndromic CFM)	42 (30%)	11 (26%)	31 (74%)

CFM, craniofacial malformations; CL, cleft lip; CLP, cleft lip and palate; CP, cleft palate; VCF, velocardiofacial syndrome. In the non-syndromic group others included children with: ear microtia (n = 3), frontonasal dysplasia (n = 1), hypoplastic jaw and microtia (n = 1), and macrostomia (n = 1). In the syndromic group other children with: Nager (n = 5), VATER/VACTERL (n = 4), Van der Woude (n = 3), Stickler (n = 3), Beckwith Wiedemann (n = 2), brachio-oto-renal (n = 2), Kabuki (n = 2), medial cleft face (n = 2), Oro-facial-digital (n = 2), Anderson-Tawil (n = 1), Brachio-oculo-facial (n = 1), Cerebro-oculo-facial (n = 1), Cornelia de Lange (n = 1), Down (n = 1), Dubowitz (n = 1), Hallermann Streiff (n = 1), Klippel Feil (n = 1), Larsen (n = 1), Moebius (n = 1), Occulo-facio-cardio-digital (n = 1), Oto-palato-digital (n = 1), Pallister-Killian (n = 1), Parry Romberg (n = 1), popliteal pterygium (n = 1), Simpson-Golabi-Behmel (n = 1), and Smith-Lemli-Opitz (n = 1) syndrome.

(48%) and Apert syndrome (43%), compared to children with CHARGE syndrome and Pfeiffer craniosynostosis who had the lowest (17%). **Figure 2** summarizes the frequency of positive screening for SDB according to the craniofacial anomaly diagnosis.

Since the SRBD subscale comprises two main components (snoring and sleepiness) and each component can be scored independently, we also analyzed these two components separately (see below).

Snoring Subscale

Overall, 28% of children screened positive for snoring. There were no statistically significant differences between snoring frequency among boys and girls (27% vs. 30%, $p = 0.45$), neither between race groups (Caucasian 28%, Asian 23%, African American 38%, $p = 0.56$). Interestingly, underweight children tended to screen positive for snoring more frequently than normal weight and overweight/obese children, but these

differences were not statistically significant (underweight 40%, normal weight 27%, overweight/obese 26%, $p = 0.13$). School-age children were more likely to screen positive for snoring than toddlers/preschoolers (33% vs. 22%, $p = 0.02$).

A similar frequency of positive screening for snoring was found between children with and without syndromes (28% vs. 28%, $p = 0.91$) and with and without CP (29% vs. 25%, $p = 0.33$). The presence of overweight/obesity did not change these findings. In children with and without syndromes, normal weight and overweight/obese children were equally likely to screen positive for snoring (27% vs. 34%, $p = 0.50$ for syndromes, and 27% vs. 23%, $p = 0.50$ for non-syndromes). Similarly, in children with and without CP there were no differences in the frequency of positive screening for snoring between normal weight and overweight/obese children (27% vs. 30%, $p = 0.66$ for CP, and 27% vs. 21%, $p = 0.38$ for no CP).

In the group of children with non-syndromic CFM, those with Robin sequence had the highest frequency of positive screening

for snoring (44%) and children with cleft lip had the lowest (19%). In the group of children with syndromic CFM, those with Treacher Collins syndrome had the highest frequency of positive screening for snoring (83%) and those with velocardio-facial/DiGeorge syndrome had the lowest (14%).

Sleepiness Subscale

Overall, 20% of children screened positive for sleepiness. Daytime sleepiness in children with CFM increased significantly between age groups, from 11% in the toddlers/preschoolers to 21% in school-age children and to 29% in adolescents ($p = 0.0001$). Caucasian race was associated with an increased frequency of positive screening for sleepiness compared to Asian children (21% vs. 4%, $p = 0.001$), but no differences were found between daytime sleepiness in African

American children and Asian children (14% vs. 4%, $p = 0.14$). Similarly, there were no differences in sleepiness between boys and girls (21% vs. 19%, $p = 0.60$) or between BMI groups (20% in underweight children, 20% in normal weight, and 19% in overweight/obese, $p = 0.94$).

Children with syndromic CFM were more likely to have daytime sleepiness than children with non-syndromic CFM (26% vs. 18%, $p = 0.05$). Nevertheless, the presence of CP was not associated with a higher frequency of daytime sleepiness (19% vs. 21%, $p = 0.66$).

In the group of children with non-syndromic CFM, those with Robin sequence had the highest frequency of sleepiness (38%) and those with CP had the lowest (12%). In the group of children with syndromic CFM, those children with velocardio-facial/DiGeorge and Crouzon syndromes had the highest frequency of daytime sleepiness (43% and 37%, respectively), while children with Apert and CHARGE syndromes did not report sleepiness (0%).

Figure 1—Frequency of positive screening for SDB according to the presence or absence of CP and the presence or absence of syndrome.

DISCUSSION

This study demonstrates a high frequency of SDB symptoms in children with CFM who were non-selected for sleep problems, irrespective of obesity. Notably, the risk for SDB in this population may be up to 9 times higher than typically developing children who present to clinic for immunizations or well-child care.²¹ The frequency of SDB in children with CFM can vary widely depending on the craniofacial anomaly, from less than 18% in children with isolated cleft lip, CHARGE, or Pfeiffer syndromes to 43% to 48% in children with Robin sequence, velocardio-facial/DiGeorge syndrome, and Apert syndrome. Given these high frequencies and the known associations between SDB and significant long-term morbidity (including behavioral problems,

Figure 2—Frequency of positive screening for SDB according to the craniofacial diagnosis.

learning difficulties, poor school performance, cardiovascular dysfunction, impaired quality of life, and depressive symptoms),²²⁻²⁷ all of which may improve when SDB is treated,^{25,28} routine screening of children with CFM may be warranted.

In contrast to typically developing children, it appears that BMI in this pediatric population was not associated with SDB symptoms. It has been previously documented in children without CFM that nocturnal obstruction is often due to obesity or increased tonsil size relative to the airway size.^{2,29} However, recent studies also show that craniofacial and pharyngeal airway morphology may play a role in the presence, severity, and treatment of SDB in typically developing children.^{30,31} In children with CFM, the pathophysiology of SDB is more complex. Indeed, while anatomical factors such as craniofacial morphology may be considered additional risk factors in general pediatric populations, in children with CFM they play a significant role in the pathophysiology of SDB. A previous study conducted in children with cleft suggested that dimensions of the airway more closely resemble those of typically developing children with obstructive apnea.¹³ Moreover, other anatomical features may play a role in SDB in this pediatric population such as macroglossia, skeletal anomalies (such as micrognathia in children with Robin sequence), or mid-face anomalies (e.g., in children with hemifacial microsomia). Therefore, the relationship between obesity and SDB in pediatric populations with CFM may be smaller due to the presence of significant additional anatomical risk factors compared to the typically developing population.

Recent studies have found that snoring and SDB symptoms in general are frequently reported in children with a repaired CP. However, many of these studies have focused mainly on children with only CP, and few of them were prospective. For example, one large retrospective medical record review of 529 children with cleft found a high frequency (22%) of SDB symptoms on review of clinical history.¹¹ In another chart review study of 459 non-syndromic children, 37.5% of children had a clinical history consistent with SDB symptoms.¹⁰ Neither of these studies used a validated instrument. In one population-based study of SDB and craniofacial anomalies, medical codes were used to identify diagnoses of obstructive sleep apnea in Washington state.³² This was then cross-checked with congenital anomaly information from birth records. While a large number of children were found to have a diagnosis of obstructive sleep apnea ($n = 1,203$), only 57 children with cleft were identified and other CFM were grouped together as “any craniofacial anomaly.” Thus, large, symptom-based screening of SDB is lacking in the CFM population. Furthermore, in children with CFM concern has been raised that palatal operations may lead to upper airway obstruction.^{15-17,33-39} In small objective studies of CP children post-surgery, the frequency of obstructive sleep apnea varies widely (10% to 93%). Thus, the true impact of palatal surgery on sleep measures is not yet clearly understood.

Daytime sleepiness is a common manifestation of SDB in adults yet has been considered infrequent in pediatric SDB despite a high prevalence of sleepiness-related behavioral manifestations in children. To our knowledge, only one previous study has reported on daytime sleepiness in children with cleft. In small study of 32 children with cleft lip and palate,⁴⁰ daytime sleepiness was assessed on an 8-point scale (with a score of 1 being very sleepy) and the mean score was approximately 6, depending

on the age group, suggesting that sleepiness was not common. In the present study, daytime sleepiness was present in 20% of children with CFM and was associated with age, race, and the presence of syndromes. A previous study by our group found that the frequency of daytime sleepiness, using the same validated questionnaire, was 12% in children attending well-child visits,²¹ suggesting that sleepiness may be higher in children with cleft. Whether this is related to underlying SDB or part of the neuro-developmental spectrum of these children is currently unknown.

Several studies suggest that children with repaired CP and other CFM are at risk for problematic behaviors and scholastic underachievement. In a small study of 23 children aged 5-7 years who had CFM, 18% of children had parent or teacher reports of externalizing problems in the clinical range.⁴¹ Data from the 1970s suggest that children with CP repair, in comparison to controls, are more likely to be delayed in starting school (31% vs. 16%), and in grade placement (43% vs. 20%).⁴² Despite the high prevalence of positive screening for SDB as well as behavioral difficulties, children with CFM are infrequently referred to the sleep clinic. This is likely for several reasons including the presence of other major medical problems that take precedence and the lack of parental as well as healthcare provider awareness regarding the impact of SDB on pediatric outcomes. Given the known associations between SDB, learning, and behavior, future studies should investigate whether SDB plays a role in the behavioral difficulties often observed in this population. Regardless, it would seem pertinent for children with cleft to be investigated for unrecognized SDB.

The major strengths of this study include the large sample size, and routine SDB screening in the Craniofacial Anomalies Clinic which allowed prospective investigation of the frequency of SDB symptoms using a validated tool, in a pediatric population non-selected for sleep problems. In addition, as a tertiary referral center, we were able to include a relatively large number of children with uncommon CFM infrequently seen in other clinics. Despite these strengths, there are several limitations. First, the lack of differences in SDB symptom frequency between races should be interpreted with caution. In typically developing children, African Americans have a higher SDB risk than Caucasians. It is possible that the limited number of African American children in the present study could explain the lack of differences between races. Secondly, while a validated screening tool was used, no SDB screening tool has been validated in this particular population. We did not perform objective sleep measures, such as nocturnal polysomnography, as this was cost-prohibitive in such a large sample. While other small studies of clinically referred CFM children have used polysomnography, sample sizes were very small; approximately 2-15 children depending on the CFM.^{8,9} In addition, polysomnography, the gold-standard for SDB diagnosis, is not always easily accessible. However, the goal of the present study was to provide SDB screening information on a heterogeneous population that is typical of large craniofacial anomalies programs, and which could provide clinically useful information that could be used by the treating physician for further decision making. From a clinical perspective, it is important to be able to screen patients, and refer those at highest risk.

In conclusion, SDB symptoms are common in pediatric populations with congenital craniofacial anomalies, particularly

in children with specific conditions such as Robin sequence and syndromes. Given our findings, we suggest that children with CFM should be routinely screened for symptoms of SDB.

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