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Sleep-disordered Breathing is Common Among Term and Near Term Infants in the NICU[1]

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Objective
Among older infants and children, sleep-disordered breathing (SDB) has negative neurocognitive consequences. We evaluated the frequency and potential impact of SDB among newborns who require intensive care.

Study Design
Term and near-term newborns at risk for seizures underwent 12-hour attended polysomnography in the neonatal intensive care unit (NICU). Bayley Scales of Infant Development, third edition (Bayley-III) were administered at 18-22 months.

Result

The 48 newborns (EGA 39.3 ± 1.6) had a median pediatric apnea-hypopnea index (AHI) of 10.1 (3.3-18.5) and most events were central (vs. obstructive). Maternal and prenatal factors were not associated with AHI. Moreover, neonatal PSG results were not associated with Bayley-III scores ($p>0.05$).

Conclusion
SDB is common among term and near-term newborns at risk for seizures. Follow-up at ages when more nuanced testing can be performed may be necessary to establish whether neonatal SDB is associated with long-term neurodevelopmental disability.

Introduction

Sleep-disordered breathing (SDB) is a heterogeneous, common group of disorders that affects 1-4% of all children(1) and may be clinically consequential among infants(2) although incidence in the neonatal period is unknown. Disordered breathing during sleep causes abnormal gas exchange, interferes with the restorative nature of sleep and has been shown to disrupt cellular and chemical homeostasis.(3) Consequences of pediatric SDB include lasting deficits in cognition, behavior, cardiac function and growth, and adverse effects(4-8)may begin very early in life. Emerging data suggest that even when symptoms of SDB occur during the first year of life and then resolve, they nonetheless predict measureable neurocognitive morbidity when the child reaches school age.(9-11) Given the possibility that early SDB diagnosis and treatment could ameliorate such long-term repercussions, we aimed to identify whether SDB is common as early as the first days of life among newborns who require intensive care. Such neonates are more likely than others to develop adverse neurodevelopmental outcomes, but the currently known risk factors are not remediable. Previously published studies have combined electroencephalogram (EEG) and non-EEG measures (such as respiratory patterns and eye movements) to study newborn sleep states in term and preterm infants(12, 13), but an extensive literature search revealed virtually no published studies that utilized gold standard polysomnography for SDB diagnosis among term and near-term newborns who were receiving care in an Neonatal Intensive Care Unit (NICU). One exception has been our own recent work on neonates with myelomeningocele(14). In a

slightly older cohort, infants underwent overnight polygraphy at one and three months of age had a median apnea-hypopnea index (AHI) of 7.8 and 4.9, respectively(15). Existing studies have demonstrated important physiologic differences during sleep in preterm and term infants, leading to the conclusion that differences exist in functional brain organization. However, these studies did not evaluate subjects for SDB.

A recent report(16) of infants born prematurely (median gestational age at birth was 26 weeks) who underwent polysomnography in a sleep laboratory prior to NICU discharge due to clinical concern for significant airway obstruction. SDB was common in this cohort and a correlation was found between higher end-tidal CO2 and subsequently lower cognitive scores on the Bayley Scales of Infant Development, Third edition (Bayley-III). However, infants born at these early gestational ages are more likely than those born later to receive the diagnosis of SDB.

We hypothesized that SDB may be a novel, modifiable risk factor for adverse outcomes among newborns who require treatment in the neonatal intensive care unit (NICU). As an initial step towards addressing this hypothesis, our primary objective was to define the prevalence and severity of SDB in a group of newborns who required NICU care due to their risk for seizures. A secondary objective was to assess whether the presence of SDB in these newborns predicted later clinical and neurodevelopmental outcomes.

Subjects and Methods

This was a prospective study of neonates born at ≥35 weeks gestation and admitted to our level IV NICU, where they were judged clinically to be at risk for seizures. The concern for possible seizures arose due to suspected or confirmed acute brain injury combined with encephalopathy, or due to stereotyped abnormal paroxysmal events, according to published guidelines from the American Clinical Neurophysiology Society.(17) We excluded infants with congenital anomalies, craniofacial abnormalities

placing them at higher risk for obstructive sleep apnea such as micrognathia, genetic conditions associated with central hypoventilation or syndromes known to affect neurodevelopment. We also excluded neonates with significantly abnormal EEG background that would result in inconclusive PSG interpretation.

Sleep-wake transition patterns for a subset of these newborns (n=28) were reported elsewhere.(18, 19) The University of Michigan Institutional Review Board approved this study and a parent of every enrolled infant provided written informed consent.

Each neonate underwent a detailed neonatal neurologic examination. Data regarding prenatal, intrapartum and post-natal hospital course were obtained from the medical record. Once the newborns were clinically stable, they underwent an 8-to-12-hour formal PSG. This test was conducted at the NICU bedside and was attended by a registered polysomnographic technologist with experience and expertise specific to children and infants. The PSG included a 9-channel neonatal-montage EEG, bilateral electro-oculography, chin surface EMG, chest and abdominal excursion (inductance plethysmography), nasal pressure, nasal/oral airflow (thermocouples), snoring sensor, oxygen saturation, ECG, bilateral anterior tibialis surface EMG, digital video, and transcutaneous carbon dioxide monitoring (TCO_2). Sleep was scored offline by a registered polysomnographic technologist, at our accredited sleep disorders center, according to standard rules for neonates.(20) Scored studies were reviewed by a physician (F.H.) who is board-certified in pediatrics, pediatric pulmonary medicine, and sleep medicine. Data collected included total sleep time; time spent in active (REM) versus quiet (non-REM) sleep; apnea-hypopnea index (AHI, respiratory events per hour of sleep); indices for obstructive apneas, central apneas, and hypopneas; mean oxygen saturation; oxygen saturation nadir; and the percent of sleep time with oxygen saturation <90%.

Respiratory events were scored according to the pediatric definitions established by the American Academy of Sleep Medicine.(21) Apnea was defined as a drop in peak signal airflow (thermocouple) excursion by ≥ 90% of the pre-event baseline. Central apnea was scored if the event was associated with absent inspiratory effort and the event either: (a) lasted ≥ 20 seconds, (b) lasted at least the duration of two breaths during baseline breathing and was associated with an arousal, awakening, or ≥3% oxygen desaturation, or (c) lasted at least the duration for two breaths during baseline breathing and was associated with a decrease in heart rate, to less than 50 beats per minute for at least 5 seconds, or less than 60 beats per minute for 15 seconds. Obstructive apnea was identified if an apneic event occurred for at least the duration of two breaths during baseline breathing and was associated with continued respiratory effort throughout the entire period of absent airflow. Hypopnea was characterized by a peak nasal pressure excursion drop by ≥ 30% of pre-event baseline, and a duration of the ≥ 30% drop that lasted for at least two breaths, when there was ≥ 3% desaturation from pre-event baseline or an associated arousal. The apnea-hypopnea index (AHI) was defined as the total number of apneas and hypopneas, divided by the total hours of recorded sleep.

The neonatal neurologic exam was used to calculate a Thompson score(22) that incorporated the complete neurologic exam, as well as fontanelle assessment, respiratory patterns, and presence of clinical seizures. Thompson scores range from 0 to 22; scores higher than 12 are associated with increased risk for adverse neurodevelopment and death before discharge following hypoxic-ischemic encephalopathy.(23)

Long-term outcome was determined in two ways. First, outcome was dichotomized as favorable versus adverse. Favorable outcome was defined as survival without severe disability (e.g. blindness, deafness, epilepsy, or severe cerebral palsy). Assignment of the dichotomous outcome was by consensus among

two senior investigators (RAS, JDB), based on all available medical records. Second, surviving children underwent a Bayley-III and neurological examination at 18-22 months of age.

Descriptive statistic calculations, univariate analyses, and multivariate linear regression were used to assess for associations between the PSG results, clinical outcomes, and neurodevelopmental measures. All computations were performed in IBM SPSS Statistics for Windows, version 22.0 (Armonk, NY: IBM Corporation).

Results

Forty-eight infants (n=21 male) were enrolled. Demographic information and the newborns' clinical profiles are available in Table 1. Polysomnogram results are presented in Table 3.

Every newborn had documented apnea and/or hypopnea and N=24 (50%) had more than ten respiratory events per hour (i.e. AHI >10), a threshold consistent with moderate to severe sleep apnea in children. The AHI was highest during active (rapid eye movement) sleep, with a median of 10 (IQR 3.3, 18.5) events per hour. Most of the respiratory events were hypopneas, and central apneas were more common than obstructive apneas (see Table 3). None of the participants had individual apneic events longer than 20 seconds (the standard NICU monitor threshold for neonatal apnea).

SDB and Neonatal Clinical Features

Explanatory variables analyzed included pregnancy complications, need for maternal medications prenatally, gestational age at time of delivery, mode of delivery, extent of neonatal resuscitation, Apgar scores, and postnatal clinical factors including anthropometrics, length of hospital stay, Thompson score, medications required, and diagnoses carried. Univariate analysis yielded no statistically significant associations between these explanatory variables and AHI, the obstructive apnea index, or the central apnea index. Additionally, no statistically significant association emerged between the infants'

Thompson scores and the indices mentioned above. Moreover, no difference in favorable versus adverse outcomes were found comparing infants who had an AHI ≤10 versus >10 (p>0.99), or infants who had a Thompson Score ≤10 versus >10 (p = 0.65), utilizing Fischer exact tests. We then performed an exploratory multivariable regression including all variables with p<0.25 in univariate analyses. The resulting multivariable linear regression models demonstrated that the presence of (a) intraventricular hemorrhage (IVH)/stroke or (b) younger gestational age were each independently associated with a higher obstructive apnea index (model r^2=0.5, p=0.001) but not a higher central apnea index. Neither large-for-gestational-age status, nor prior need for intubation was associated with obstructive or central sleep apnea.

SDB and Clinical/Neurodevelopmental Long-term Outcomes

Follow-up clinical data were available for 37 subjects. Thirty subjects (81% of those with follow-up data) survived without severe disability. Twenty-eight of the original subjects returned for Bayley-III at 18-22 months (Table 2). In exploratory univariate analyses, virtually no significant associations emerged between dichotomous clinical outcome (favorable versus adverse), or cognitive, language or motor Bayley-III scale scores, and PSG results including AHI, central or obstructive apnea indices, and minimum oxygen saturation nor neonatal clinical features (all p > 0.05). The only exception was that the Bayley-III Language score did show an association with minimum oxygen saturation during neonatal PSG (Pearson *rho* = -0.34, p = 0.04). Clinical predictors of a lower Bayley-III Language score also included longer length of stay in the NICU (Pearson *rho* -0.40, p= 0.019) and an increased number of anti-seizure medications required during the NICU course (Pearson *rho* -0.55, p= 0.001).

Discussion

This is one of the first study that utilized bedside PSG, the gold standard diagnostic tool, to assess for SDB in newborn infants who required intensive care. In this sample of infants at risk for seizure, every

subject met standard criteria for pediatric SDB(24) (AHI > 1) and half had more than ten apneas or hypopneas per hour. Interestingly, none of the infants in this sample had clinically-suspected SDB prior to their PSG recording. Moreover, the traditional definition of apnea in the NICU (>20 seconds without respiratory effort), if used alone, under-detected SDB in this vulnerable patient population.

Although it may not be surprising that neonates with neurologic risk factors should have SDB, it is of interest that infants in our cohort were more likely to have a higher obstructive apnea index, instead of a higher central apnea index, if they carried the diagnosis of an intracranial hemorrhage or were born at younger gestational ages. Central apneas might arise from brainstem dysfunction, medication influence, or other factors. Obstructive apneas were relatively rare, but potentially clinically significant, and we speculate they might arise in conjunction with abnormal tone, supine positioning, higher risk of laryngomalacia in infants born at younger gestational ages, or other factors related to the need for NICU care.

Other analyses of older infants have reported high prevalence of SDB, but none studied SDB among newborns in the NICU setting. A longitudinal study designed to describe the prevalence, persistence and characteristics of SDB in young children(9) reported that 80.8% of six-month old infants demonstrated at least one symptom of SDB. That study utilized a broad definition of SDB that included parental report of any mouth breathing, snoring, or breath holding during sleep and did not include PSG-defined SDB.

Parental report of habitual infant snoring in the first six months of life (a sign of obstructive SDB) is associated with measureable decreases in cognitive and developmental scores when assessed by Bayley-III at six months of age.(10) Moreover, a longitudinal population-based study found that even if parent-reported symptoms of SDB peaked at six months of age and subsequently resolved, such children in comparison to those without a similar history showed worse behavioral scores at four and seven years of age.(11) The results of these two studies suggest that brain development may be negatively

impacted by SDB, even if symptoms are present only transiently during infancy. In contrast, our study for the most part did not demonstrate an association between SDB and 18-22 month Bayley-III scores. However, neurocognitive consequences of neonatal SDB may be subtle at such early ages, might be masked by the larger effect of neonatal brain injury on outcome, or might not be detectable by the Bayley-III. Other quantitative PSG-derived data (low frequency EEG power and proportion of quiet sleep) are independent predictors of Bayley-III scores(19). Longer-term follow-up might be needed for the impaired phenotype to emerge, or to assess more effectively for associations between early SDB and subsequent executive function or attentional measures.

A recent prospective follow-up study(25) sought to determine the prevalence of SDB in school-aged children with a history of prematurity. In this prospective follow-up analysis of the Caffeine for Apnea of Prematurity (CAP) study, preterm infants were enrolled at birth and underwent an ambulatory PSG when they reached 5-12 years of age. Neonatal sleep was not assessed. At the time of follow-up, children were diagnosed with obstructive sleep apnea if PSG results indicated AHI ≥ 2 events per hour or they had a history of adenoidectomy/tonsillectomy. Almost 20% of children born with birth weights of 500 - 1,250 g had evidence of obstructive sleep apnea, a form of SDB, at school-age. In his commentary on this study, Brockmann(26) noted that the potential burden of SDB is likely quite significant, given the fact 9.6% of worldwide pregnancies results in preterm delivery. A concerted effort to define clinically-significant SDB in this at-risk patient population, and to evaluate for long-term neurodevelopmental consequences, is required.

Moreover, inefficient quiet sleep patterns in newborns have been associated with abnormal neurologic examination scores and 18-month Bayley-III scores.(18, 19) Multiple studies have shown that premature infants are at greater risk than term infants for attention and learning disorders, delayed cognitive function, and social-emotional difficulties.(27) Whether sleep pathophysiology during the neonatal

period may contribute to such outcomes remains unknown, but some preliminary research suggests this possibility. A study of sleep patterns, defined by behavioral observations and not PSG,(28) demonstrated that premature infants (25-34 weeks gestation at birth) who were noted to have immature rather than organized sleep-wake transitions had lower scores on cognitive, verbal and executive function tests when they reached five years of age.

Although we used gold standard, attended PSG to define SDB, this study has some limitations. Each infant underwent detailed, intensive monitoring that limited the feasible sample size in this single-center analysis. Additionally, complete follow-up data for infants who underwent PSG during their NICU admission was not achieved, as most of the study population did not meet criteria for continued visits in a high-risk infant follow-up clinic. The criteria for referral to this clinic are standard in our NICU (Table 4) and only infants that meet these clinical criteria are evaluated in this clinic. Furthermore, the Bayley-III evaluates cognitive, motor and language ability at the 18-22 month period. We were unable to assess for subtler differences in learning, behavior, or executive function that may become evident later in childhood. Although comparison between sleep in neonates at risk for seizures and normal term neonates might be interesting, intensive 12-hour polysomnographic monitoring in completely healthy infants in the first days after birth is not feasible, at least in the United States. Families with infants at risk for seizures usually understand the medical necessity for EEG monitoring, and in that case, the additional leads required for full polysomnography is often an acceptable escalation. Few, if any parents of normal term neonates, would volunteer to spend additional time in a hospital to undergo intensive monitoring where no component is medically necessary. Additionally, the PSGs in our study were performed for research rather than clinical purposes, as none of the current study patients had clinically suspected apnea. Subsequent specific interventions as management for clinically significant SDB were not required or monitored by the research protocol. Thresholds and approaches to management of SDB

in neonates remain controversial but can include oxygen via nasal cannula, caffeine, and close observation of the infant.

Moreover, as no "normal" neonatal SDB thresholds are widely agreed upon by the sleep research or clinical communities, studies that compare presence and absence of SDB in neonates to subsequent outcomes of interest could have limited success. At this point it is difficult to know if the PSG results are indicative of significant SDB in the neonatal population. The best opportunity to make such research more valuable, among patients for whom polysomnography is feasible, is to study variation in outcomes in relation to a range of SDB levels documented in the first days of life. Such research could eventually help to define what elements or levels of neonatal SDB are impactful, even in the absence of data from normal newborns. Our study represents one of the first and most thorough attempts to accomplish this.

Conclusion

SDB as defined by current standards for children appears to be highly frequent among term and near-term newborns at risk for neonatal seizures. As previous literature has established that SDB diagnosed in this manner among older infants and children is associated with adverse neurocognitive outcomes, our findings provide rationale for longitudinal study of newborns who required intensive care, to establish whether SDB in neonates may be a modifiable risk factor for long-term neurocognitive disability.

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Conflict of Interest:

Meera Meerkov: The author declares no conflict of interest.

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Table 1: Demographic and clinical profile for 48 newborns at risk for seizures who underwent an attended polysomnogram in the NICU.

Characteristic	**Value***
Gestational age at birth, weeks	39.3 ± 1.6
Gender	21 male (44%)
Birthweight, kg	3.37 ± 0.55
Outborn**	29 (60.4%)
Intrapartum Complications	31 (65%)

Apgar Score – 1 minute	6 (0-9)
Neurologic exam (Thompson) Score	4 (0-15)
Seizures	22 (46%)
Intracranial Hemorrhage	1 (2%)
Length of NICU Stay (days)	10 (3-27)

* n (%), mean ± s.d or median (range)
** Provided simply to give some broad context for the infants in this NICU.

Table 2: Results of neurodevelopmental testing performed at 18-22 months for newborns at risk for seizures who underwent an attended polysomnogram in the NICU.

Characteristic	**Value***
Survival without severe disability, among n=37	30 (81%)
Bayley-III‡ – Cognitive Score, among n=28	100 (55-125)
Bayley-III‡ – Motor Score, among n=26	91 (46-118)
Bayley-III‡– Language Score, among n=27	91 (47-121)

* n (%) or median (range)
‡ Bayley-III = Bayley Scales of Infant and Toddler Development, Third Edition. Some children were unable to complete all three subscale assessments.

Table 3: Polysomnographic results for 48 newborns who required NICU care.

Characteristic	**Median (IQR)**
Total Recording Time (min)	723.2 (698.4-723.3)
Total Sleep Time (TST) (min)	569.5 (494.0-631.5)
% of TST in Quiet Sleep	44.6 (35.3-53.1)

% of TST in Active Sleep	39.6 (27.2-46.2)
% of TST in Indeterminate Sleep	15.8 (11.1-22.4)
Wake (% of Total Recording Time)	18.5 (11.0-32.0)
Sleep Efficiency (%)	83.3 (75.4-89.4)
Arousal Index (Number arousals/hour of sleep)	12.3 (7.0-18.2)
Apnea-Hypopnea Index (AHI, events/hour of sleep)	10.1 (3.3-18.5)
Quiet Sleep AHI	3.7 (1.5-8.6)
Active Sleep AHI	17.1 (5.8-30.2)
Obstructive apnea index	0.5 (0.1-1.7)
Central apnea index	1.0 (0.2-4.1)
Hypopnea Index	5.3 (2.3-12.5)
Mean SpO_2%	96 (95-98)
Minimum SpO_2%	81 (74-86)
% of Sleep Time with SpO2 <90%	2.7 (0.8-8.2)

Table 4: Criteria for Referral to High Risk Infant Follow-Up Clinic.

	High-risk Group	**Mod-risk Group**
Birthweight	< 1250 grams or GA ≤ 28 weeks	1251-1500 grams IUGR/SGA
Neuro	Hypoxic-ischemis encephalopathy Abnormal nero exam at discharge Grade III or IV IVH Periventricular leukomalacia Porencephaly/Ventriculomegaly Microcephaly Hydrocephalus Cooling	Documented Seizures Grade I or II IVH Documented Meningitis Congenital infection Exchange transfusion
Pulmonary	ECMO BPD on home O2, diuretics or pulm meds Tracheostomy CDH Complex congenital anomolies	Prolonged vent: Term > 7 days Preterm > 14 days CLD requiring Pulm meds
Other	Failure to grow Twin-Twin Transfusion Team member discretion	Hypoglycemia unresponsive to treatment Bilirubin > 20 mg/dL at term Team member Discretion