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SCIENTIFIC INVESTIGATIONS

Neurodevelopmental Outcomes at Two Years of Age for Premature Infants Diagnosed With Neonatal Obstructive Sleep Apnea

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Study Objectives: Neurocognitive deficits have been shown in school-aged children with sleep apnea. The effect of obstructive sleep apnea (OSA) on the neurodevelopmental outcome of preterm infants is unknown.

Methods: A retrospective chart review was performed for all preterm infants (< 37 weeks) who had neonatal polysomnography (PSG) and completed neurodevelopmental assessment with the Bayley Scales of Infant and Toddler Development, 3rd Edition, between 2006 to 2015 at Riley Hospital. Exclusion criteria included grade IV intraventricular hemorrhage, tracheostomy, cyanotic heart disease, severe retinopathy of prematurity, craniofacial anomalies, or central and mixed apnea on PSG. Sleep apnea was defined as an apnea-hypopnea index (AHI) > 1 event/h. Regression analyses were performed to find a relationship between PSG parameters and cognitive, language, and motor scores.

Results: Fifteen patients (males: n = 10) were eligible for the study. Median postmenstrual age at the time of the PSG was 41 weeks (37–46). Median AHI for the cohort was 17.4 events/h (2.2–41.3). Median cognitive, language, and motor scores were 90 (65–125), 89 (65–121), and 91 (61–112), respectively. Mean end-tidal CO_2 (median 47 mm Hg [25–60]) negatively correlated with cognitive scores (P = .01) but did not significantly correlate with language or motor scores. AHI was not associated with cognitive, language, or motor scores.

Conclusions: The median score for cognitive, language, and motor scores for preterm infants with neonatal OSA were within one standard deviation of the published norm. Mean end-tidal CO_2, independent of AHI, may serve as a biomarker for predicting poor cognitive outcome in preterm infants with neonatal OSA.

Commentary: A commentary on this article appears in this issue on page 1233.

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INTRODUCTION

Sleep plays an essential role in learning, memory consolidation, and cognition.[1] Sleep-disordered breathing (SDB) results in periods of occlusion of the upper airway during sleep, often associated with oxygen desaturations, arousals, and impaired sleep quality. SDB in preschool children has been associated with impaired executive functioning, attention, receptive vocabulary, and behavioral problems.[2] Even in the absence of obstructive sleep apnea (OSA) as diagnosed by polysomnography (PSG), SDB symptoms have been associated with reduced executive function and memory skills in 5-year-old children.[3] Reduction in nocturnal arousals in preschool children with SDB was associated with improved attention and aggressive behavior.[4] There is a strong association of SDB with deficits in cognitive abilities and academic achievement during school age, particularly in those who were born preterm.[5] Sleep apnea clearly has significant developmental and behavioral implications, and because children born preterm are more likely to receive a diagnosis of sleep apnea, compared to children born full term,[6] it is important to assess the association of sleep apnea with neurocognitive outcomes in this population.

BRIEF SUMMARY

Current Knowledge/Study Rationale: Preterm infants are an at-risk population for poor neurodevelopmental outcomes as well as sleep-disordered breathing (SDB). Sleep apnea has significant developmental and behavioral implications; however, the effect of neonatal SDB on the neurodevelopmental outcomes of preterm infants is unknown.

Study Impact: Although there is a high level of SDB in preterm infants, the median score for cognitive, language and motor scores were still within one standard deviation of the published norm. Mean end-tidal CO_2, independent of apnea-hypopnea index, in polysomnography may be worth consideration as a biomarker for predicting poor cognitive outcome in this high-risk population.

Preterm infants are at high risk for suboptimal neurodevelopmental outcomes on account of a host of neonatal comorbidities and disrupted neuronal maturation.[7] Risk factors for poor neurodevelopment include low gestational age, birth weight, presence of bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), severe neurological injury, pulmonary hypertension, sepsis, absence of antenatal steroids, patent ductus arteriosus (PDA) ligation, prolonged ventilation, prolonged total parenteral nutrition, and postnatal growth

retardation.[8–14] In addition to medical morbidities, preterm infants have reduced cerebral oxygenation during active sleep at post-term corrected age.[15] Preterm infants with SDB and associated sleep disruption may be at increased risk of reduced cerebral oxygenation. However, the effect of neonatal OSA on the neurodevelopmental outcomes of preterm infants is unknown. Capnography during PSG is challenging,[16] particularly in neonates. Although existing literature suggests no effect of permissive hypercapnia, during the first few days of life, on neurodevelopmental outcome,[17,18] there are no published data on the effect of sustained hypercapnia during sleep on neurocognitive outcomes in preterm infants.

The aim of our study was to assess cognitive/motor and language development at 2 years of age in preterm infants with documented neonatal OSA. Our hypothesis was that the severity of neonatal OSA would correlate with worsening cognitive, motor, and language development.

METHODS

This is a retrospective study evaluating preterm infants (< 37 weeks) cared for at Riley Hospital for Children at IU Health who received neonatal PSG between January 2006 and August 2015 prior to discharge from the neonatal intensive care unit and completed neurodevelopmental assessment with the Bayley Scales of Infant and Toddler Development, 3rd Edition (BSID-III), at 2 years of age at the Indiana University Newborn Follow-up Program. Exclusion criteria included grade IV intraventricular hemorrhage, tracheostomy, severe retinopathy of prematurity (stage 4 and stage 5), cyanotic heart disease, or syndromic craniofacial anomalies.

After institutional review board approval, demographics, medical morbidities, and results of neurodevelopmental testing were obtained from the hospital medical records. Postmenstrual age was defined as the sum of birth gestational age and chronological age. For the children who participated in the National Institute of Child Health and Human Development Neonatal Research Network (NRN) General Database and Follow-up study (inborn infants < 1000 g and/or < 27 weeks) data were obtained from the NRN local registry and for those outside of this cohort, data was manually extracted from medical records. Each baby had undergone a polysomnogram prior to discharge from the neonatal intensive care unit. The indications for the PSG were clinical concern for significant upper airway obstruction or for oxygen titration in patients with BPD at term corrected age. BPD is one of the most common morbidities in premature neonates. Although multiple definitions have been proposed, one commonly accepted version includes oxygen dependence at 28 postnatal days and severity and stratification as mild, moderate, or severe at 36 weeks postconceptual age (gestational age < 32 weeks) or at 56 days (gestational age > 32 weeks) based on supplemental oxygen delivery (ie, room air, fraction of inspired oxygen (FiO_2) 0.22–0.29, and FiO_2 > 0.30, respectively).[19] For the purpose of the study, we extracted the obstructive apnea-hypopnea index (AHI) from the medical records. Because most of the patients were on oxygen supplementation during the study, we did not include central or mixed apneas; their scoring was confounded by the presence of oxygen supplementation.

Polysomnography

PSGs were attended studies performed in the sleep laboratory and included the following monitoring parameters: electroencephalogram (EEG), electrooculogram, chin electromyogram, electrocardiogram, thermistor and pressure transducer airflow signals, respiratory inductance plethysmography or thoracic impedance measurement (prior to 2007), continuous oximetry, and end-tidal CO_2 ($ETCO_2$) monitoring. The collection software was Sandman v 9.0 (Embla systems LLC, Tonawanda, New York, United States). Oxyhemoglobin saturation was measured via pulse oximetry (Masimo, Irvine, California, United States). $ETCO_2$ was measured at the nose using BCI Capnocheck (Smiths Medical PM, Inc Waukesha, Wisconsin, United States) with side-stream sampling. Nasal airflow was acquired with a nasal cannula (Salter Labs, Arvin, California, United States).

PSGs were staged per scoring guidelines from Anders et al.[20] Before 2007, the institutional criteria followed for scoring respiratory events were: apnea for airflow limitation of 80% or greater from baseline for at least 2 breaths and hypopneas for airflow limitation of 30% or greater for at least 2 breaths duration associated with either ≥ 4% desaturation or an arousal. After 2007, the American Academy of Sleep Medicine (AASM) respiratory rules for children were followed for scoring respiratory events.[21] Before 2007, institutional criteria were followed for scoring arousals and awakenings. During non-rapid eye movement (Quiet & Indeterminate) sleep, arousals were scored as change in EEG frequency from theta to alpha or beta or from delta to theta, alpha, or beta for 3 seconds to 15 seconds. After 15 seconds, the EEG change was scored as an awakening. All gross body movements were scored as either arousals or awakenings consistent with the duration of the event. In rapid eye movement (Active) sleep, in addition to an EEG frequency change, an additional elevation of electromyogram amplitude during the event, was also required. After 2007, arousal index was scored as per AASM scoring criteria.[21] PSGs were reviewed and reported by board-certified pediatric sleep medicine physicians.

OSA was defined as AHI > 1 event/h. Severe sleep apnea was defined as AHI > 15 events/h. Data on mean $ETCO_2$, mean oxygen saturations, arousal index, and sleep efficiency were collected. If the study was performed on oxygen, the mean saturations on oxygen support was reported. Because of the physiological limitations of rapid respiratory rate, low tidal volume, the higher effect of apparatus dead-space in neonates, and the ventilation perfusion mismatch that affects patients with BPD, we defined hypoventilation as a mean $ETCO_2 \geq 45$ mm Hg.

Supplemental Oxygen Protocol

Oxygen titration goals were to maintain oxygen saturation (SaO_2) at 90% or greater. If the baseline SaO_2 was less than 90%, for ≥ 5 minutes then supplemental oxygen was initiated and the level adjusted to maintain saturations > 90%.

Table 1—Baseline characteristics and neonatal course of the entire study population (n = 15).

Birth gestation age, weeks, median (IQR:min–max)	26 (1:24–34)
Birth weight, g, median (IQR:min–max)	830 (280:660–2010)
Sex, male, n (%)	10 (67)
Effective FiO_2 ≥ 30% (defined by STOP-ROP data) at 36 weeks gestation, n (%)	9 (60)
Effective FiO_2 at 36 weeks gestation, %, median (IQR:min–max)	30 (19:21–100)
Days on conventional ventilator, median (IQR:min–max)	12 (23:0–40)
Days on CPAP, median (IQR:min–max)	13 (20:0–52)
Days on oxygen, median (IQR:min–max)	110 (65:11–120)*
PDA requiring surgery, n (%)	2 (13)
Grade 1/2/3 intraventricular hemorrhage, n (%)	5 (33)
Periventricular leukomalacia, n (%)	0 (0)
Retinopathy of prematurity stage 3, n (%)	2 (13)
Presence of pharyngomalacia/laryngomalacia/tracheomalacia on bronchoscopy performed around the time of sleep study, n (%)	12 (80)

* = Neonatal Research Network registry stops counting after 120 days. CPAP = continuous positive airway pressure, FiO_2 = fraction of inspired oxygen, IQR = interquartile range, max = maximum, min = minimum, PDA = patent ductus arteriosus, STOP-ROP = Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity.

Bayley Scales of Infant and Toddler Development

Toddler neurodevelopment was assessed with the BSID-III.[22] This validated tool uses developmental play tasks to compare motor, language, and cognitive development compared to standardized age norms.

Statistics

Univariate regression analysis was performed to find a relationship between cognitive, language, and motor composite scores and neonatal course as well as PSG parameters (AHI and mean $ETCO_2$). For significant outcomes on univariate analyses, we performed multivariate regression analysis. Pearson correlation was performed to find a relationship between AHI and mean $ETCO_2$. We divided the group based on mean $ETCO_2$ less than or equal to 45 mm Hg and compared the neonatal course, sleep study parameters and language, cognitive and motor scores between the 2 groups by Wilcoxon nonparametric rank-sum test and Fisher exact test, as applicable. Where conceptual models called for it, multivariable analyses were performed; although with the small sample size, models were performed with one covariate at a time using Bonferroni corrections to control for type I error. Analyses were performed with SAS v9.4 (SAS Institute, Cary, North Carolina, United States).

RESULTS

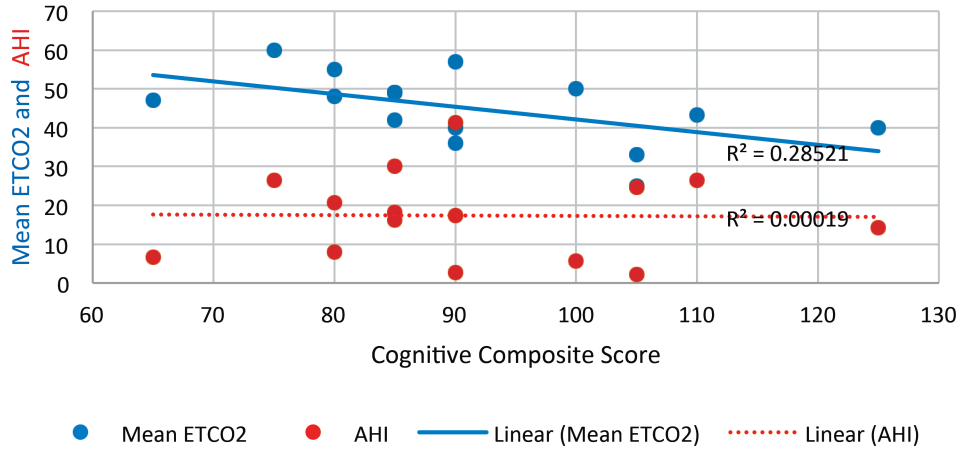
Fifteen patients (males: n = 10) were eligible for the study. Baseline characteristics and neonatal intensive care course has been described in **Table 1**. Eleven patients (73%) were on oxygen support during PSG. Median AHI for the cohort was 17.4 events/h (2.2–41.3). Median value of mean saturation was 99% (94% to 99.8%). Median arousal index was 14 events/h (7.5–23.4). Median sleep efficiency was 83% (67.4% to 93.8%). Median $ETCO_2$ during PSG was 47 mm Hg (25–60). The sleep apnea was obstructive in nature. Median age at performance of BSID-III testing was 22 months (corrected for prematurity). Median cognitive composite score, language composite score, and motor composite score were 90 (interquartile range [IQR]:min-max 25: 65–125), 89 (IQR:min-max 32: 65–121) and 91 (IQR:min-max 16.75: 61–112, 1 missing data), respectively, for the entire study sample.

AHI and mean $ETCO_2$ correlation did not reach statistical significance. Mean $ETCO_2$ negatively correlated with cognitive scores (P = .04) but not language or motor scores **(Figure 1).** AHI did not correlate with cognitive, language, or motor scores. In a multivariable model (using one covariate at a time to maintain power) after adjusting for birth gestational age, days on ventilator, days on oxygen and birth weight, a higher mean $ETCO_2$ was associated with lower cognitive scores (P = .01). **Table 2** is a comparison of baseline characteristics, neonatal course, sleep study parameters, and language, motor, and cognitive scores in the study sample divided into 2 groups based on mean $ETCO_2$ < 45 or > 45 mm Hg. Median language and cognitive scores were significantly lower in the group with mean $ETCO_2$ > 45 mm Hg.

DISCUSSION

This study suggests a high level of sleep apnea in preterm infants with a high prevalence of BPD. Ours is the first study to explore the relationship between OSA and cognitive outcomes in preterm infants. Our study shows that the mean $ETCO_2$ was associated with lower cognitive scores. A high mean $ETCO_2$ during PSG could potentially serve as a biomarker for predicting lower cognitive outcomes in this high-risk population. However, the median score for all 3 composite scores was still within one standard deviation of the published norm. There have been concerns that BSID-III testing may underestimate developmental delay.[23,24] In the light of this knowledge, our

Figure 1—Relationship between cognitive composite score versus AHI and mean $ETCO_2$.



AHI = apnea-hypopnea index, $ETCO_2$ = end-tidal CO_2.

Table 2—Comparison of baseline characteristics, neonatal course and sleep study parameters in the two groups based on mean $ETCO_2$ < 45 mm Hg.

	Mean $ETCO_2$ < 45 mm Hg (n = 7)	Mean $ETCO_2$ > 45 mm Hg (n = 8)	*P*
Clinical Measures			
Birth gestation age, weeks, median (min–max)	26 (25–34)	25.5 (24–26)	.03
Birth weight, g, median (min–max)	1050 (770–2010)	805 (660–950)	.04
Sex, male, n (%)	3 (43)	7 (88)	.12
Effective FiO_2 ≥ to 30% (defined by STOP-ROP data) at 36 weeks gestation, n (%)	3 (43)	6 (75)	.31
Effective FiO_2 at 36 weeks gestation, median (min–max)	0.21 (0.21–1.00)	0.30 (0.25–0.40)	.48
Days on conventional ventilator, median (min–max)	5 (0–28)	18 (4–40)	.04
Days on CPAP, median (min–max)	20 (0–52)	11.5 (0–48)	.56
Days on oxygen, median (min–max)	55 (11–120)	120 (80–120)	.02
PDA requiring surgery, n (%)	0 (0)	2 (25)	.46
Grade 1/2/3 intraventricular hemorrhage, n (%)	1 (14)	4 (50)	.16
Retinopathy of prematurity stage 3, n (%)	0 (0)	2 (25)	.46
Presence of pharyngoamalacia/laryngomalacia/tracheomalacia on bronchoscopy performed around the time of sleep study, n (%)	6 (86)	6 (75)	> .99
Postmenstrual age at the time of PSG, weeks, median (min–max)	40 (38–44)	41 (37–46)	.81
PSG Measures			
Apnea-hypopnea index, median (min–max)	16.2 (2.2–41.3)	17.8 (5.6–30)	.86
Value for mean saturations, median (min–max)	97.8 (94–99.3)	99.15 (97.9–99.8)	.05
Arousal index, median (min–max)	13.4 (7.5–23.4)	14.55 (7.6–20.8)	.66
Sleep efficiency, median (min–max)	83.6 (67.4–92)	83 (74.7–93.8)	.83
Neurodevelopmental Parameters			
Cognitive score, median (min–max)	105 (85–125)	82.5 (65–100)	.01
Language score, median (min–max)	100 (77–121)	75.5 (65–106)	.04
Motor score, median (min–max)	91 (85–107)	91 (61–112)	.65

CPAP = continuous positive airway pressure, $ETCO_2$ = end-tidal CO_2, FiO_2 = fraction of inspired oxygen, max = maximum, min = minimum, PDA = patent ductus arteriosus, PSG = polysomnography, STOP-ROP = Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity.

results may be underestimating poor cognitive, language, and motor outcome in these infants.

Despite excluding infants with severe neurological injury, tracheostomy, and severe retinopathy of prematurity, our patients remained highly morbid. Sixty percent of our patients were on greater than 30% FiO_2 at 36 weeks of corrected age, consistent with severe BPD. Infants with BPD are known to suffer frequent episodes of hypoxemia and desaturations,[25]

which could impair the development of cognitive functions.[26] Additionally, 80% of our patients had some form of airway obstruction confirmed by airway endoscopy (pharyngo/laryngo/tracheomalacia) at the time of sleep study. Our patients had an elevated median AHI compared to published norms for children,[27] which supports existing data that preterm infants are more likely to have SDB.[5,6,28] This may be multifactorial, including upper airway obstruction[29] and/or chronic lung parenchymal involvement with low pulmonary reserve. Our patients also had an elevated mean $ETCO_2$, which could result from a combination of airway obstruction and ventilation perfusion mismatch secondary to BPD.

Seventy-three percent of our patients were on oxygen at the time of neonatal PSG. This may have led to underestimation of their uncorrected mean oxygen saturations. However, oxygen supplementation typically will not prevent obstructive episodes from occurring and the infant may still experience upper airway obstructive events resulting in arousals and sleep fragmentation. As these patients were continuously being treated with oxygen, it is unlikely that prolonged uncorrected hypoxia contributed to the neurocognitive effect in our study. Our patients had increased AHI and arousal index as well as poor sleep efficiency, suggesting that despite oxygen supplementation, preterm neonates are at risk for adverse outcomes of sleep apnea. A review of the literature does not reveal normative data on arousal indices of neonates. In a study by Traeger et al.,[30] arousal index in 2- to 9-year-old children was reported as 8.8 ± 3.8 events/h (2.8–18.3). Our cohort had a higher arousal index with a sleep efficiency of 83%. Normative data on neonatal PSG is important to decide whether this elevated arousal index is a function of age or a manifestation of OSA. Regardless, this poor fragmentation of sleep may certainly affect cognitive outcomes.

It is known that sleep apnea can cause impaired executive functioning and behavior problems. Functional magnetic resonance imaging data in adults have suggested that SDB significantly alters functional connectivity in the cerebellar, frontal, parietal, temporal, occipital, limbic and basal ganglia regions. This impairment in network organization may result in altered responses in autonomic, cognitive, and sensorimotor functions.[31] Our results did not show any association between AHI and composite scores. Despite the significantly elevated AHI of our study sample, the cognitive scores were within one standard deviation of published norms. Although Ng and Chan[32] have reviewed normative data on infant PSG, the reviewed studies do not include neonates. Therefore, what is considered severe OSA in the older child and is currently being extrapolated to neonates in clinical practice may not apply to neonates.[33] However, we were limited by small sample size.

AHI and mean $ETCO_2$ did not correlate significantly in our study, which is consistent with existing literature.[34] It has been suggested that the utility of nocturnal capnometry may go beyond apnea detection and quantification of hypoventilation syndromes. Instead it may reflect the balance of apnea and postapnea duration, which are not captured by AHI.[35] Jaimchariyatam et al. suggested that nocturnal elevation of CO_2 may be due to a ventilatory impairment in the balance between accrual of CO_2 (longer apnea duration) and more importantly the unloading of CO_2 (longer postapnea duration). This study proposed use of exhaled CO_2 as a physiological marker of disease severity that is independent of AHI.[35]

Our study had a high median $ETCO_2$ (47, 25–60 mm Hg). Sixty percent of our patient sample had BPD. Permissive hypercapnia-intentionally allowing alveolar hypoventilation and increased partial pressure of carbon dioxide ($PaCO_2$) has been advocated as a means to decrease ventilator-induced lung injury and BPD.[36] Existing literature suggests no effect of permissive hypercapnia on neurodevelopmental outcome.[17,18] Additionally, the Childhood Adenotonsillectomy, or CHAT, trial did not report any correlation of percentage of total sleep time (TST) with $ETCO_2 > 50$ mm Hg with changes on the cognitive and behavioral assessment at median age of 7.1 years. The median $ETCO_2$, while asleep, of that study sample was 45 mm Hg,[34] which is a little lower than in our study. However, our study did show a significant association between nocturnal hypercarbia and cognitive composite scores. There are two significant points to consider. Most of the cited literature has correlated TST above $ETCO_2 > 50$ mm Hg with neurodevelopmental outcome. In our study, we have utilized a separate measure (mean $ETCO_2$) for correlation. The second point of interest is that in the study on infants with permissive hypercapnia,[18] neurocognitive outcomes were correlated to arterial CO_2 levels only within the first 14 days of life. However, in our study, $ETCO_2$ was estimated at a median chronological age of 4 months. Studies have demonstrated in adults that the current $ETCO_2$ sampling devices may underestimate arterial CO_2 by 5–10 mm Hg, based on the pathophysiology of the patient.[16,37,38] This underestimation may be greater in children, who physiologically have a higher respiratory rate, which may be further worsened with BPD. Additionally, the dilutional effect of any concurrent oxygen supplementation during $ETCO_2$ measurement could also have played a role. Thus, the arterial $PaCO_2$ may have been much higher in our sample of preterm infants, even when corrected to full term. An alternate definition from current polysomnographic pediatric hypoventilation criteria may therefore be necessary in neonates and young infants.

SDB encompasses a wide spectrum ranging from primary snoring to OSA. As per AASM guidelines, PSG criteria for pediatric hypoventilation have been defined as at least 25% of TST with hypercapnia ($PaCO_2 > 50$ mm Hg). However, we did not have consistent reporting of percentage of TST with hypercapnia in all PSG. We therefore used mean $ETCO_2$ as a surrogate for hypoventilation. Paruthi et al. demonstrated that percentage TST $ETCO_2 > 50$ mm Hg did not correlate with changes in cognitive or behavioral measures at 5 to 9.9 years of age.[34] Data on prematurity were not available for this study sample.[34] Based on our study results, mean $ETCO_2$ may be a more sensitive marker to detect cognitive outcome and its role should be explored further, particularly in the neonatal age group.

Limitations

Our study comprises a small cohort of preterm infants due to strict exclusion criteria and to exclude the confounding effects of known predictors of poor neurodevelopmental outcome. We did not have data on a repeat PSG prior to BSID-III testing to confirm persistence or resolution of SDB in the interim. We did

not have data on any interventions, such as adenoidectomy or tonsillectomy, performed between the PSG and BSID-III testing. We were unable to correlate $ETCO_2$ with blood gas CO_2 level at the time of PSG, as these data were unavailable. The coadministration of oxygen with CO_2 during neonatal PSG could have introduced a dilutional effect of $ETCO_2$ estimation. These are limitations of a retrospective study with access to existing available data. We also did not have consistent data on maternal education or socioeconomic status in our patients, which could play a role in the neurodevelopmental outcomes. Finally, this is the experience of a single center with institutional practice biases that could affect the study results.

CONCLUSIONS

In conclusion, there is a high prevalence of SDB in preterm infants with dynamic airway collapse and bronchopulmonary dysplasia in the neonatal period. Mean $ETCO_2$ negatively correlates with cognitive outcome. Preterm neonates with SDB should be closely monitored for cognitive delays. This study highlights the importance of normative data on neonatal sleep apnea to better interpret thresholds of clinical significance.

ABBREVIATIONS

AASM, American Academy of Sleep Medicine
AHI, apnea-hypopnea index
BSID, Bayley Scales of Infant and Toddler Development
BPD, bronchopulmonary dysplasia
CO_2, carbon dioxide
EEG, electroencephalogram
$ETCO_2$, end-tidal CO_2
FiO_2, fraction of inspired oxygen
NEC, necrotizing enterocolitis
NRN, Neonatal Research Network
OSA, obstructive sleep apnea
$PaCO_2$, partial pressure of carbon dioxide
PDA, patent ductus arteriosus
PSG, polysomnography
SDB, sleep-disordered breathing
TST, total sleep time

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