Neonatal seizures in the era of therapeutic hypothermia

Keeping it cool

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The neonatal brain is potentially wired for seizures based on the timing and severity of disease states in the context of vulnerabilities of the immature brain.[1] Seizures in neonates are often the presenting sign of potential brain injury from multiple etiologies, including asphyxia or hypoxic ischemic encephalopathy (HIE). Seizures may also result from diverse causes of neonatal encephalopathy, with those in the neonatal period portending a worse neurodevelopmental prognosis if associated with damage to the developing brain.[2] The diagnosis of seizures in the neonatal population, however, can be challenging. Seizures are often subtle; they may be associated with autonomic symptoms or fail to display clinical manifestations coincident with electrographic seizures.[3]

Distinguishing seizures from nonseizure movement disorders requires clinical judgment anchored by bedside EEG monitoring.[4] Conventional EEG is considered the gold standard for the diagnosis of neonatal seizures. The American Clinical Neurophysiology Society has guidelines for continuous EEG monitoring in the neonatal population.[5] Clinical scenarios requiring continuous monitoring to capture seizures include HIE as well as other causes of neonatal encephalopathy.

Therapeutic hypothermia has become the standard of care for neuroprotective rescue of newborns with presumed acute HIE close to the time of delivery. Hypothermia in the HIE population can reduce morbidity and mortality and is a safe neurotherapeutic intervention when given within a short time window after the asphyxia insult.[6] Questions remain as to whether cooling reduces the incidence of seizures in neonates with HIE. Low et al.[7] found that hypothermia did not reduce the total number of seizures in a hypothermic group compared with a normothermic group with moderate HIE but demonstrated that the total number of minutes seizing was reduced in the hypothermic group.

In this issue of *Neurology*®, Glass et al.[8] report on a cohort of infants with HIE from 3 different centers who underwent therapeutic hypothermia and continuous EEG monitoring. Monitoring was initiated within the first day of life and continued for at least 24 hours. Seizures occurred in nearly half of the infants in this study, with most of the seizures developing during the period of cooling. The authors found that the early EEG background, rather than clinical signs of encephalopathy, was the most predictive of seizures. These findings are important. First, seizures occur frequently despite the use of hypothermia; second, selected clinical/demographic factors remain poor predictors of infants who will express seizures. Watchful surveillance for seizures given the incidence and implications for long-term development is therefore an important diagnostic role for the neonatal neurologist of this vulnerable population. The conclusion that early EEG background was the only reliable predictor of seizures supports the American Clinical Neurophysiology Society guidelines regarding the use of continuous EEG monitoring for encephalopathic neonates.[5] This study is strengthened by the involvement of 3 different sites in addition to the review of neonatal EEGs by skilled neurophysiologists.

The authors recruited participants based on National Institute of Child Health and Human Development criteria,[9] which select for children who likely experienced intrapartum HIE rather than other causes of neonatal encephalopathy. A broader definition of neonatal encephalopathy and seizures would alternatively consider conditions in the antepartum period as well as closer to delivery, potentially involving maternal, placental, and fetal conditions that synergistically result in a neonatal brain disorder. Examples of such factors associated with neonatal encephalopathy include outborn vs inborn delivery status, placental abnormalities such as chorioamnionitis, and antepartum maternal/fetal diseases detected and monitored by fetal surveillance testing. While this does not negate the authors' findings regarding a cohort with presumed intrapartum HIE, a more heterogeneous cohort of neonates with encephalopathy and seizures would encompass a more representative cohort of the general population, who clinically reflect a continuum of antepartum and intrapartum disease risk associated with EEG-confirmed seizures and background abnormalities. Neonatal encephalopathy may be double the incidence of HIE.[10]

Despite these limitations, the principal finding that early EEG background is the greatest predictor of subsequent seizures in infants with HIE remains

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an important contribution. Child neurologists and neonatologists who care for these patients should consider these neurophysiologic phenotypes for diagnostic and therapeutic priorities. Continuous EEG monitoring is essential beyond conventional EEG or amplitude-integrated EEG to provide more accurate spatial and temporal detection of seizures as well as an estimate of seizure burden. Does earlier identification and treatment of neonatal seizures improve outcome beyond the use of therapeutic hypothermia? Novel preventive, rescue, and repair neurotherapeutic strategies in combination with hypothermia should be designed to assess efficacy and outcome. Continuous EEG monitoring is currently the most accurate bedside detector of seizures in the context of the timing and causes of a neonatal encephalopathy.

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