## Title

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# 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 $CO_2$ > 50 mmHg either by end-tidal or transcutaneous> 25% of total sleep time) and hypoxemia (time spent with $O_2$ saturation <88% >5 min) were ascertained.

**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).

**Conclusion—**This study highlights the high prevalence of SDB in infants with DS referred to a sleep center, and supports early PSG assessment in this patient population.

### Keywords

Down syndrome; sleep disordered breathing; pediatric; sleep apnea

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## 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.[1] Infants with DS (I-DS) are at a high risk of congenital morbidity including congenital heart disease, gastrointestinal disorders, and metabolic abnormalities[2-4] frequently requiring intensive care unit admission.[5-7]

Sleep disordered breathing (SDB) is a common comorbidity imposing additional burden on I-DS.[8] Unique craniofacial features of DS, macroglossia, and shortened palate and midface hypoplasia along with generalized hypotonia make I-DS highly susceptible to obstructive sleep apnea (OSA).[9] Additionally, these patients are at risk for hypoxemia and hypoventilation due to coexisting conditions such as congenital heart disease, smaller lung volumes and hypotonia.[10,11] Cardiovascular and neurocognitive consequence of longstanding and untreated childhood SDB[12,13] can be even more detrimental in children with DS. In particular, the risk of pulmonary hypertension and cor-pulmonale in children with DS[14] can be markedly increased in the presence of SDB. Moreover, impaired sleep quality affects daytime function, behavior and quality of life.[15] Therefore, screening for SDB in its entirety (i.e., beyond OSA) is important in early childhood. The American Academy of Pediatrics (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,.[16] 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 the diagnostic portion of the split night (split to $O_2$) studies were included. A decision about diagnostic only vs. split night study was made by ordering physicians. In the case of split night studies, AHI >1/hr was used to determine the timing of the initiation of the $O_2$ therapy.[17]. The study was approved by the Seattle Children's Hospital., Seattle, WA, Institutional Review Board Study Number 00003376.

### Sleep study and respiratory scoring:

**1) Sleep study:** Polysomnography (PSG) was pursued at the discretion of sleep clinician and was performed according to the American Academy of Sleep Medicine (AASM) criteria[18] 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 (EOG), electromyogram (EMG) of the submentalis muscle, and right and left tibialis anterior muscles, nasal pressure transducer and thermistor sensors, respiratory effort signals for thorax and abdomen, oximetry, a single-lead electrocardiogram, and video and audio recording. Either capnography (End-tidal $CO_2$ [$ETCO_2$]) or transcutaneous $CO_2$ ($TCCO_2$) or both were performed. Calibrations were performed per routine standard by technicians. Sleep stages (Rapid eye movement [REM], non-REM) and respiratory events were scored by a certified sleep technologist and reviewed by board-certified sleep physician according to the AASM criteria.[18]

**2) Respiratory scoring:** We collected obstructive apnea hypopnea index (oAHI)(/hr), central apnea index (cAI) (/hr), % time spent with $CO_2$ levels > 50 mmHg, % time spent with saturations <88% (T88), and $O_2$ saturation nadir ($minO_2sat$). Reference data for infant PSG scoring is scarce. For this study, OSA was defined as oAHI>=1/hr patterning after the scoring rule for children. Severe OSA was defined by oAHI≥10/hr.[19] Central apnea is frequently observed in healthy infants. For this study, CSA was defined as central apnea index (CAI) >= 5/hr in accordance with pediatric scoring rules and pediatric consensus recommendations.[20] We used Medicare rule that defines sleep hypoxemia as T88 greater than 5 minutes.[21] 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 $CO_2$ levels > 50 mmHg as measured by $ETCO_2$ or $TCCO_2$ 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), IQR 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.

### 1) OSA

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).

### 2) Hypoxemia

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.

### 3) Hypoventilation

Hypoventilation was present in 10 (25%) infants. Characteristics of infants with hypoventilation is depicted in Table 3. There were no statistically significant differences in the group with hypoventilation compared with the group without hypoventilation in terms of age, sex, severity of OSA or presence of hypothyroidism. However, there was a suggestion of association between hypothyroidism and hypoventilation (OR: 5.5 [0.96-34.4], p=0.056).

## Discussion

All I-DS had OSA with majority exhibiting severe OSA. Hypoxemia and hypoventilation were also common.

Despite the well-established notion about the high prevalence of OSA in children with DS, 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.[22] Another study that included both infants and children with DS revealed that about two thirds of the infants had moderate to severe OSA (oAHI>5/hr).[19] Even though there has not been any systematic examination of OSA prevalence in normal developing infants making it impossible to make a comparison, the OSA burden found in the I-DS patients included in this study (Severe OSA was present in 80%) is clearly noteworthy. Thus, it is possible that the severity of OSA in infants may be higher than older children with DS.[23] 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 I-DS met OSA criteria with most of them exhibiting severe OSA, we were unable to explore factors associated with OSA or severity of OSA. Unlike a study by Water et al., which showed that the younger age (< 2 vs. ≥ 2 yrs old) exhibited more severe OSA, we were unable to show any association between the age and the severity of OSA likely due to the limited age range of our cohort.[19] 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.[24] In healthy children, short duration (<20 s) CSAs in sleep are considered physiologic in the setting of a sigh, REM sleep and movement. However, there is paucity of studies examining CSA in unselected infant population. Thus, 'normal' value of CAI is uncertain in infants and the criteria used to define significant CSA in this study was based on adult practice.[18] 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.[11] 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 $TCCO_2$ regardless of the presence of OSA and its severity.[25] In that study, investigators noted correlation between BMI and maximum $CO_2$ 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, even thought it was e statistically not significant possibly related to small sample size. While no conclusion can be made due to lack of statistical significance, the authors postulate it is possible 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.[26] We did not examine the association of body habitus with hypoventilation given the limited standard tools to measure the infant body habitus.

OSA leads to poor sleep by frequent sleep disruption and deprivation of restful sleep. In this study we observed poor sleep as evidenced by a low proportion of REM sleep (23%) compared to what is known for in healthy infants. Poor sleep resulting from OSA in turn leads to daytime sleepiness, fatigue, mood change[27], and deficits in memory[28], cognition[29], and executive function[30], all of which may have more significant implications in I-DS given the inherent intellectual, cognitive, and emotional challenges associated with DS.[27] Moreover, gas exchange abnormality associated with SDB can unavoidably impact on the risk of cardiovascular disease including pulmonary hypertension in individuals with DS.[31] 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. The main limitation of the study is the retrospective nature which can include selection bias. Sleep study was not

performed systematically in all I-DS but rather performed among the I-DS who were referred to sleep center. Reference data used to define SDB in this study can be debatable but this was largely due to lack of universally accepted criteria in infants.

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. These findings propel us to consider early screening of SDB in this population.

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**Table 1.**

Baseline Characteristics (N=40)

| Variable | Mean (SD) or N (%) (Total) |
|---|---|
| Age (Month) | 6.6 (3.0) |
| Sex (Male) | 26 (65%) |
| Ethnicity (White) (N=34) | 24 (70.6%) |
| Any Congenital heart disease | 27 (67.5%) |
| Pulmonary hypertension | 2 (5%) |
| Hypothyroidism | 8 (20%) |
| Hematological malignancy | 5 (12.5%) |
| Gastrointestinal abnormality (GERD, Hirschsprung disease, Dysphagia) | 20 (50%) |

Ethnicity information was not available in 6 infants.

**Table 2.**

Baseline sleep characteristics (N=40)

| Variable | Mean (SD) | IQR | Range |
|---|---|---|---|
| AHI (/hr) | 38.7 (32.3) | 16.9, 47.7 | 1.8-146.1 |
| oAHI (/hr) | 34.6 (32.3) | 13.1, 40.9 | 1.1-146.1 |
| CAI (/hr) | 3.5 (3.4) | 1.1, 5.2 | 0-15.3 |
| Minimum $O_2$ saturation (%) | 80 (9.8) | 75.8, 87.4 | 50.3-90.3 |
| Time spent with $O_2$ saturation ≤ 88% (min) * ( one outlier excluded) (N=39) | 11.0 (24.8) | 0, 3.4 | 0-40.8 |
| % sleep time with $ETCO_2$≥ 50 mmHg (%) | 9.5 (22.8) | 0, 3.4 | 0-88 |
| % sleep time with $TCCO_2$≥ 50 mmHg (%) | 37.0 (40.3) | 3.3, 90 | 0-100 |
| Total limb movement index (/hr) | 6.9 (5.4) | 2.4, 10.5 | 1.1-23.3 |
| REM (%) (Diagnostic study, N=13) | 23.4 (6.0) | 22.0, 26.0 | 7.5-33.1 |
| N3 (%) (Diagnostic study, N=13) | 36.0 (13.9) | 28.6, 37.8 | 20.9-68.3 |
| REM (%) (Split study N=27) | 15.1 (10.4) | 7.7, 23.0 | 0-31.3 |
| N3 (%) (Split study N=27) | 59.5 (19.3) | 44.9, 68.6 | 23.7-100 |

AHI, apnea hypopnea index; oAHI, obstructive apnea hypopnea index; CAI, central apnea index; $ETCO_2$, end-tidal $CO_2$; REM, rapid eye movement; $TCCO_2$, transcutaneous $CO_2$. REM and N3 were described by sleep study type (diagnostic study [N=13]; split study [N=27])

**Table 3.**

Characteristics of infants with hypoventilation (N=40)

| | Hypoventilation (N=10) | No hypoventilation (N=30) | P value |
|---|---|---|---|
| Age (months) | 5.9 (3.0) | 6.9 (3.1) | 0.4 |
| Sex (Male %) | 70 | 63.3 | 0.7 |
| Congenital heart disease (%) | 7 (70) | 21 (70) | 1.0 |
| Hypothyroidism (%) | 4 (40) | 4 (13.3) | 0.07 |
| Severe OSA (%) | 8 (80) | 26 (86.7) | 0.61 |

OSA, obstructive sleep apnea