



COMMENT

Early EEG in neonates with mild hypoxic–ischemic encephalopathy: more than meets the eye

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Neonatal hypoxic–ischemic encephalopathy (HIE) is a key contributor to adverse neurodevelopmental outcomes, with HIE severity correlating with severity of neurodevelopmental disability. It was previously believed that infants with mild HIE had normal neurodevelopment. However, recent studies suggest that infants with mild HIE are also at risk for neurodevelopmental impairments.¹ A recent multicenter cohort study reported that children with mild HIE have lower cognitive composite scores than healthy controls at age 2–3 years.² A systematic review reported adverse neurodevelopmental outcomes in approximately 25% of infants with mild encephalopathy.³ Timing of neurodevelopmental outcome assessment is also emerging as a key issue in understanding the neurodevelopmental consequences of mild HIE: normal neurodevelopmental outcomes were seen at 2 years of age,⁴ but lower Intelligence Quotient scores were observed at 5 years when compared to children without HIE.⁵ Thus, long-term neurodevelopmental follow-up is critical in infants with mild HIE as neurodevelopmental impairments may become more apparent with age. Neonates characterized as having mild HIE based on early clinical examinations can have brain injury on magnetic resonance imaging.^{6,7} Together, these findings suggest that mild HIE is not as “benign” as previously believed. Advanced neuroimaging and neurophysiologic studies may provide insight into structural and functional brain abnormalities that contribute to the neurodevelopmental impairments seen in children with mild HIE.

With the introduction of therapeutic hypothermia, there has been a significant reduction in mortality and morbidity of neonates with HIE.⁸ However, at present, therapeutic hypothermia is the standard of care for infants with moderate-to-severe HIE only and must be initiated within 6 hours of life. Neonates with mild HIE were excluded from clinical trials of therapeutic hypothermia as it was previously believed that these infants had normal neurodevelopmental outcomes. Thus, the benefit of therapeutic hypothermia for neurodevelopmental outcomes in infants with mild HIE is unknown. Recently, more centers have begun using therapeutic hypothermia in neonates with mild HIE, although it is not considered standard of care in this population.⁹ As reviewed in this recent position paper, rigorous clinical trials are required to determine whether therapeutic hypothermia improves neurodevelopmental outcomes in newborns with mild HIE.¹⁰

Clinical trials of therapeutic hypothermia are difficult to perform in newborns with mild HIE due in part to challenges in patient selection. As described by Sarnat,¹¹ neonates with mild HIE may appear normal or have subtle findings on early neurological examinations. The level of encephalopathy increases in severity over time, particularly in the subsequent 2–3 days of life. This

evolution in neurological examination findings coupled with the need to initiate therapeutic hypothermia within the first 6 hours of life presents challenges in using clinical examination to identify newborns with mild HIE for clinical trials. Thus, biomarkers of mild HIE would be helpful in identifying patients with mild HIE for clinical trials of therapeutic hypothermia. In particular, abnormalities in electroencephalography (EEG) background and heart rate variability (HRV) have been described in newborns with HIE, with an association between severity of abnormalities in these measures and severity of HIE.^{12,13} However, early abnormalities in EEG background and HRV in newborns with mild HIE are not yet well described. Identifying early markers of mild HIE using EEG background and HRV could potentially serve as biomarkers of mild HIE and assist with the selection of appropriate patients for clinical trials of therapeutic hypothermia.

In this issue of *Pediatric Research*, Garvey et al. used qualitative and quantitative analyses to evaluate EEG and HRV abnormalities in the first 6 hours of life in term neonates with mild HIE ($n = 58$) compared to matched healthy term newborns ($n = 16$). Newborns from four prospective studies were included if they met criteria for mild HIE as defined in the PRIME study¹; notably, neurophysiologists were not blinded to patient group. Qualitative analysis of EEG background features revealed at least one abnormality in the EEG recording of 72% infants with mild HIE. The qualitative EEG abnormalities most predictive of mild HIE were the absence of sleep–wake cycling and the presence of diffuse slow waves. Consistent with qualitative EEG analyses, quantitative measurements of EEG amplitude, spectral shape, and interhemispheric connectivity revealed significantly increased power in the delta band in neonates with mild HIE compared to healthy term newborns. The study team did not observe any significant differences in measures of HRV between groups. Overall, the authors demonstrate qualitative and quantitative differences in EEG background, particularly in sleep–wake cycling and excessive slow wave activity, in infants with mild HIE that can be seen within the first 6 hours of life—during the window for initiation of therapeutic hypothermia.

The findings of the study by Garvey et al. raise important questions and point toward avenues for future research. The authors observed early EEG abnormalities during a period when the neurological abnormalities in infants with mild HIE are still evolving making it difficult to clinically identify these infants. Their findings suggest that EEG could be used as an ancillary measure of HIE severity in patients with suspected mild HIE with subtle or even normal neurological examinations in order to select patients for clinical trials of therapeutic hypothermia. However, in clinical

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practice, continuous EEG monitoring may not be available or accessible in many centers as it is resource intensive. It would be especially challenging to initiate continuous EEG monitoring within the timeframe of the first 6 hours of life required to initiate therapeutic hypothermia. Instead, many centers use amplitude EEG (aEEG) monitoring, which is available as a bedside neuromonitoring tool to clinicians in the Neonatal Intensive Care Unit (NICU). It would be important to determine whether the changes seen with continuous EEG monitoring are also visualized with aEEG monitoring as it would allow for easier identification and selection of infants with mild HIE, particularly within the timeframe of the first 6 hours of life required for initiation of therapeutic hypothermia. This may serve as an opportunity to use aEEG as a measure of encephalopathy severity by neonatal transport teams that are sent by many centers to assess and transfer neonates from delivery hospitals to tertiary care NICUs for therapeutic hypothermia.

Garvey et al. observed alterations in EEG background, particularly in sleep–wake cycling and excessive slow wave activity, in infants with mild HIE compared to healthy term newborns within the first 6 hours of life. Sleep–wake cycling has long been recognized as an important indicator of the severity of neonatal HIE with the onset of sleep–wake cycling carrying important prognostic information.¹⁴ This prior experience suggests that the early alterations in sleep–wake cycling could be observed with aEEG. The importance of sleep–wake cycling in neonates with mild HIE is especially notable given the recent recognition that sleep-related reorganization of neural activity on EEG in preterm neonates carries novel prognostic information.¹⁵ The association between early sleep–wake cycling and long-term neurodevelopmental outcomes in neonates with mild HIE warrants further investigation.

EEG background abnormalities predict neurodevelopmental outcomes in neonates with HIE. In particular, EEG background at 36 and 48 h of life has been associated with severity of neurodevelopmental disability in infants with HIE who received hypothermia.¹³ A normal early EEG within 6 hours of life has been associated with normal neurodevelopmental outcomes.⁴ The study by Garvey et al. addresses an important evidence gap: the relationship between abnormalities in early EEG background and neurodevelopmental outcomes in newborns with mild HIE. Their findings of EEG changes in neonates with mild HIE reinforces that there is more than meets the eye in this group of neonates. Importantly, early EEG predictors of adverse neurodevelopmental outcomes in newborns with mild HIE could be used to identify infants at highest risk for neurodevelopmental impairments and targeted for therapeutic trials, such as therapeutic hypothermia. Furthermore, neonates at high risk for adverse outcomes could be followed more closely with better access to early intervention strategies. Understanding EEG background abnormalities in infants with mild HIE may also provide insight into functional alterations in the brain that underlie the neurodevelopmental outcomes seen in this population.

There is more than meets the clinical “eye” in neonates with mild HIE including early EEG changes and neurodevelopmental impairments outcomes that were not as benign as previously believed and become more apparent with age.³ The new findings by Garvey et al. suggest a role for early aEEG to identify neonates with mild HIE for clinical trials as neurologic abnormalities evolve in the first few days of life.¹¹ Early EEG abnormalities in infants with mild HIE may also provide insight into functional brain alterations contributing to adverse neurodevelopmental outcomes in this population. Given findings in the term HIE

population and from neonates born preterm, a better understanding of the neurobiology of sleep disturbances is warranted. Future studies should also consider longitudinal advanced neuroimaging and neurophysiologic tools to understand the trajectory of brain changes that underlie the neurodevelopmental abnormalities seen in infants with mild HIE providing further insight into potential interventions.

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ADDITIONAL INFORMATION

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