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COMMENTARY

Infants Sleep for Brain

Commentary on Bandyopadhyay et al. Neurodevelopmental outcomes at two years of age for premature infants diagnosed with neonatal obstructive sleep apnea. *J Clin Sleep Med.* 2017;13(11):1311–1317.

Madeleine M. Grigg-Damberger, MD[1]; Kathy M. Wolfe, MD[2]

[1]Departments of Neurology, Clinical Neurophysiology, Epilepsy and Sleep Medicine, University of New Mexico School of Medicine, Albuquerque, New Mexico; [2]Department of Neurology, University of New Mexico School of Medicine, Albuquerque, New Mexico

Piaget thought play was the major "work" of children,[1] but for neonates and young infants, it is sleep. Infants born at term average 16 to 18 hours per day sleeping, 50% of it in REM sleep.[2,3] Premature infants spend even more time asleep; 80% of it in REM sleep. The greater time spent sleeping in infancy and early childhood is thought to reflect the crucial role sleep (especially REM sleep) plays in fostering optimal brain development, cognition, and behavior.

In this issue of the *Journal of Clinical Sleep Medicine*, Bandyopadhyahy et al.[4] retrospectively identified 15 infants born extremely premature who had neonatal obstructive sleep apnea (OSA) on neonatal polysomnography (PSG) done at a median age of 41 weeks postmenstrual age (PMA) and chronological age of 4 months. The authors correlated PSG findings with neurodevelopmental outcomes on the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) at age 2 years (and as part of an ongoing longitudinal study of infant development). The median obstructive apnea-hypopnea index (OAHI) was 17 events/h of sleep (abnormal defined as an OAHI > 1 events/h of sleep). Using multiple regression analyses, the authors found the only significant PSG correlate was an elevated mean end-tidal CO_2 ($ETCO_2$) > 45 mm Hg, which correlated with lower cognitive scores on the BSID-III (a modest one standard deviation below the mean). $ETCO_2$ levels may have been even higher because 73% were on supplemental oxygen during the PSG (likely to lead to lower $ETCO_2$ levels by dilution).

Most of these infants had severe bronchopulmonary dysplasia (BPD). BPD is currently defined as the need for supplemental oxygen at 36 weeks PMA or ≥ 28 days following birth,[5] and the condition was severe in 60% of these infants (based on a FiO_2 requirement > 30% FiO_2 > 36 weeks PMA). BPD appears to be caused by varying combinations of maternal chorioamnionitis or preeclampsia, postnatal mechanical ventilation, hyperoxia, and inflammation in infants born extremely premature.[6] Of note, BPD develops in only half of extremely premature infants.

Despite so many advances in the management of extremely premature infants, the incidence of BPD has not significantly diminished. It remains the most frequent adverse outcome for infants less than 30 weeks PMA and the most common chronic lung disease of infancy. It may be the longest-lasting obstructive lung disease in humans, often unrecognized and untreated in BPD survivors.[5,7–9] More than half of 11-year-olds with a history of BPD had chronic cough and asthma-like symptoms than their term-born peers, but fewer than half were treated.[8] Adults who had BPD as infants are at increased risk for subclinical right ventricular dysfunction, obstructive lung disease, exercise intolerance, emphysema, asthma-like symptoms, and reduced quality of life due to respiratory symptoms.[6] One study found that these adults were twice as likely to report wheezing and three times more likely to use asthma medications than controls.[9]

Is an elevated $ETCO_2$ on a neonatal PSG a biomarker for neurodevelopmental outcome? Permissive hypercapnia (intentionally reducing tidal volumes to increase $ETCO_2$ levels and mild hypercapnia during the first 2 weeks following birth) is one of the treatment strategies that neonatologists have been using to decrease risk for ventilator-induced lung injury and BPD. The PHELBI study (a large prospective randomized multicenter study examining the adverse effects of permissive hypercapnia done for 2 weeks following very premature births) found permissive hypercapnia did not further compromise neurodevelopmental outcomes at age 2 years.[10] In this study, hypercapnia was identified on overnight PSG performed a mean of 4 months following birth.

There are no comparable studies to evaluate whether elevated $ETCO_2$ at 41 weeks PMA after extremely premature birth is concerning, especially because of the study limitations. Study limitations include: small sample size, lack of controls without OSA, data on interventions for OSA, no correlation of $ETCO_2$ with arterial blood gas, supplemental oxygen during the PSG, and PSG was not repeated when neurodevelopmental testing was done to assess whether OSA had persisted.

The design of this study did not permit detailed analysis of sleep architecture. Four prospective studies have shown poor-quality sleep in hospitalized premature and term infants has lasting effects on later cognitive functioning.[11–13] One study showed infants born preterm compared to those born term at the same PMA had shorter sleep cycles, less trace alternant, more REM sleep, more/longer arousals, more body movements, and more rapid eye movements.[7] Less REM sleep time

in 81 infants born 32 to 36 weeks PMA was associated with poorer developmental outcomes on the BSID-II at 6 months.[11] Premature infants who had longer periods of sustained sleep, more time spent in REM sleep, and more periods of REM sleep with rapid eye movements had better cognitive outcomes. Another study of 65 infants born premature whose mothers reported they slept poorly as neonates exhibited poorer attention and greater distractibility at 4 and 18 months than those who slept well.[12] Sleep/wake transitions from non-rapid eye movement sleep to wakefulness in 143 infants born mean 32 weeks PMA were associated with greater neonatal neuromaturation, less negative emotionality, and better verbal, symbolic, and executive competencies at age 5 years.[13] However, REM sleep then crying, and short episodes of REM and non-rapid eye movement sleep predicted poorer outcomes.

Such findings have prompted interventions to improve sleep quality in neonatal intensive care units including kangaroo care (placing baby upright against the parent's bare chest to sleep), environmental noise reduction, lights on 7:00 AM to 7:00 PM (and off the rest of the time), nonpharmacological treatments for pain, and postponing routine care and procedures when the infant is sleeping.[14–18] More studies exploring the effects of poor sleep in infants spending many days or months of their lives in neonatal intensive care are needed to identify best treatment approaches to optimize neurobehavioral outcomes.

CITATION

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Address correspondence to: Dr. Madeleine M. Grigg-Damberger, The University of New Mexico, Department of Neurology, MSC10 5620, 1 University of New Mexico, Albuquerque, NM 87131; Tel: (505) 272-3342; Fax: (505) 272-6692; Email: smdamberg@msn.com

DISCLOSURE STATEMENT

The authors report no conflicts of interest.