

Current Literature

In Clinical Science



Neonatal Encephalopathy, MRI Lesions, and Later Epilepsy: No Harm, No Foul?

Risk Factors for Epilepsy in Children With Neonatal Encephalopathy.

Glass HC, Hong KJ, Rogers EE, Jeremy RJ, Bonifacio SL, Sullivan JE, Barkovich AJ, Ferriero DM. *Pediatr Res* 2011;70(5):535–540.

We examined neonatal predictors of epilepsy in term newborns with neonatal encephalopathy (NE) by studying children enrolled in a longitudinal, single center cohort study. Clinical data were obtained through chart review, and MRI was performed in the neonatal period. We administered a seizure questionnaire to parents of children aged ≥ 12 mo (range, 12 mo to 16.5 y) to determine the outcome of epilepsy. The association between clinical predictors and time to onset of epilepsy was assessed using Cox proportional hazards regression. Thirteen of 129 children developed epilepsy: all had neonatal seizures and brain injury on neonatal MRI. Of the newborns with neonatal seizures, 25% (15.8/1000 person-years) developed epilepsy, with the highest hazard ratios (HRs) in the newborns with status epilepticus (HR, 35.8; 95% CI, 6.5–196.5). Children with severe or near-total brain injury were more likely to develop epilepsy compared with those with only mild or moderate injury (HR, 5.5; 95% CI, 1.8–16.8). In a multivariable analysis adjusting for degree of encephalopathy and severe/near-total brain injury, status epilepticus was independently associated with epilepsy. These data add to information regarding epilepsy pathogenesis and further aid clinicians to counsel parents regarding the likelihood that a newborn with NE will develop epilepsy.

Commentary

Neonatal encephalopathy refers to the clinical manifestations of acute perinatal brain injury, most commonly as a result of a hypoxic-ischemic insult. Neonatal seizures are a potentially treatable manifestation of moderate to severe neonatal encephalopathy and have long been recognized as a risk factor for later developmental deficits (1). The million-dollar question is: are seizures merely a marker for injury severity (2) or do neonatal seizures contribute to the injury (3)? If the latter is true, then seizures should be treated aggressively. However, neonatal seizures can only reliably be identified by electrographic monitoring (4) and are frequently refractory to anticonvulsant treatment (5). Further, there are theoretical reasons to be concerned that some treatment strategies for neonatal seizures could be toxic (6). Experimental anticonvulsant neurotoxicity has only been demonstrated with high dosages, has only been demonstrated acutely, and has only been demonstrated in normal animals rather than injured animals, let alone in animals with repetitive seizures. Nevertheless, the possibility of toxicity makes it all the more important to know whether successful treatment of neonatal seizures actually benefits the patient.

Unfortunately, the evidence regarding the harm conferred by neonatal seizures is complex, and the absence of effective therapies has made it impossible to rigorously test whether developmental outcomes are improved if seizures are stopped. Syndromes such as benign familial neonatal convulsions and transient hypocalcemia provide reasonable clinical evidence that neonatal seizures in otherwise healthy infants don't cause obvious harm (7). Experimental data from otherwise healthy animals support the idea that perinatal seizures can be well tolerated (8), at least in modest amounts (3, 9). The key descriptor for both clinical and experimental studies is "otherwise healthy." Recent experimental studies have found that seizures occurring in the setting of a variety of brain injuries do induce substantial neuronal death (10, 11). Further, experimental (12) and clinical (13) observations are leading to more effective treatments for neonatal seizures, and studies utilizing these new treatments are beginning to demonstrate improved neuronal survival after brain injury (14). However, direct evidence that the improved outcome is owing to improved seizure control has not yet been published.

The difficult clinical decisions as to how aggressively to search for and treat neonatal seizures can be made more confidently when we can accurately assess an encephalopathic neonate's risk for permanent injury. One robust outcome is the development of chronic epilepsy. The National Collaborative Perinatal Project (NCP) established that the risk of epilepsy after moderate to severe neonatal encephalopathy was 20 to 25 percent in survivors (15). The NCP study collected neonatal



data from the dawn of intensive neonatal care: 1959 to 1965. Follow-up of these neonates did not include imaging, but an important finding was that in patients with early evidence of severe encephalopathy (10-minute Apgar score ≤ 3), the incidence of epilepsy was 0% in patients without cerebral palsy (i.e., motor manifestation of perinatal brain injury) versus 50% in patients who had motor manifestations of perinatal brain injury (15).

The NCPP data suggest that in the setting of neonatal encephalopathy, epilepsy after brain injury is far more likely when there are other manifestations of permanent brain injury. This finding is supported by a subsequent MRI study of survivors of neonatal encephalopathy that found epilepsy occurred only in patients with cerebral palsy. Further, epilepsy only occurred in patients with MRI evidence of perinatal injury (16). Similar findings were reported in a larger study by van Kooij et al. (17): all of the survivors of perinatal encephalopathy who developed epilepsy had moderate to severe MRI sequelae of perinatal injury; none of the survivors of neonatal encephalopathy with no or mild MRI changes developed epilepsy.

The report by Glass and coworkers now compellingly bridges the gap between 10-minute Apgar predictors, subsequent imaging data, and epilepsy. Glass and coworkers studied several risk factors including severity of neonatal encephalopathy, clinical and electrographically confirmed neonatal seizures, acute and convalescent MRI, and epilepsy. They found the same rate of epilepsy after neonatal seizures (25%) as the NCPP study from 50 years ago. Although etiologies of seizures have changed (e.g., hypocalcemic neonatal seizures are much less common now) and neonatal care has been revolutionized since the early 1960s, the care of neonatal seizures has not changed. Thus, the similar incidence of epilepsy, while not good news, may not be so surprising. Glass et al. also found that neonatal status epilepticus was associated with a much higher incidence of later epilepsy (83%). Excluding patients with status epilepticus, EEG-confirmed seizures conferred a much higher risk of subsequent epilepsy (26%) than clinical seizures (11%). This is congruent with the low correlation between clinical and electrographic signs of neonatal seizures (4). This finding supports the use of electrographic data as the gold standard for diagnosis of neonatal seizures. The high rate of false-positive clinical diagnoses of neonatal seizures may explain the poor predictive value of clinical neonatal seizures in some studies (2) as well as the efficacy of hypothermia for neonatal seizures diagnosed by electrographic (13) but not clinical (18) criteria. Thus, the data of Glass and coworkers confirmed the prior findings linking permanent injury and epilepsy and extended them to show that *only patients with clear acute MRI evidence of neonatal injury developed epilepsy*.

Bringing this back to the pressing question regarding care of newborns with neonatal encephalopathy: should we invest the considerable resources necessary to detect electrographic neonatal seizures (4)? The study by Glass and coworkers provides evidence for the utility of electrographic monitoring of cooled and at-risk neonates. The Glass study, along with all prior clinical outcome studies dating back to the NCPP report, also indicates that after neonatal brain insult, epilepsy only occurs in the setting of clinically and MRI-detectable permanent brain injury. Although this has sometimes been reduced

in animal models to the catchy phrase “no hole, no epilepsy,” MRI sequelae of neonatal brain injury other than porencephaly are also predictive of later epilepsy. We still do not have a compelling answer for the companion question: how aggressively should we treat electrographic neonatal seizures? The answer to that question awaits more effective therapies. The good news is that new therapies are currently undergoing clinical trials (clinicaltrials.gov NCT00830531, NCT01434225, NCT00884052, NCT01475656).

by Kevin Staley, MD

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