

Comorbidities in Infants with Obstructive Sleep Apnea

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Study Objective: The clinical characteristics of obstructive sleep apnea (OSA) in infants have been insufficiently characterized. Our aim was to describe identifiable comorbidities in infants with obstructive sleep apnea, which may assist in recognizing these patients earlier in their disease course and help improve management.

Methods: This was a single-center, retrospective study involving infants 0-17 months of age with a diagnosis of OSA on the basis of clinical features and nocturnal polysomnography (PSG) at the Mayo Clinic Center for Sleep Medicine between 2000 and 2011. Patients were excluded if they had central apnea accounting for greater than 50% of respiratory events. OSA severity was determined by the apnea-hypopnea index (AHI).

Results: One hundred thirty-nine patients were included. Based upon the AHI, they were subdivided into mild (AHI < 5; 30%), moderate (AHI 5-9; 30%), or severe (AHI > 10; 40%) categories. Comorbidities included gastroesophageal reflux in 95/139 (68%), periodic limb movements in sleep in

59/139 (42%), craniofacial abnormalities in 52/139 (37%), neuromuscular abnormalities in 47/139 (34%), prematurity in 41/139 (29%), genetic syndromes in 41/139 (29%), laryngomalacia/tracheomalacia in 38/139 (27%), and epilepsy in 23/139 (17%) of subjects. Severity of OSA correlated with prematurity, having a genetic syndrome, or neuromuscular abnormality. Multispecialty evaluation was needed for 119/139 (86%).

Conclusion: Comorbidities in infants with OSA differ from those of older children. Based upon the comorbidities identified in our study population, it appears that appropriate management of infants with OSA requires a multidisciplinary approach involving genetics, gastroenterology, pulmonology, otolaryngology, neurology, and general pediatrics.

Keywords: infant, obstructive sleep apnea, polysomnography, sleep disorders, sleep disordered breathing

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Infants experience a wide range of sleep disordered breathing patterns, such as apparent life threatening episodes, apnea of prematurity, central apnea, and obstructive sleep apnea (OSA). There is limited information available about OSA in this age group.¹ OSA is defined as recurrent episodes of complete or partial upper airway obstruction, disrupting normal ventilation and sleep continuity.¹ It is diagnosed on the basis of clinical history, physical examination, and nocturnal polysomnography. If unrecognized and untreated, it can lead to serious complications.¹⁻⁷

Besides anatomical and physiological predisposition towards airway obstruction, congenital abnormalities of the airway and factors like gastroesophageal reflux are not uncommon in this age group.¹ The Cleveland Children's Sleep and Health Study (CCSHS) demonstrated that children born prematurely had a 3-fold increase in the odds for childhood sleep disordered breathing (SDB) compared with their full-term peers.² Furthermore, the association between SDB and childhood cognitive impairment is stronger in preterm than term infants.³

In children, besides impairment of cognition, attention and executive functions, SDB has also been linked to growth retardation and cor pulmonale.⁴⁻⁷ These severe sequelae can be avoided with early diagnosis, especially as a growing body of evidence exists that treatment may improve quality of life and neurocognitive function.⁸

Our aim was to identify significant comorbidities in infants with OSA, which may facilitate early suspicion, definitive

BRIEF SUMMARY

Current Knowledge/Study Rationale: The clinical characteristics of obstructive sleep apnea (OSA) in infants have been insufficiently characterized. Our aim was to describe identifiable comorbidities in infants with OSA, which may assist in recognizing these patients earlier in their disease course and help improve management.

Study Impact: Obstructive sleep apnea in infants is associated with different multisystem comorbidities than older children. A multidisciplinary approach is recommended for effective management of infant OSA.

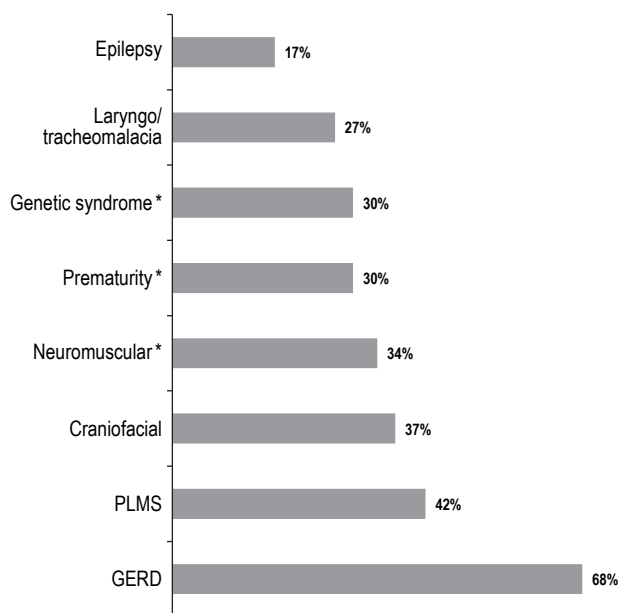
diagnosis, and comprehensive management of this disorder in infancy.

METHODS

This was a single-center, retrospective study of infants 0-17 months of age with OSA. The diagnosis was based on a combination of clinical features and nocturnal polysomnography at Mayo Clinic Center for Sleep Medicine between 2000 and 2011.

In this time period, 238 infants in the 0- to 17-month age range underwent comprehensive sleep consultation, including PSG. Patients were excluded if they had central apnea accounting for > 50% of apneas, leaving us with 139 patients. Electronic records of these patients were reviewed for demographic and clinical characteristics. Apnea severity was determined by the AHI—an index ≥ 10 was considered severe, 5-9 moderate, and < 5 mild OSA. Periodic limb movements (PLMs)

Figure 1—Comorbidities in infants with OSA.



* Comorbidities correlated to OSA severity

were identified using the American Academy of Sleep Medicine (AASM) Manual for the Scoring of Sleep and Associated Events (2013). OSA and PLMs diagnostic criteria were unchanged during the study period.

Data pertaining to patient demographics, clinical characteristics, and patient outcomes were gathered. Length and weight information was extracted from notations made at the time of the sleep center visit. All patients were evaluated by a certified sleep specialist (SK or RL). Important associated diagnoses were identified, including prematurity, epilepsy (these patients were excluded if the seizures contributed to > 50% of the apneas recorded), laryngomalacia and tracheomalacia, neuromuscular dysfunction (such as hypotonia), gastroesophageal reflux, periodic limb movements in sleep, and craniofacial abnormalities (Figure 1). Patients needing multidisciplinary evaluation were identified. Multidisciplinary evaluation was defined arbitrarily as the need for ≥ 3 types of subspecialists.

Statistically significant comorbidities (Figure 1) were identified utilizing the Cochran-Armitage test for trend using the JMP statistical software package (Version 9, SAS Institute Inc, Cary, NC).

RESULTS

There were 238 infants 0-17 months of age with obstructive sleep apnea. Of these 238 infants, 99 were excluded owing to central apnea accounting for ≥ 50% of the AHI. The remaining 139 subjects constituted the study population. Infant characteristics, including demographics are shown in Table 1. The presenting symptoms are summarized in Figure 2.

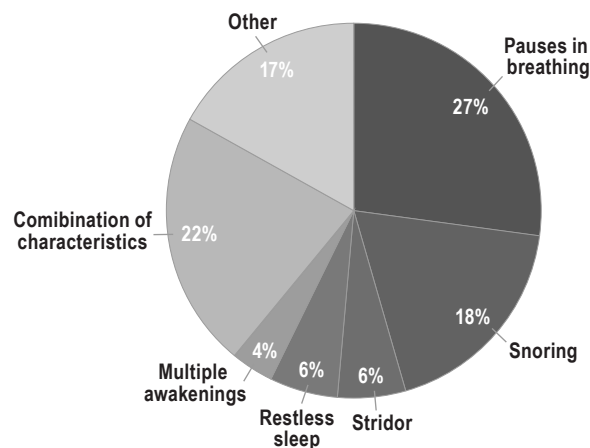
On the basis of AHI, patients were diagnosed with mild 42/139 (30%), moderate 42/139 (30%), or severe 55/139 (40%) OSA. The mean AHI was 16 (SD ± 18). Mean weight

Table 1—Participant demographics (N = 139).

	N	%
Male	84	60
Term	98	70
Caucasian	108	78*
	Mean	SD
Weight % at presentation	32	32
Above 90 th percentile	8%	
Below 3 rd percentile	33%	
Mean age at PSG (months)	9.5	5.4

* African American 3%, Hispanic 8%, and others 11%.

Figure 2—Presenting symptoms.



percentiles at presentation were 45%, 34%, and 21% for infants with mild, moderate, and severe OSA, respectively. Of 46/139 (33%) patients with weight percentile at presentation ≤ 3%, 29/46 had severe OSA (53%, 95% CI 48% to 77%, p-value < 0.0001). Multispecialty evaluation was needed for 119/139 (86%) patients. These subspecialties included pulmonology when intrinsic airway disease was identified, gastroenterology and endocrinology for failure to thrive, neurology for management of epilepsy and genetic syndromes, and otolaryngology for structural airway disease.

There were 41/139 (29%) premature infants with a diagnosis of OSA; of these 41 infants, 23/41 (56%) had severe OSA (OR 2.6, 95% CI 1.25-5.63, p = 0.01). Of 41/139 (29%) infants with a known genetic syndrome, 22/41 (54%) had severe OSA (OR 2.28, 95% CI 1.09-4.84, p = 0.0290). The most commonly seen genetic syndrome was Trisomy 21 in 12/41 (30%). Others were achondroplasia, Prader-Willi syndrome, Pierre Robin sequence, Crouzon syndrome, De Lange syndrome, mitochondrial disorder, otopalatodigital syndrome, and Joubert syndrome. Of 47/139 (34%) infants with neuromuscular abnormalities such as hypotonia, 26/47 (55%) had severe OSA (OR 2.56, 95% CI 1.25-5.35, p = 0.0104); 22 of 47 (47%) of these patients with neuromuscular disorders also had an underlying genetic syndrome.

Other comorbidities included gastroesophageal reflux in 95/139 patients (68%, OR 1.22, 95% CI 0.59-2.58, p = 0.60) [69/139 (50%) were on antireflux medications such as ranitidine

or a proton pump inhibitor], periodic limb movement of sleep (PLMS) in 59/139 (42%, OR 0.60, 95% CI 0.29-1.21, $p = 0.15$), craniofacial abnormalities in 52/139 (37%, OR 1.2, 95% CI 0.59-2.42, $p = 0.61$), laryngomalacia and/or tracheomalacia in 38/139 (27%, OR 0.85, 95% CI 0.39-1.83, $p = 0.69$), epilepsy in 23/139 (17%, OR 0.59, 95% CI 0.21-1.5, $p = 0.28$). These comorbidities were not found to have a statistically significant correlation with obstructive sleep apnea severity (**Figure 1**).

DISCUSSION

Many prior pediatric studies that investigated obstructive sleep apnea have focused on older children.⁹⁻¹² The American Academy of Pediatrics (AAP) 2012 recommendation is limited, in that only children over one year of age should be screened for OSAS at health maintenance visits.¹³ This is partially due to complexity of patients younger than 1 year of age and limited treatment options, unlike older children in whom adenotonsillectomy is the front-line treatment.

Our study tried to identify comorbidities commonly seen in this population and determine if there was a correlation with OSA severity. The literature suggests that premature infants may be at higher risk for OSA secondary to anatomical and physiologic variances, including immature respiratory drive, upper airway size, and increased chest wall compliance.^{1,14,15} Former preterm children were found to have sleep disordered breathing rates 3-5 times higher than children born full term, although this was based on a study using overnight home cardiorespiratory monitoring instead of full laboratory-based polysomnography.² Our cohort of infants with OSA also demonstrated this relationship between prematurity and OSA severity.

Analysis of our cohort also suggested that infants with failure to thrive (based on weight at presentation less than the third percentile) had more severe OSA. Other studies have suggested that the increased metabolic demand of OSA may contribute to their failure to thrive. Inversely, factors related to their failure to thrive, such as congenital anomalies of the upper airway, may put them at risk for more severe OSA. Growth velocity has been shown to improve in patients with failure to thrive after treatment of OSA.¹⁶

Presence of genetic syndromes in our patient population was associated with more severe OSA, which is likely secondary to factors that predispose infants to OSA, including hypotonia, and craniofacial and airway abnormalities. Examples of conditions with this phenotype, including CHARGE, Crouzon, and Treacher Collins syndrome have been reported.¹

Other comorbidities commonly encountered in this population, such as gastroesophageal reflux (GER), PLMS, craniofacial abnormalities, laryngomalacia and/or tracheomalacia, and epilepsy did not seem to have a statistically significant correlation with OSA severity. In regard to GER, some of the patients were on treatment for this at the time of PSG, which may have altered its contribution to OSA. Reviewing the literature shows that although GERD is commonly seen in infants with OSA, the relationship between the two is controversial.^{17,18} It may be that GERD directly triggers OSA in some infants through the laryngeal chemoreflex or results in upper airway swelling without a clear temporal association.¹ The need for multidisciplinary programs such as aerodigestive clinics in the assessment

of sleep related breathing problems is highlighted by this study. There is increasing awareness of the need for such multidisciplinary clinics.¹⁹ Indeed, we have now moved to evaluating infants with complex upper airway problems through a multidisciplinary, aerodigestive clinic.

There were some limitations to our study. First, this was a single-center retrospective analysis of a relatively homogenous local population. Our experience as an international referral center for complex cases is also not unique, as children's hospitals around the country are encountering similar sleep related breathing problems in infants and management issues.¹⁹ Second, as this was a descriptive study we were unable to compare the data we obtained to a standardized group of patients in this age range. In regard to periodic limb movements, we acknowledge that this is a controversial issue as there are extremely limited data for this population. Infants in this age range normally have gross body movements related to the maturational phenomena in motor control.²⁰ In our study, PLMs were identified as periodic movements predominantly seen in NREM sleep. Gross body movements or those associated with sleep disordered breathing were not included as PLMs. In a study of 18 children with restless legs syndrome (RLS), Picchietti et al. reported that 10/18 subjects had onset of symptoms in infancy.²¹ Since RLS and PLMs are closely linked, it is not improbable that our infant population showed PLMs. Scholle et al. performed overnight polysomnography for 9 healthy infants with a mean age of 1.4 years and reported a PLMS index of 9.6 per hour.²² It remains unclear if PLMs are physiologic or pathologic in this age group but suggests infants may have a higher index that declines with age.

In summary, our data demonstrate that OSA of infancy is often associated with significant multisystem morbidity. Attention to genetic syndromes, neuromuscular, and neurodevelopmental disorders is recommended in patients of this age for effective, comprehensive management.

REFERENCES

1. Katz ES, Mitchell RB, D'Ambrosio CM. Obstructive sleep apnea in infants. *Am J Respir Crit Care Med* 2012;185:805-16.
2. Rosen CL, Larkin EK, Kirchner HL, et al. Prevalence and risk factors for sleep-disordered breathing in 8- to 11-year-old children: association with race and prematurity. *J Pediatr* 2003;142:383-9.
3. Emancipator JL, Storfes-Isser A, Taylor HG, et al. Variation of cognition and achievement with sleep-disordered breathing in full-term and preterm children. *Arch Pediatr Adolesc Med* 2006;160:203-10.
4. Weissbluth M, Davis AT, Poncher J, Reiff J. Signs of airway obstruction during sleep and behavioral, developmental, and academic problems. *J Dev Behav Pediatr* 1983;4:119-21.
5. Blunden S, Lushington K, Kennedy D, Martin J, Dawson D. Behavior and neurocognitive performance in children aged 5-10 years who snore compared to controls. *J Clin Exp Neuropsychol* 2000;22:554-68.
6. Chervin RD, Ruzicka DL, Archbold KH, Dillon JE. Snoring predicts hyperactivity four years later. *Sleep* 2005;28:885-90.
7. Brouillette RT, Fernbach SK, Hunt CE. Obstructive sleep apnea in infants and children. *J Pediatr* 1982;100:31-40.
8. Chervin RD, Ruzicka DL, Giordani BJ, et al. Sleep-disordered breathing, behavior, and cognition in children before and after adenotonsillectomy. *Pediatrics* 2006;117:e769-78.
9. Aurora RN, Zak RS, Karipipat A, et al. Practice parameters for the respiratory indications for polysomnography in children. *Sleep* 2011;34:379-88.
10. Bixler EO, Vgontzas AN, Lin HM, et al. Sleep disordered breathing in children in a general population sample: prevalence and risk factors. *Sleep* 2009;32:731-6.
11. O'Brien LM, Holbrook CR, Mervis CB, et al. Sleep and neurobehavioral characteristics of 5- to 7-year-old children with parentally reported symptoms of attention-deficit/hyperactivity disorder. *Pediatrics* 2003;111:554-63.

12. Marcus, CL, Brooks LJ, Draper KA, et al. Diagnosis and management of childhood obstructive sleep apnea syndrome. *Pediatrics* 2012;130:e714-55.
13. Montgomery-Downs HE, Young ME, Ross MA, Polak MJ, Ritchie SK, Lynch SK. Sleep-disordered breathing symptoms frequency and growth among prematurely born infants. *Sleep Med* 2010;11:263-67.
14. Youngblut JM, Brooten D, Singer LT, Standing T, Lee H, Rodgers WL. Effects of maternal employment and prematurity on child outcomes in single parent families. *Nurs Res* 2001;50:346-55.
15. Monahan KJ, Larkin EK, Rosen CL, Graham G, Redline S. Utility of noninvasive pharyngometry in epidemiologic studies of childhood sleep-disordered breathing. *Am J Respir Crit Care Med* 2002;165:1499-503.
16. McNamara F, Sullivan CE. Obstructive sleep apnea in infants and its management with nasal continuous positive airway pressure. *Chest* 1999;116:10-6.
17. Arad-Cohen N, Cohen A, Tirosh E. The relationship between gastroesophageal reflux and apnea in infants. *J Pediatr* 2000;137:321-6.
18. Di Fiore J, Arko M, Herynk B, Martin R, Hibbs AM. Characterization of cardiorespiratory events following gastroesophageal reflux in preterm infants. *J Perinatol* 2010;30:683-7.
19. Khatwa UA, Rosen R, Chou EH, Licameli GR. Multidisciplinary team approach for the evaluation of children with sleep disorders. In: Kothare SV, Kotagal S, eds. *Sleep in childhood neurological disorders*. Demos Medical New York, 2011:399-423.
20. Kohyama J, Shimohira M, Iwakawa Y. Maturation of motility and motor inhibition in rapid-eye-movement sleep. *J Pediatr* 1997;130:117-22.
21. Picchiatti DL, Stevens DL, Hanna E. Early manifestations of restless legs syndrome in childhood and adolescence. *Sleep Med* 2008;9:770-81.
22. Scholle S, Scholle HC. Leg movements and periodic leg movements during sleep in the development across childhood and adolescence from 1 to 18 years. *Sleep Med* 2014;15:1068-74.

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