The burden of sleep disordered breathing in infants with Down syndrome referred to tertiary sleep center

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Abstract

Introduction Children with Down Syndrome (DS) are at high risk of sleep disordered breathing (SDB). We aimed to examine the burden of SDB in infants with DS referred to tertiary sleep center. Methods Infants ([?]12 months old) with DS who underwent consecutive polysomnography (PSG) at a single academic sleep center over a 6-year period were included. OSA (obstructive apnea hypopnea index [oAHI]>1/hr), central sleep apnea (central apnea index>5/hr) and the presence of hypoventilation (% time spent with CO2 > 50 mmHg either by end-tidal or transcutaneous> 25% of total sleep time) and hypoxemia (time spent with O2 saturation <88% >5 min) were ascertained. For infants who underwent adenotonsillectomy (AT), we compared the SDB metrics before and after the AT. Results A total of 40 infants were included (Mean age 6.6 months, male 66%). PSGs consisted of diagnostic (n=13) and split night (n=27, 68%) studies. All met criteria for OSA with mean oAHI 34.6 (32.3). Central sleep apnea was present in 11 (27.5%) of infants. A total of 11 (27.5%) had hypoxemia. Hypoventilation was present in 10 (25%) infants. There was a trend of association between hypothyroidism and hypoventilation (OR: 5.5 [0.96-34.4], p=0.056). Among 13 infants who underwent AT and had a follow up PSG, severity of OSA markedly reduced after AT (oAHI difference: 34/hr [29], p=0.0002). Conclusion This study highlights the high prevalence of SDB in infants with DS and supports early PSG assessment in this patient population.

Introduction

Down syndrome (DS) is one of the most common birth defects in the United States with approximately 6000 births annually, resulting in an estimated birth prevalence of 14 per 10,000 live births.(Parker et al. 2010) Infant with DS (I-DS) are at a high risk of congenital morbidity including congenital heart disease, gastrointestinal disorders, and metabolic abnormalities(Benhaourech et al. 2016; Miller and Cosgriff 1983; Stoll et al. 2015) frequently requiring intensive care unit admission.(Martin et al. 2018; Seither et al. 2021; So et al. 2007)

Sleep disordered breathing (SDB) is a common comorbidity imposing additional burden on I-DS.(Lee et al. 2018) Unique craniofacial features of DS, macroglossia, and shortened palate and midface hypoplasia along with generalized hypotonia make I-DS highly susceptible to OSA.(Maris et al. 2014) Additionally, these patients are at risk for hypoxemia and hypoventilation due to coexisting conditions such as congenital heart disease, smaller lung volumes and hypotonia.(Fan et al. 2017; Wong and Rosen 2017) Cardiovascular and neurocognitive consequence of longstanding and untreated childhood SDB(Capdevila et al. 2008; Greene and Carroll 1997) can be even more detrimental in children with DS. In particular, the risk of pulmonary hypertension and cor-pulmonale in children with DS(Breslin et al. 2014) can be markedly increased in the presence of SDB. Moreover, impaired sleep quality affects daytime function, behavior and quality of life.(Bassell et al. 2015) Therefore, screening for SDB in its entirety (i.e., beyond OSA) is important in early childhood. The American Academy of Pediatrics (AAP)'s published anticipatory guidelines for children with DS recommends that a discussion be held with the parents at least once during the first 6 months of life to screen for symptoms suggestive of OSA; snoring, witnessing breathing pauses, heavy breathing,

uncommon sleep positions, frequent nocturnal awakening, daytime symptoms and/or behavioral concerns that could be associated with poor sleep.(Bull 2011) The AAP also recommends referral to a sleep physician for further examination and evaluation of a possible OSA if any of the symptoms occur. Despite these recommendations, I-DS are not commonly referred for SDB evaluation. The AAP recommends assessing for symptoms of OSA, and recommends referral to a pediatric sleep laboratory for polysomnography (PSG) by 4 years of age for all children with DS due to poor correlation between parent report and PSG results but suggests it to be performed after the first year of life,.(Bull 2011) By age 4 years old a child with OSA may already have negative outcomes or comorbidities associated with untreated hypoxemia or hypoventilation. Despite the clinical implication of SDB in early age, studies exclusively examining infants with DS are rare. In this study we aimed to assess the prevalence of OSA, central sleep apnea (CSA), sleep hypoxemia and sleep hypoventilation, and the impact of adenotonsillectomy (AT) on SDB in I-DS.

Methods

Study design and Subjects : This is a retrospective descriptive study of a single academic sleep center. I-DS ([?]12 months old) who underwent PSG at Seattle Children's hospital over a 6-year period (2015-2021) were included. If there were multiple studies, the first study was chosen. Both diagnostic and split night (split to O2) studies were included. For follow up PSGs following AT, the first follow up study was chosen. The study was approved by the Seattle Children's Hospital., Seattle, WA, Institutional Review Board Study Number 00003376.

Sleep study and Clinical Data : PSG was performed according to the American Academy of Sleep Medicine (AASM) criteria(Berry et al. 2012) and data were recorded using the Sandman Elite Natus system (Natus Medical Incorporated, Pleasanton, CA, USA). Parameters recorded included electroencephalogram (EEG; two frontal, two central, and two occipital channels, referred to the contralateral mastoid); electro-oculogram, electromyogram (EMG) of the submentalis muscle, EMG of the right and left tibialis anterior muscles, respiratory signals, effort signals for thorax and abdomen, oximetry, a single-lead electrocardiogram, and video and audio recording. Either capnography (End-tidal CO2 [ETCO2]) or transcutaneous CO2 (TCCO2) or both were performed. Calibrations were performed per routine standard by technicians. Epochs were scored by a certified sleep technologist and board-certified sleep physician according to the AASM criteria.(Berry et al. 2012) Respiratory events were classified as obstructive apnea or hypopnea, according to the above-mentioned AASM criteria, and the duration and stage (Non rapid eye movement (NREM) or rapid eye movement (REM)) of each event were annotated by a certified sleep technologist. We collected obstructive apnea hypopnea index (oAHI)(/hr), central apnea index (cAI) (/hr), % time spent with CO2 levels $>$ 50 mmHg, % time spent with saturations $<$88% (T88), and O2 saturation nadir (minO2sat). OSA was defined as oAHI$>$=1/hr. Severe OSA was defined by oAHI[?]10/hr. CSA was defined as central apnea index (CAI) $>$= 5/hr. Hypoxemia was defined as T88 greater than 5 minutes. One infant had underlying hypoxemia at baseline resulting in extreme T88 value. This infant was excluded for analyses involving T88. Hypoventilation was defined as % time spent with CO2 levels $>$ 50 mmHg as measured by ETCO2 or TCCO2 greater than 25%. Demographics and other medical history were obtained by reviewing electronic medical record.

Analysis : Distributions of patient characteristics and PSG results were expressed by mean (SD) or number (%) as appropriate. Severity of OSA between infants who underwent diagnostic studies and split night studies (diagnostic portion only) were compared using unpaired t test or Mann-Whitney in case of nonparametric distribution. Comparison of SDB metrics between pre and post AT within infants were made by paired t test or Wilcoxon Signed-Rank test in case of nonparametric distribution. Due to skewed distribution of AHI, nonparametric analysis was performed for all AHI-related analyses. Based on the borderline univariate analysis results wherein hypothyroidism was disproportionately more common in infants with hypoventilation, we performed logistic regression to assess the relationship between hypothyroidism and hypoventilation adjusting for OSA severity (severe OSA vs. no severe OSA). All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC)

Results

A total of 40 infants were identified out of 525 children with DS who underwent PSG. Mean age was 6.6 (3.0) months and male comprised 65% of the cohort. The PSG studies included diagnostic (n=13, 33%) and split night (n=27, 67%) cases. The demographic characteristics and comorbidities of included I-DS are shown in the Table 1. PSG sleep characteristics are described in Table 2. All met criteria for OSA with mean oAHI 34.6 (32.3). Severe OSA was present in 34 (85%) infants. CSA was present in 11 (27.5%) of infants. No association was found between age and oAHI or CAI (Pearson correlation(r): -0.1 and 0.02 respectively, P=NS for both). Infants who underwent split studies had more severe OSA when compared with those who underwent diagnostic study. (AHI: 44.7/hr (33.7) vs. 14.8 (9.0), p=0.003), T88 (Mean 12.5 min vs. 0.2 p=0.03) and minO2sat (77.6% vs. 85.8, p=0.01). A total of 11 (27.5%) infants had T88 >5 min qualifying for hypoxemia. Hypoxemia was more common in I-DS with hypoventilation (60 vs. 16.7%, p=0.008). Hypoxemia was also more common among those with severe OSA vs. no severe OSA (32.4 vs. 0%, p=0.16) but this difference was not statistically significant. Hypoventilation was present in 10 (25%) infants. Characteristics of infants with hypoventilation is depicted in Table 3. In logistic regression there was a trend of association between hypothyroidism and hypoventilation (OR: 5.5 [0.96-34.4], p=0.056).

There were 13 infants who underwent AT and had a follow up PSG allowing us to compare the SDB metrics. Time interval between the two PSGs ranged 6 months to 2 years. Severity of OSA markedly decreased (Mean oAHI reduction: 34/hr [29], p=0.0002) (Figure 1). minO2sat also improved post AT (Mean minO2sat increase 9.7% (11.1), P=0.009).

Discussion

The purpose of the study was to assess SDB burden among I-DS referred to sleep center. All I-DS had OSA with majority exhibiting severe OSA. Hypoxemia and hypoventilation were also common. Among those who underwent AT, short term outcome shows marked improvement of OSA.

A high prevalence of OSA in children with DS has been described. A recent meta-analysis of 18 studies including 2,000 children with DS showed the prevalence of OSA to be about 50% by the conventional diagnostic threshold,(Lee et al. 2018) which represents a 10-fold higher risk than in the general pediatric population.(Marcus et al. 2012) Studies exclusively examining SDB in infant have been rare. Similar to our study, a previous single center study revealed virtually all I-DS who underwent sleep study manifested OSA and, alike our study, with a great proportion exhibiting severe OSA.(Goffinski et al. 2015) In our study severe OSA was present in 80% of I-DS. Thus, it is possible that the severity of OSA in infants may be higher than older children with DS.(Nerfeldt and Sundelin 2020) While the true prevalence of OSA is difficult to assess from clinical setting due to selection bias, it is reasonable to believe that the OSA risk is at its extreme even at a very young age in I-DS. Because all included infants met OSA criteria with most of them exhibiting severe OSA, we were unable to explore factors associated with OSA or severity of OSA. Not surprisingly, OSA was more severe in I-DS who underwent split study (vs. diagnostic) as young children with more severe OSA or anticipated to be more severe OSA tend to undergo O2 titration study in clinical practice.

In addition to OSA, CSA was also highly prevalent in I-DS. CSA during sleep is common in the preterm, newborn period and during infancy.(S et al. 2014) In healthy children, short duration (<20 s) CSAs in sleep are considered physiologic in the setting of a sigh, REM sleep and movement.(S et al. 2014) However, there is paucity of studies examining CSA in unselected infant population. Regardless, we suspect that high occurrence of CSA events noted in our study may not be unique to I-DS. A study by Fan et al. showed that CSA (as measured by CAI) was associated with younger age in the very youngest cohort (0-3 yrs old) in their review of children with DS who underwent PSG.(Fan et al. 2017) They reasoned that the improvement of CSA may be due to maturity of the respiratory control system with aging in younger children. However, such a relationship with age was not demonstrated in our study.

Sleep hypoxemia was also common affecting nearly 30% of I-DS in our study. As expected, hypoxemia was more common among those who exhibited hypoventilation and severe OSA in our study. Despite the notion that individuals with DS are at risk for hypoventilation, studies examining this very aspect in DS has

been rare. A recent case control study by Richard et al. including children with and without DS revealed that children with DS have increased TCCO2 regardless of the presence of OSA and its severity.(Richard et al. 2020) In that study, investigators noted correlation between BMI and maximum CO2 speculating that obesity might be a contributing factor to the hypoventilation. Our study is the first to closely inspect hypoventilation exclusively in I-DS. In our study, 25% of I-DS met the criteria for hypoventilation. Interestingly, we found that I-DS with comorbid hypothyroidism had about 5 times higher odds of having hypoventilation, albeit borderline statistical significance likely related to small sample size. This alludes to the fact that hypotonia resulting from hypothyroidism, may play an important role in hypoventilation. The incidence of hypothyroidism in children with DS is 5.5%–10% but higher in the first year of life.(King et al. 2014) We did not examine the association of body habitus with hypoventilation given the limited variability of the BMI in our cohort.

In the subcohort of I-DS who underwent AT, we observed marked improvement in the severity of OSA as measured by oAHI and minO2sat. This is consistent with previous studies mainly including older children (older than infant age) that showed improvement of OSA following the AT.(Abdel-Aziz et al. 2017; Maris et al. 2017; Nerfeldt and Sundelin 2020) Average reduction in AHI was reportedly about 50% according to the systematic review.(Nation and Brigger 2017) Despite this, AT is not entirely curative in most cases and residual OSA is common.(Galluzzi and Garavello 2021) Moreover, complication rates of AT is higher in children with DS.(Goldstein et al. 1998; Yumusakhuylu et al. 2016) Thus, despite the marked improvement in OSA shown in our study, long term outcome and safety of AT in infants should be investigated in the future study.

OSA leads to poor sleep by frequent sleep disruption and deprivation of restful sleep. Poor sleep resulting from OSA in turn leads to daytime sleepiness, fatigue, mood change(Sánchez et al. 2009), and deficits in memory(Wallace and Bucks 2013), cognition(Pierobon et al. 2008), and executive function(Saunamäki et al. 2009), all of which may have more significant implications in I-DS given the inherent intellectual, cognitive, and emotional challenges associated with DS.(Sánchez et al. 2009) Moreover, gas exchange abnormality associated with SDB can unavoidably impact on the risk of cardiovascular disease including pulmonary hypertension in individuals with DS.(Bush et al. 2018) Thus, in view of our study findings, early screening of SDB as early as infants should be considered. This will become more feasible with the advance and emergency of more convenient technology that enables SDB evaluation in the home setting.

The strengths of this study are the exclusive investigation of infants and the comprehensive evaluation of all spectrum of SDB including hypoventilation. Moreover, to our knowledge this is the first study that examined the change in SDB metrics following the AT in I-DS. The main limitation of the study is related to inherent weakness of the retrospective study including selection bias. Such bias could have impacted the severity of SDB and the treatment outcome following the AT.

In conclusion, we report the excessively high burden of SDB among I-DS referred to tertiary sleep center. OSA was present in the entire cohort and was mostly severe in nature. In addition to OSA and CSA, sleep hypoxemia and hypoventilation were all common. There was significant improvement in OSA following AT in a subcohort. These findings propel us to consider early screening of SDB and possibly AT in this population.

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Figure 1. Improvement of obstructive sleep apnea severity following adenotonsillectomy. Obstructive apnea hypopnea index (oAHI) before and after adenotonsillectomy (AT) is depicted.

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