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COMMENT

Early respiratory dysfunction and later brain injury: double jeopardy?

Stephannie M. Baehl Voller[1,2] and Nicolas F. M. Porta[1,2]

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Bronchopulmonary dysplasia (BPD) is the most common complication associated with prematurity and is more prevalent in extremely premature infants.[1] Due to advances in neonatal care, more extremely premature infants are surviving leading to new management challenges and the need to investigate mechanisms and risk factors influencing both short- and long-term morbidity associated with BPD.[2] One major morbidity associated with BPD is neurodevelopmental impairment, which is often accompanied by white matter injury (WMI). Infants with BPD may have impairment in cognition, education, and behavior.[3,4] BPD has been associated with cerebral palsy (CP) in infants born extremely preterm who continue to require both supplemental oxygen and mechanical ventilation at 36 weeks postmenstrual age (PMA).[5] Independently, WMI may predict cognitive and motor outcomes in preschool-age children born preterm. Clinical variables, including BPD, enhance the predictive strength for cognitive and motor outcomes in these children.[6] Prolonged duration of mechanical ventilation is associated with smaller brainstem volumes along with white matter abnormalities.[7] Smaller pons and medulla volumes predict adverse motor outcomes at preschool age.[7,8]

BPD is a consistent and strong independent risk factor for neurodevelopmental impairment and studies have investigated the effect of prolonged invasive ventilation in neonates with BPD. Increased time requiring invasive respiratory support has been associated with greater adverse neurodevelopmental impairment, leading to the development of treatment strategies that decrease invasive mechanical ventilation exposure.[9,10] Unfortunately, due to significant lung disease and respiratory dysfunction, many neonates would not survive without this higher level of support and require mechanical ventilation to provide adequate oxygenation and ventilation. Identifying potentially useful biomarkers or modifiable exposures during the patient's need for mechanical ventilation may help mitigate severe lung injury and optimize neurodevelopment. Optimal evaluation of the roles of early respiratory support exposures on later neurodevelopmental outcomes in children with BPD is challenging. Infants with BPD who require prolonged respiratory support are more likely to be exposed to sedation and systemic corticosteroids, both associated with neurodevelopmental impairment. The chronicity of the exposures and the condition makes it challenging to assess the timing of the insult, and whether the exposure becomes an outcome in itself (infants who need more respiratory support tend to need it longer too). In addition to causing direct mechanical and oxidative lung injury, prolonged mechanical ventilation and other morbidities that are associated with BPD, such as chorioamnionitis, neonatal sepsis, and necrotizing enterocolitis (NEC), may further complicate causal pathways between BPD and brain injury. These comorbidities can aggravate lung injury through mechanical factors (due to greater and/or longer need for mechanical ventilation) or biologic alterations related to the generation of systemic inflammation, which has been linked to brain injury in premature neonates. Further exploration of the association between these pro-inflammatory conditions and brain injury may help identify other additional opportunities.

Known respiratory precursors of BPD include early cumulative supplemental oxygen (CSO) and cumulative mean airway pressure (CMAP). CSO has been shown to be an independent predictor of BPD and BPD or death at 36 weeks PMA.[11] CMAP also predicts BPD or death at 36 weeks PMA after adjustment for supplemental oxygen exposure.[11] In a recent volume of *Pediatric Research*, Grelli et al.[12] again demonstrate that early CSO and CMAP are associated with the later determination of BPD. The authors further investigated the association of CSO and CMAP with WMI and neurodevelopment. This association had not been previously studied, and represents potentially modifiable exposures that could impact important outcomes in at-risk infants.

Grelli et al. conclude that CSO and CMAP during the first 28 days of life predict WMI as well as BPD. In this study, WMI was not associated with adverse neurodevelopmental outcome as hypothesized by the authors. This finding may be attributed to low power for the analysis and relatively lower risk in the study cohort. Only five infants with moderate–severe WMI had neurodevelopmental assessments using the Bayley Scales of Infant and Toddler Development, 3rd edition (Bayley-III). Future studies enrolling infants at higher risk for brain injury with more robust neurodevelopmental follow-up data would be helpful in determining the impact of WMI and neurodevelopmental outcome in this population.

Although in this study, WMI was not found to be an important mediator between BPD and adverse neurodevelopmental outcomes, Grelli et al. found that CSO was independently associated with decreased language and cognitive performance on the Bayley-III at 30 months corrected age. These data suggest that early need for greater respiratory support may predict neurodevelopmental impairment. With this knowledge, providers may advocate for earlier implementation of rehabilitation therapies such as speech therapy, occupational therapy, and physical therapy in higher-risk infants, which may ultimately improve long-term outcomes. Prior studies have shown that infants with BPD benefit from early intervention, both in terms of cognitive

[1]Department of Pediatrics/Neonatology, Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA and [2]Department of Pediatrics, Northwestern University Feinberg School of Medicine, Chicago, IL, USA
Correspondence: Nicolas F. M. Porta (n-porta@northwestern.edu)

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and motor development.[13] In addition, providing a neurodevelopmentally oriented approach to infants with BPD may result in improved outcomes.[14]

The authors recognized some additional limitations to their study, including small sample size, short follow-up period of 30 months corrected age, loss to follow-up, and perhaps, most importantly, low rate of severe BPD. However, their data show a novel association between early respiratory support, late WMI, and adverse neurodevelopmental outcomes. This study provides some hints regarding the influence of respiratory status on brain health and raises the important question of whether modifications in clinical practice regarding respiratory support in the first month of life can lead to improved neurodevelopmental outcomes. Further investigation regarding threshold exposure and outcome would be especially helpful in providing more specific guidance for parents and clinical strategies for providers. Specifically, it will be important to determine whether the modest differences shown by Grelli et al. are magnified in a larger cohort of patients with more substantial lung disease and greater risk for WMI. It is also important to recognize that the goal may not simply be to minimize respiratory support (early or late), but rather optimize it. Overly aggressive weaning of respiratory support, in the hopes of minimizing exposure to invasive respiratory support, may also lead to neurologic injury through chronically insufficient cerebral oxygenation or increased periods of physiologic instability that can produce intermittent hypoxemic events. Inadequate respiratory support may also impede the successful implementation of rehabilitation therapies. In addition to optimizing respiratory support, avoiding other sources of inflammation and proinflammatory states in the preterm neonate maybe critical for improved outcomes.

Novel research strategies aimed at fine measurement of respiratory support exposures and specific assessment of neurocognitive outcome, such as was targeted in this article, are critical in the ongoing path toward a better understanding of what we are actually doing, and how to do it better. Ultimately, further investigation may lead to a better understanding of the mechanisms by which respiratory dysfunction and treatment strategies affect neurodevelopmental outcomes in premature infants.

ADDITIONAL INFORMATION

Competing interests: The authors declare no competing interests.

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REFERENCES

1. Stoll, B. J. et al. Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. *Pediatrics* **126**, 443–456 (2010).
2. Davidson, L. M. & Berkelhamer, S. K. Bronchopulmonary dysplasia: chronic lung disease of infancy and long-term pulmonary outcomes. *J. Clin. Med.* **6**, 4 (2017).
3. Gallini, F., Arena, R., Stella, G., Frezza, S. & Maggio, L. Neurodevelopmental outcomes of premature infants with bronchopulmonary dysplasia. *Acta Biomed.* **85**, 30–34 (2014).
4. Cheong, J. L. Y. & Doyle, L. W. An update on pulmonary and neurodevelopmental outcomes of bronchopulmonary dysplasia. *Semin. Perinatol.* **42**, 478–484 (2018).
5. Van Marter, L. J. et al. ELGAN Study Investigators. Does bronchopulmonary dysplasia contribute to the occurrence of cerebral palsy among infants born before 28 weeks gestation? *Arch. Dis. Child Fetal Neonatal Ed.* **96**, F20–F29 (2011).
6. Cayam-Rand, D. et al. Predicting developmental outcomes in preterm infants: a simple white matter injury imaging rule. *Neurology* **93**, e1231–e1240 (2019).
7. Guillot, M. et al. Mechanical ventilation duration, brainstem development, and neurodevelopment in children born preterm: a prospective cohort study. *J. Pediatr.* **226**, 87–95 (2020). e3.
8. Raffay, T. M. & Martin, R. J. Preemie brains don't like mechanical ventilation. *J. Pediatr.* **226**, 12–14 (2020).
9. Walsh, M. C. et al. Extremely low birthweight neonates with protracted ventilation: mortality and 18-month neurodevelopmental outcomes. *J. Pediatr.* **146**, 798–804 (2005).
10. Vliefenthart, R. J. S. et al. Restricted ventilation associated with reduced neurodevelopmental impairment in preterm infants. *Neonatology* **112**, 172–179 (2017).
11. Wai, K. C. et al. Early cumulative supplemental oxygen predicts bronchopulmonary dysplasia in high risk extremely low gestational age newborns. *J. Pediatr.* **177**, 97–102e102 (2016).
12. Grelli, K. N. et al. Bronchopulmonary dysplasia precursors influence risk of white matter injury and adverse neurodevelopmental outcome in preterm infants. *Pediatr. Res.* https://doi.org/10.1038/s41390-020-01162-2, Online ahead of print (2020).
13. Van Hus, J. et al. Early intervention leads to long-term developmental improvements in very preterm infants, especially infants with bronchopulmonary dysplasia. *Acta Paediatr.* **105**, 773–781 (2016).
14. Bauer, S. et al. Factors associated with neurodevelopmental impairment in bronchopulmonary dysplasia. *J. Pediatr.* **218**, 22–27 (2020).