Published in final edited form as:

J Pediatr. 2009 September ; 155(3): 305–306. doi:10.1016/j.jpeds.2009.04.036.

Do seizures contribute to neonatal hypoxic-ischemic brain injury?

Faye S. Silverstein, MD

Departments of Pediatrics and Neurology, University of Michigan, Ann Arbor, MI

In the pediatric age group, the risk of seizures is highest in the neonatal period [1]. Yet, neonatal seizures are often refractory to conventional anticonvulsant drug therapy. An important unresolved question for neonatal clinicians is whether aggressive medical treatment of seizures is warranted, particularly because the etiology of seizures is invariably a significant determinant of neurodevelopmental outcome and experimental studies with animal models have raised concerns about potential neurotoxicity of anticonvulsant drugs in neonates [2]. The clinical scenario in which this dilemma emerges most frequently is in the setting of acute hypoxic-ischemic brain injury. Neonates with encephalopathy and seizures as a result of asphyxial brain injury are at substantial risk for poor neurodevelopmental outcome, and their seizures are often difficult to control quickly and completely.

A post-hoc analysis of data from the Cool-Cap hypothermia treatment trial revealed that absence of seizures was an independent predictor of better 18 month outcome in asphyxiated neonates [3]. Yet, a recent Cochrane Review that evaluated available data to determine if anticonvulsants could prevent mortality and morbidity in full term newborns with perinatal asphyxia concluded that “anticonvulsant therapy to term infants in the immediate period following perinatal asphyxia cannot be recommended for routine clinical practice, other than in the treatment of prolonged or frequent clinical seizures” [4]. However, this analysis was substantially confounded by the limited efficacy of routinely used antiepileptic drugs in neonates [5]. Thus, in this population, it has been very difficult to determine whether seizures cause/amplify neonatal brain injury, and, more importantly, whether prevention and/or early effective treatment of seizures would improve neurodevelopmental outcomes.

Perhaps the most frequently cited clinical data indicating that neonatal seizures are deleterious in this setting are the results of a magnetic resonance spectroscopy study that was performed in neonates with antecedent asphyxia and seizures [6]. The major findings were that seizure severity (based on a clinical score) contributed to abnormal brain metabolism (increased lactate to choline ratio) and to measures of neuronal injury (reduced N-acetyl-aspartate to choline ratio). In a thought-provoking article in this issue of *The Journal* [7], Glass et al report complementary data that address this complex issue. They compared cognitive and motor outcomes at age four years in 77 children who were born at term, who were at risk for hypoxic-ischemic brain injury, and who all had brain magnetic resonance imaging (MRI) in the newborn period. About one third (25/77) had clinically detected neonatal seizures. Neonatal MRI's were classified with respect to anatomic distribution and severity of acute injury. Neonatal seizure severity was classified based on a scoring system devised by the authors. Multivariate regression was applied to examine the effect of seizures on outcomes, controlling for the

Address correspondence to: FS Silverstein MD, University of Michigan, 8301 MSRB3, Ann Arbor, MI 48109-5646, fsilvers@med.umich.edu Fax: 734-764-4279.
Edited by AJ and WFB

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

severity of MRI-documented brain injury. The major findings were that adjusting for MRI-classified injury severity, full scale intelligence quotients (FSIQ) were substantially lower and likelihood of abnormal neuromotor exams was higher after severe neonatal seizures. Trends for reductions in FSIQ decrements were similar but of lesser magnitude after mild-moderate seizures.

These results were interpreted as providing evidence that neonatal seizures, in the setting of birth asphyxia, are associated with worse neurodevelopmental outcomes, and that these trends are independent of the severity of MRI-detected acute hypoxic-ischemic brain injury. The findings and their interpretation are plausible. Association does not prove causation, and as the authors acknowledge in their discussion, the impact of seizure therapies could not be distinguished from the effects of seizures.

Strengths of this study include the prospective data collection with carefully analyzed neonatal MRI's and systematic four year follow-up assessments. The major limitation of the study design is the reliance on clinical evaluation for classification of seizure diagnosis and severity. In neonates, clinical judgment is an imperfect method for the diagnosis of seizures; both over- and under-diagnosis are possible, particularly in encephalopathic infants. Electroencephalography (EEG) remains essential for confirmation of the diagnosis of neonatal seizures. Persistent electrographic seizures in neonates are associated with poor neurodevelopmental outcomes [8]. The finding that 11/25 infants in the clinical seizure group had normal EEG's could reflect limited sampling data, effective treatment prior to the EEG and/or misdiagnosis. There is now broad consensus that future studies of neonatal seizures must include detailed electrophysiological monitoring data. Whether this will be achieved with conventional EEG, limited montage EEG and/or some type of amplitude-integrated EEG device is a controversial topic beyond the scope of this commentary [9].

Many clinicians remain skeptical that seizures contribute to hypoxic-ischemic brain injury. In fact this controversial issue is relevant to all age groups and is not restricted to neonates. Experimental studies that have addressed this question have yielded contradictory findings [10,11]. In the study cited by Glass [11], immature rats underwent a very mild hypoxic-ischemic insult, followed by infusion of the glutamate agonist kainate, which elicited prolonged seizures; only the combination of the two treatments resulted in hippocampal neuronal injury. An intriguing follow-up study in the same model demonstrated that prevention of fever substantially attenuated seizure-related amplification of brain injury [12].

In asphyxiated neonates, deep nuclear structures (basal ganglia and thalamus) are often most severely damaged, and the mechanism(s) whereby seizures exacerbate this type of injury could be questioned. Yet, there are several credible mechanisms whereby seizures could amplify ischemic brain injury. Prolonged seizures could increase brain temperature, and thereby increase metabolic demands throughout brain. Seizures increase local cerebral blood flow and may "steal" perfusion from injured brain regions. These mechanisms could, in turn, limit the glucose and oxygen supply required to sustain endogenous protective and repair mechanisms in injured tissue. In addition, prolonged seizures may result in increased production of diffusible neurotoxic molecules (e.g. cytokines, reactive oxygen species) that can directly contribute to ischemic cell damage.

The results of the Glass study [7] provide new evidence that clinically detected seizures are associated with worse neurodevelopmental outcome in neonates with hypoxic-ischemic brain injury. These results should encourage investigators to take the next critical steps – to undertake research to determine if rapid and effective treatment of neonatal seizures will improve neurological outcome in this population.

Acknowledgments

Supported in part by USPHS awards HD 60348 and HL 094345.

Abbreviations

MRI	magnetic resonance imaging
EEG	electroencephalography
HIE	hypoxic-ischemic encephalopathy
FSIQ	full scale intelligence quotients

References

1. Silverstein FS, Jensen FE. Neurological Progress: Neonatal Seizures. *Ann Neurol* 2007;62:112–20. [PubMed: 17683087]
2. Bittigau P, Sifringer M, Genz K, Reith E, Pospischil D, Govindarajulu S, Dzietko M, Pesditschek S, Mai I, Dikranian K, Olney JW, Ikonomidou C. Antiepileptic drugs and apoptotic neurodegeneration in the developing brain. *Proc Natl Acad Sci U S A* 2002;99:15089–94. [PubMed: 12417760]
3. Wyatt JS, Gluckman PD, Liu PY, Azzopardi D, Ballard R, Edwards AD, Ferriero DM, Polin RA, Robertson CM, Thoresen M, Whitelaw A, Gunn AJ. CoolCap Study Group. Determinants of outcomes after head cooling for neonatal encephalopathy. *Pediatrics* 2007;119:912–21. [PubMed: 17473091]
4. Evans D, Levene MI, Tsakmakis M. Anticonvulsants for preventing mortality and morbidity in full term newborns with perinatal asphyxia. *Cochrane Database Syst Rev* 2007;18(3):CD001240. [PubMed: 17636659]
5. Painter MJ, Scher MS, Stein AD, Armatti S, Wang Z, Gardiner JC, Paneth N, Minnigh B, Alvin J. Phenobarbital compared with phenytoin for the treatment of neonatal seizures. *N Engl J Med* 1999;341:485–9. [PubMed: 10441604]
6. Miller SP, Weiss J, Barnwell A, Ferriero DM, Latal-Hajnal B, Ferrer-Rogers A, Newton N, Partridge JC, Glidden DV, Vigneron DB, Barkovich AJ. Seizure-associated brain injury in term newborns with perinatal asphyxia. *Neurology* 2002;58:542–8. [PubMed: 11865130]
7. Glass H, Glidden D, Jeremy RJ, Barkovich AJ, Ferriero DM, Miller SP. Clinical Neonatal Seizures are Independently Associated with Outcome in Infants at Risk for Hypoxic-Ischemic Brain Injury. *J Pediatr*. 2009in press
8. McBride MC, Laroia N, Guillet R. Electrographic seizures in neonates correlate with poor neurodevelopmental outcome. *Neurology* 2000;55:506–13. [PubMed: 10953181]
9. Silverstein FS, Jensen FE, Inder T, Hellstrom-Westas L, Hirtz D, Ferriero DM. Improving the Treatment of Neonatal Seizures: National Institute of Neurological Disorders and Stroke Workshop Report. *J Pediatr* 2008;153:12–15. [PubMed: 18571526]
10. Towfighi J, Housman C, Mauger D, Vannucci RC. Effect of seizures on cerebral hypoxic-ischemic lesions in immature rats. *Brain Res Dev Brain Res* 1999;113:83–95.
11. Wirrell EC, Armstrong EA, Osman LD, Yager JY. Prolonged seizures exacerbate perinatal hypoxic-ischemic brain damage. *Pediatr Res* 2001;50:445–54. [PubMed: 11568286]
12. Yager JY, Armstrong EA, Jaharus C, Saucier DM, Wirrell EC. Preventing hyperthermia decreases brain damage following neonatal hypoxic-ischemic seizures. *Brain Res* 2004;1011:48–57. [PubMed: 15140643]