



Neonatal Seizures Due to Hypoxic-Ischemic Encephalopathy: Should We Care?

Clinical Seizures in Neonatal Hypoxic-Ischemic Encephalopathy Have No Independent Impact on Neurodevelopmental Outcome: Secondary Analyses of Data From the Neonatal Research Network Hypothermia Trial.

Kwon JM, Guillet R, Shankaran S, Laptook AR, McDonald SA, Ehrenkranz RA, Tyson JE, O'Shea TM, Goldberg RN, Donovan EF, Fanaroff AA, Poole WK, Higgins RD, Walsh MC; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. *J Child Neurol* 2011;26(3):322–328.

It remains controversial as to whether neonatal seizures have additional direct effects on the developing brain separate from the severity of the underlying encephalopathy. Using data collected from infants diagnosed with hypoxic-ischemic encephalopathy, and who were enrolled in an National Institute of Child Health and Human Development trial of hypothermia, we analyzed associations between neonatal clinical seizures and outcomes at 18 months of age. Of the 208 infants enrolled, 102 received whole body hypothermia and 106 were controls. Clinical seizures were generally noted during the first 4 days of life and rarely afterward. When adjustment was made for study treatment and severity of encephalopathy, seizures were not associated with death, or moderate or severe disability, or lower Bayley Mental Development Index scores at 18 months of life. Among infants diagnosed with hypoxic-ischemic encephalopathy, the mortality and morbidity often attributed to neonatal seizures can be better explained by the underlying severity of encephalopathy.

Commentary

Most child neurologists approach the hospital neonatal intensive care unit (NICU) with fear and trepidation. The most frequent consultation, which leads to this sense of unease, is a newborn term infant with hypoxic-ischemic encephalopathy (HIE) who has now just started to develop seizures. Unlike seizures in older children, to some extent, for whom some evidence-based guidelines do exist, neonatal seizures are often beyond our comfort zone.

Why? For one, seizures are common with HIE and can be extremely subtle to the extent of being not clinically observable in nearly half of neonates (1, 2). Additionally, the relatively new technology of amplitude-integrated EEG (aEEG) has emerged in the NICU as standard-of-care, in which long epochs of information derived from limited electrode channels, is typically interpreted by neonatologists (3). The true value and benefit of this technology is unclear. Last, as shown both by the authors of this paper in a previous article (4) and by a recent Cochrane group analysis (5), commonly used anticonvulsants for neonates such as phenobarbital and phenytoin, are unproven at best and harmful at worst.

Certainly it is difficult for a neonatologist, nurse, parent, or neurologist to stand at the incubator and watch a neonate convulse. However, if our treatments do not work, and the seizures are not having any true impact on the child's long-term outcomes, then perhaps watching is the appropriate intervention. We know from the infantile spasms literature that the underlying etiology trumps the success of treatment in regard to long-term development (6). In many cases of epilepsy, the seizures are mostly a symptom of an abnormal brain structure or genetic etiology, as opposed to a true epileptic encephalopathy. Neonates who are in the intensive care unit with HIE are under close, intense, respiratory and hemodynamic supervision and protection; a brief seizure will likely have minimal systemic impact.

It is into the fray of this exceptional equipoise that this research by Kwon and colleagues from the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network is now available. Just 4 years ago in this same journal (*Journal of Child Neurology*), the same first two authors evaluated 146 infants with seizures, by a phone survey, and determined that phenobarbital prophylaxis did not improve neurologic outcomes after up to 12 years (4). They continue to question the status quo by addressing in this current study whether clinical (not solely electrographic) seizures in neonates with HIE have a true independent direct effect on development, as measured by the Bayley Mental Development Index (MDI) at 18 months of age. Data from the



Neonatal Research Network's trial of therapeutic hypothermia had suggested that seizures at enrollment were associated with a poor outcome (7). The authors attempted to determine if that finding was still true, when examining for the entire hospital course of these neonates, and "whether the seizures themselves have an independent impact on the immature neonatal brain and are responsible for additional damage."

Their findings were that with univariate analysis there was both double the risk of seizures in children with severe HIE (44% vs 21%, $p < 0.001$) and an MDI score less than 70 (40% vs 20%, $p = 0.02$). When statistically controlling for both the effects of hypothermia and severe HIE, however, the effects of neonatal seizures no longer had a significant influence (odds ratio 1.93 (0.83–4.48), $p = 0.13$). Based on this, Kwon and colleagues concluded that "the presence of neonatal seizures cannot cause added harm in the setting of neonatal encephalopathy."

The authors thoroughly acknowledged the limitations of this study in a paragraph that was approximately half the length of the entire discussion section. They appropriately point out that clinical seizures are subtle, but that EEG was not required in the study protocol. In addition, a "high percentage" of infants received anticonvulsant drugs. Secondary etiologies for seizures other than HIE were not accounted for, and MRI was not available for analysis.

These limitations and more were pointed out in an editorial in the same journal one issue later by Glass, Ferriero, and Miller, three authors very familiar with neonatal seizures (8). These authors had in fact published results 2 years prior, reporting that seizures were independently associated with poor outcome in HIE (9). Perhaps part of their impetus for writing this editorial was a single word in the study, which they italicized in their correspondence, "cannot cause added harm..." (9).

Glass and colleagues went on to highlight that there is a difference between statistical and clinical significance: an odds ratio of 1.93 might not be statistically significant, but that represents a doubling (or even higher) of the risk of developmental disability. In addition, they pointed out that transient seizures at enrollment, as specified by this current study, may be very different in impact on a neonate than ongoing, persistent, and perhaps even difficult-to-control seizures. They finally asked for more information regarding the influence of hypothermia on seizures, for which the authors then provided further data demonstrating no effect on the outcome (10).

So where do we go from here? As mentioned by the authors of this article and the correspondence, a prospective study utilizing continuous video-EEG is one step, albeit an

expensive one. In addition, the population would need to be large, multicenter, and homogenous in etiology. Last, and perhaps most important, neonatologists and child neurologists alike need better treatments, especially if we do find that seizures in fact matter and are independently detrimental. Then and only then is this debate truly relevant: if our hands are tied by ineffective or harmful treatments, then matter or not, neonates with HIE are in trouble despite our best assistance.

by Eric Kossoff, MD

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