Published in final edited form as:

J Pediatr. 2011 November ; 159(5): 731–735.e1. doi:10.1016/j.jpeds.2011.07.015.

Seizures and MRI brain injury in newborns cooled for hypoxic ischemic encephalopathy

Hannah C. Glass, MDCM^{1,2}, Kendall B. Nash, MD^{1,2}, Sonia L. Bonifacio, MD², A. James Barkovich, MD^{1,3}, Donna M. Ferriero, MD^{1,2}, Joseph E. Sullivan, MD^{1,2}, and MariaRoberta Cilio, MD, PhD^{1,4}

¹Department of Neurology, University of California, San Francisco

²Department of Pediatrics, University of California, San Francisco

³Department of Radiology and Biomedical Imaging, University of California, San Francisco

⁴Division of Neurology, Bambino Gesù Children's Hospital, Rome, Italy

Abstract

Objective—To describe the association between electrographic seizures and brain injury judged from magnetic resonance imaging (MRI) in newborns treated with hypothermia.

Study design—56 newborns treated with hypothermia were monitored using video-EEG through cooling and rewarming, and imaged at a median of 5 days. EEGs were reviewed for seizures and status epilepticus. Moderate-severe injury on MRI was measured using a classification similar to one predicting abnormal outcome in an analogous population.

Results—Seizures were recorded in 17 newborns, five with status epilepticus. Moderate-severe injury was more common in newborns with seizures (RR 2.9; 95%CI 1.2–4.5; $P=0.02$), and present in all with status epilepticus. Children with moderate-severe injury had seizures that were multifocal, later onset, and more likely to have ongoing seizures following 20mg/kg phenobarbital. Newborns with only subclinical seizures were as likely to have injury as compared with those whose seizures had a clinical correlate (57% vs. 60%).

Conclusions—Seizures remain a risk factor for brain injury in the setting of therapeutic hypothermia, especially in neonates with status epilepticus, multifocal onset seizures, and need for multiple medications. However, 40% were spared from brain injury, suggesting that the outcome following seizures is not uniformly poor in children treated with therapeutic hypothermia.

Keywords

Intensive care; Infant, newborn; Hypothermia, induced; Seizures; Electroencephalography; Magnetic resonance imaging

© 2011 Mosby, Inc. All rights reserved.

Address correspondence to: Hannah C. Glass, University of California San Francisco, Department of Neurology Box 0663, 521 Parnassus Avenue, C-215, San Francisco, CA 94143-0663, Phone: 415-514-3277, Fax: 415-502-5821, Hannah.Glass@ucsf.edu.

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.

The authors declare no conflicts of interest.

Neonatal seizures are an important risk factor for impaired neurodevelopment in the setting of hypoxic-ischemic encephalopathy[1-4][5, 6]. Although the adverse outcome is thought to be primarily related to brain injury caused by hypoxia-ischemia, there is also increasing evidence from animal models and human studies that seizures themselves may be harmful to the developing brain, especially in the setting of underlying injury[7-12]. Most studies of neonatal seizures have relied on clinical observation. However, increased use of video-electroencephalogram (EEG) monitoring has highlighted the fact that seizures in newborns are often subclinical[13-15], and that clinicians are poor at clinically distinguishing seizures from non-seizure spells[16, 17]. There has been debate as to the importance of seizures that are electrographic only as compared with those that manifest obvious clinical signs.

Previous studies have demonstrated a clear relationship between seizure burden, and injury on MRI[18]. However, little is known regarding seizure frequency, localization, timing of onset and clinical expression of seizures and their relationship to MRI injury, especially in the setting of therapeutic hypothermia.

The objective of this study was to examine the association between electrographic seizures, both with and without clinical signs, and brain injury as detected by MRI in a cohort of term newborns treated with therapeutic hypothermia.

Methods

We examined a cohort of newborns who were treated with therapeutic hypothermia using whole body cooling at University of California, San Francisco, between November 2007 and May 2010. A subset of these subjects were reported by Nash et al[19]. Inclusion criteria for hypothermia at UCSF were based on those used in randomized controlled trials[1, 20-22] and have been reported in detail previously[23]. Clinical data were extracted from electronic medical records and bedside charts. A pediatric neurologist measured the maximal degree of encephalopathy over the first 3 days of life on a scale of 0-6 that considers feeding, alertness, tone, respiratory status, reflexes, and seizures[24]. Clinical and electrographic seizures were treated with lorazepam, phenobarbital, fosphenytoin and/or levetiracetam according to institutional guidelines. The Committee on Human Research at the University of California, San Francisco, approved the study.

EEG

Conventional video-EEG using the NicoletOne monitoring system was performed in all subjects. Surface electrodes were applied by a trained technologist according to the international 10-20 system, modified for neonates. Monitoring was initiated as part of routine clinical care as soon as possible after admission to the intensive care nursery (mean 10 ± 3 hours of life), and was maintained throughout the duration of therapeutic hypothermia and rewarming according to institutional clinical guidelines in all but two of the surviving newborns (mean duration of EEG recording 89 ± 25 hours). A neurophysiologist (MRC or JS) reviewed the archived full-length video-EEG recordings to evaluate for the presence of electrographic seizures and status epilepticus, as well as seizure localization and clinical correlates. An electrographic seizure was defined as a repetitive, evolving, and stereotyped waveform, with a definite beginning and end, with a minimum duration of 10 seconds and minimum amplitude of 2 microvolts[25, 26]. Status epilepticus was defined as continuous electrographic seizure activity for at least 30 minutes, or recurrent electrographic seizures for at least 50% of 1-3 hours of recording time[26, 27]. EEG background at the onset of recording was classified into one of 5 patterns as previously described[19, 28]: 1) normal for gestational age, including recordings with transient discontinuity for less than 50% of the recording, with presence of distinct state changes; 2) excessively discontinuous, with persistence of discontinuous activity occupying more than

50% of the recording, and consisting of bursts of normal activity separated by abnormally long, interburst intervals of more than 6 seconds duration, and amplitude $>5\mu\text{V}$ and $<25\mu\text{V}$, with poor state changes; 3) depressed and undifferentiated, with persistently low-voltage background activity with amplitude between $5\mu\text{V}$ and $15\mu\text{V}$ and without normal features; 4) burst suppression, invariant and unreactive pattern of bursts of paroxysmal activity with mixed features but no age-appropriate activity, lasting less than 10 seconds, and alternating with periods of marked voltage attenuation with amplitude $\leq 5\mu\text{V}$; 5) extremely low voltage, invariant and unreactive pattern, with amplitude $<5\mu\text{V}$ or with no discernible cerebral activity.

Magnetic Resonance Imaging

Infants were imaged using a specialized neonatal head coil on a 1.5 Tesla SignaEchoSpeed system (GE Medical Systems) at a median age of 5 days (range 4 to 14 days). All infants were normothermic at the time of imaging. Imaging sequences, including spoiled gradient echo volumetric T1, axial spin echo T2 MR imaging, and diffusion-weighted imaging, were optimized for the neonatal brain, as previously described [23, 29, 30]. The severity of brain injury was measured using conventional T1 and T2 (short and long echo) MRI, and diffusion weighted-imaging. A pediatric neuroradiologist who was blinded to the clinical history prospectively evaluated MRI images. Injury to the basal ganglia/thalamus and the watershed areas were scored independently using a system that is strongly predictive of neurodevelopmental outcome following neonatal encephalopathy [29, 31]. Brain injury was categorized as “none-mild” or “moderate-severe” using a classification similar to one that was highly predictive for neurologic disability at 18 months of age in newborns treated with hypothermia [32]. Moderate-severe injury was considered present when there was injury to the basal ganglia/thalamus (abnormal signal in the thalamus and lentiform nucleus, or more extensive injury) and/or the watershed areas (abnormal signal in anterior or posterior watershed cortex and white matter, or more extensive involvement). Newborns were also grouped into “basal ganglia/thalamus” or “watershed” patterns of injury on the basis of the predominant site of injury on MRI, as previously described [29]. Newborns were considered to have a predominant watershed pattern of injury when the watershed scores were higher than the basal ganglia/thalamus scores, and a basal ganglia/thalamus predominant injury when the basal ganglia/thalamus scores were as high as or higher than the watershed scores. Newborns were considered to have “near total brain injury” when injury scores were maximal in both the basal ganglia/thalamus and watershed regions.

Statistical Analysis

Statistical analyses were performed using Stata 10.1 software (Stata Corp, College Station, Texas). Chi-squared and Fisher exact tests were used to compare dichotomous variables and t-test was used for continuous variables. Wilcoxon Rank Sum test (Mann-Whitney U) was used to compare nonparametric data. We considered a p value ≤ 0.05 significant.

Results

During the study period, 61 newborns were treated with hypothermia and monitored with conventional video-EEG. Of these, 56 were evaluated with MRI and were included in this study. The clinical characteristics of the subjects with and without seizures are presented in Table I.

Eight newborns were treated with a phenobarbital loading dose of 20mg/kg prior to the initiation of monitoring: six for suspected clinical seizures and two for seizures on amplitude-integrated EEG (aEEG). Two of these infants (one with suspected clinical seizures and one with aEEG seizures) went on to have electrographic seizures recorded

onconventional video-EEG. Overall, electrographic seizures were recorded in 17 newborns (30%), five of whom had status epilepticus (9%). Four newborns had electrographic seizures evident at the onset of monitoring (two with status epilepticus). Of those with electrographic seizures, 7 (41%) never had seizures with a clinical correlate that was detectible on the video recording. Of those with status epilepticus, three (60%) never had recognizable clinical signs of seizure. Subjects with seizures were more likely to have an abnormal EEG background at the onset of recording (94% vs 66%, $p=0.0002$) (Table II).

Seizures and Risk of Moderate-Severe Brain Injury

Moderate-severe brain injury was present in 59% of newborns with seizures as compared with 26% of those without seizures (RR 2.3; 95% CI 1.2-4.5; $P=0.02$) (Table III). There was no apparent difference in the risk of moderate-severe injury between newborns with clinically apparent seizures (60%) and those with only subclinical seizures (57%, RR 1.1; 95% CI 0.5-2.4, $P=0.9$). Of the six children who were treated for suspected clinical seizures prior to arrival at our center, two (33%) had moderate-severe brain injury, which was similar to those without early suspected clinical seizures (36%, RR 0.93; 95% CI 0.3-3.0). All five newborns with status epilepticus had moderate-severe injury ($P=0.04$).

Seizure characteristics in the newborns with moderate-severe injury differed from those in the children with no-mild injury. Children with moderate-severe injury had seizures that were, on average, later onset (median 18.3 hours vs. 12.1 hours of life, $P=0.001$), and less likely to be recorded within the first 12 hours of life (0% vs. 43%, $P=0.05$). The two newborns that were treated with antiepileptic drugs (AEDs) prior to EEG monitoring had later onset of seizures as compared with those who were not treated prior to monitoring (22.9 vs 15.3 hours), though the difference was not significant ($P=0.2$). Newborns with moderate-severe injury had seizures that were more difficult to control (30% had seizure resolution with a single loading dose of 20mg/kg of phenobarbital vs. 100% of those with no-mild injury, $P=0.004$).

MRI Findings in Newborns with Seizures

Of the newborns with seizures, ten had moderate-severe injury, whereas seven had either no injury (four newborns) or only mild injury. Imaging characteristics of the newborns with and without seizures are presented in Table IV. Newborns with seizures were more likely to have cortical injury (59% vs 31%, $p=0.05$) and near total brain injury (29% vs 5%, $P=0.01$).

There was no consistent association between seizure localization and location of MRI injury (Table V; **available at** www.jpeds.com). Some children had seizures that localized to a clear focus of injury and others had no apparent injury in the location of the seizure onset. The two newborns with multifocal onset seizures had maximal injury in both the basal ganglia/thalamus and watershed areas (i.e. near total brain injury).

Discussion

In this cohort of 56 newborns with moderate-severe HIE who were cooled using whole body hypothermia, status epilepticus, multifocal seizures, and seizures that were resistant to a single loading dose of 20mg/kg of phenobarbital were associated with moderate-severe injury on neonatal MRI. Newborns whose electrographic seizures never had an obvious clinical correlate were as likely to have moderate-severe injury as those who had electrographic seizures with a clinical correlate.

Previous studies have demonstrated that electrographic seizures are a risk factor for adverse outcome in the setting of HIE, with rates of death and disability ranging from 60-100% [5,

6]. We show that seizures remain a risk factor for adverse outcome in the setting of therapeutic hypothermia. However, children with seizures that are easily treated with a first line agent may be spared moderate or severe brain injury, suggesting that the outcome following seizures is not uniformly poor in children treated with therapeutic hypothermia. This finding is consistent with preclinical models of therapeutic hypothermia that show neuroprotection in spite of a lack of reduction in the number of delayed seizures [33].

The finding that a greater burden of seizures was important corroborates results by Van Rooij et al, who reported a relationship between seizure duration detected with aEEG and degree of MRI injury. Pisani et al also found that status epilepticus was a stronger risk factor than recurrent seizures for adverse neurodevelopmental outcome, and McBride et al, showed that having >75 seizures was associated with microcephaly, severe CP, and failure to thrive [5, 18, 27].

In this study, newborns with subclinical seizures diagnosed with video-EEG monitoring were as likely to have MRI injury as those whose seizures had clinical signs. This finding supports data from Bjorkman et al, who examined newborn piglets subjected to a hypoxic-ischemic insult, and found that animals with seizures had worse MRI, histological injury and neurobehavior when compared with those without seizures, even if the seizures had no obvious clinical signs [34]. In addition, Connell et al showed that seizures detected using a two-channel recorder were equally likely to be associated with adverse neurodevelopmental outcome whether or not they were associated with clinical signs [35].

The finding that seizure onset beyond the first 12 hours of life is not only common in newborns with HIE, but is associated with moderate-severe injury on MRI challenges conventional clinical thinking about the relationship between timing of onset of neonatal seizures and severity of insult. Rafayet al found that seizures within the first 12 hours of life were more likely to indicate HIE than stroke [36]. Only 14% of newborns in that cohort had seizure onset after 12 hours of life, compared with 82% of our cohort. However, the later onset of seizures in the more severely affected newborns is in keeping with the fetal sheep model, where longer duration of ischemia was associated with more prolonged EEG suppression, and delayed transition to epileptiform activity [37]. The reasons for the difference may include the following: (1) EEG versus clinical diagnosis of seizures; (2) use of continuous EEG monitoring; or (3) differences in the evolution of energy failure, injury and seizures in newborns who are treated with therapeutic hypothermia.

Though our study is strengthened by high quality data acquisition, it is not without limitations. First, monitoring was initiated, on average, at 10 hours of life, and so we may have missed very early onset seizures in some subjects, including those with moderate-severe brain injury. EEG recording in the first hours of life was not possible due to factors including delayed recognition of neurological signs, need for transport from a referring center, patient access, and the time required to place a full montage. Nonetheless, monitoring was initiated within 12 hours of life in 75% of subjects. Furthermore there was no difference in timing of onset of recording among those with and without brain injury. Given the usual course for neonatal seizures, we believe that it is unlikely that neonates with moderate-severe injury had early seizures that spontaneously resolved prior to the onset of monitoring only to recur at a later time point. However, this possibility does not change the clinically relevant finding that late emergence of seizures is associated with injury. Second, the long-term clinical outcome data for this cohort are not yet available. Rutherford et al reported that MRI remains highly predictive of outcome in newborns treated with hypothermia [38], suggesting that the MRI results are likely to remain predictive as this cohort matures into childhood. Finally, the small number of subjects with seizures prohibits multivariable analysis.

The results of this study have implications for diagnosis, treatment and counseling for neonatal seizures that occur in the setting of therapeutic hypothermia. The high rate of electrographic seizures with onset after the first 12 hours of life suggests that short-term, intermittent EEG recording - as is routine in many centers - is inadequate for detecting the full burden of electrographic seizures in cooled newborns. Further, the similar severity of brain injury in newborns with electroclinical seizures as compared with those with seizures without clinical correlate supports the need for randomized controlled trials to evaluate the practice of treating only infants with convulsive seizures. Finally, these data may aid counseling for families regarding prognosis in newborns with seizures in the setting of therapeutic hypothermia.

Acknowledgments

Supported by the NIH/NCRR UCSF-CTSI (grant UL1 RR024131) and NIH/NINDS (grants 5P50NS035902 and NS40117). H.G. is supported by NIH/NINDS K23NS066137 and the Neonatal Brain Research Institute at UCSF. The contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH.

References

1. Gluckman PD, Wyatt JS, Azzopardi D, Ballard R, Edwards AD, Ferriero DM, et al. Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentre randomised trial. *Lancet*. 2005; 365(9460):663–70. [PubMed: 15721471]
2. Al-Macki N, Miller SP, Hall N, Shevell M. The spectrum of abnormal neurologic outcomes subsequent to term intrapartum asphyxia. *Pediatr Neurol*. 2009; 41(6):399–405. [PubMed: 19931160]
3. Tekgul H, Gauvreau K, Soul J, Murphy L, Robertson R, Stewart J, et al. The current etiologic profile and neurodevelopmental outcome of seizures in term newborn infants. *Pediatrics*. 2006; 117(4):1270–80. [PubMed: 16585324]
4. Murray DM, Boylan GB, Ryan CA, Connolly S. Early EEG findings in hypoxic-ischemic encephalopathy predict outcomes at 2 years. *Pediatrics*. 2009; 124(3):e459–67. [PubMed: 19706569]
5. McBride MC, Laroia N, Guillet R. Electrographic seizures in neonates correlate with poor neurodevelopmental outcome. *Neurology*. 2000; 55(4):506–13. [PubMed: 10953181]
6. Boylan GB, Pressler RM, Rennie JM, Morton M, Leow PL, Hughes R, et al. Outcome of electroclinical, electrographic, and clinical seizures in the newborn infant. *Dev Med Child Neurol*. 1999; 41(12):819–25. [PubMed: 10619280]
7. Montgomery EM, Bardgett ME, Lall B, Csernansky CA, Csernansky JG. Delayed neuronal loss after administration of intracerebroventricular kainic acid to preweanling rats. *Brain Res Dev Brain Res*. 1999; 112(1):107–16.
8. McCabe BK, Silveira DC, Cilio MR, Cha BH, Liu X, Sogawa Y, et al. Reduced neurogenesis after neonatal seizures. *J Neurosci*. 2001; 21(6):2094–103. [PubMed: 11245693]
9. Lynch M, Sayin U, Bownds J, Janumpalli S, Sutula T. Long-term consequences of early postnatal seizures on hippocampal learning and plasticity. *Eur J Neurosci*. 2000; 12(7):2252–64. [PubMed: 10947804]
10. Glass HC, 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*. 2009; 155(3):318–23. [PubMed: 19540512]
11. Wirrell EC, Armstrong EA, Osman LD, Yager JY. Prolonged seizures exacerbate perinatal hypoxic-ischemic brain damage. *Pediatr Res*. 2001; 50(4):445–54. [PubMed: 11568286]
12. Miller SP, Weiss J, Barnwell A, Ferriero DM, Latal-Hajnal B, Ferrer-Rogers A, et al. Seizure-associated brain injury in term newborns with perinatal asphyxia. *Neurology*. 2002; 58(4):542–8. [PubMed: 11865130]

13. Scher MS, Alvin J, Gaus L, Minnigh B, Painter MJ. Uncoupling of EEG-clinical neonatal seizures after antiepileptic drug use. *Pediatr Neurol*. 2003; 28(4):277–80. [PubMed: 12849880]
14. Biagioni E, Ferrari F, Boldrini A, Roversi MF, Cioni G. Electroclinical correlation in neonatal seizures. *Eur J Paediatr Neurol*. 1998; 2(3):117–25. [PubMed: 10726833]
15. Clancy RR, Legido A, Lewis D. Occult neonatal seizures. *Epilepsia*. 1988; 29(3):256–61. [PubMed: 3371282]
16. Malone A, Ryan CA, Fitzgerald A, Burgoyne L, Connolly S, Boylan GB. Interobserver agreement in neonatal seizure identification. *Epilepsia*. 2009; 50(9):2097–101. [PubMed: 19490044]
17. Murray DM, Boylan GB, Ali I, Ryan CA, Murphy BP, Connolly S. Defining the gap between electrographic seizure burden, clinical expression and staff recognition of neonatal seizures. *Arch Dis Child Fetal Neonatal Ed*. 2008; 93(3):F187–91. [PubMed: 17626147]
18. van Rooij LG, Toet MC, van Huffelen AC, Groenendaal F, Laan W, Zecic A, et al. Effect of treatment of subclinical neonatal seizures detected with aEEG: randomized, controlled trial. *Pediatrics*. 2010; 125(2):e358–66. [PubMed: 20100767]
19. Nash KB, Bonifacio SL, Glass HC, Sullivan JE, Barkovich AJ, Ferriero DM, et al. Video-EEG monitoring in newborns with hypoxic-ischemic encephalopathy treated with hypothermia. *Neurology*. 2011; 76(6):556–62. [PubMed: 21300971]
20. Azzopardi DV, Strohm B, Edwards AD, Dyet L, Halliday HL, Juszczak E, et al. Moderate hypothermia to treat perinatal asphyxial encephalopathy. *N Engl J Med*. 2009; 361(14):1349–58. [PubMed: 19797281]
21. Eicher DJ, Wagner CL, Katikaneni LP, Hulsey TC, Bass WT, Kaufman DA, et al. Moderate hypothermia in neonatal encephalopathy: efficacy outcomes. *Pediatr Neurol*. 2005; 32(1):11–7. [PubMed: 15607598]
22. Shankaran S, Laptook AR, Ehrenkranz RA, Tyson JE, McDonald SA, Donovan EF, et al. Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. *N Engl J Med*. 2005; 353(15):1574–84. [PubMed: 16221780]
23. Bonifacio SL, Glass HC, Vanderpluym J, Agrawal AT, Xu D, Barkovich AJ, et al. Perinatal Events and Early Magnetic Resonance Imaging in Therapeutic Hypothermia. *J Pediatr*. 2010
24. Miller SP, Latal B, Clark H, Barnwell A, Glidden D, Barkovich AJ, et al. Clinical signs predict 30-month neurodevelopmental outcome after neonatal encephalopathy. *Am J Obstet Gynecol*. 2004; 190(1):93–9. [PubMed: 14749642]
25. Clancy RR, Legido A. The exact ictal and interictal duration of electroencephalographic neonatal seizures. *Epilepsia*. 1987; 28(5):537–41. [PubMed: 3653058]
26. Scher MS, Hamid MY, Steppe DA, Beggarly ME, Painter MJ. Ictal and interictal electrographic seizure durations in preterm and term neonates. *Epilepsia*. 1993; 34(2):284–8. [PubMed: 8453938]
27. Pisani F, Cerminara C, Fusco C, Sisti L. Neonatal status epilepticus vs recurrent neonatal seizures: clinical findings and outcome. *Neurology*. 2007; 69(23):2177–85. [PubMed: 18056582]
28. Holmes GL, Lombroso CT. Prognostic value of background patterns in the neonatal EEG. *J Clin Neurophysiol*. 1993; 10(3):323–52. [PubMed: 8408599]
29. Miller SP, Ramaswamy V, Michelson D, Barkovich AJ, Holshouser B, Wycliffe N, et al. Patterns of brain injury in term neonatal encephalopathy. *J Pediatr*. 2005; 146(4):453–60. [PubMed: 15812446]
30. Barkovich AJ, Miller SP, Bartha A, Newton N, Hamrick SE, Mukherjee P, et al. MR imaging, MR spectroscopy, and diffusion tensor imaging of sequential studies in neonates with encephalopathy. *AJNR Am J Neuroradiol*. 2006; 27(3):533–47. [PubMed: 16551990]
31. Barkovich AJ, Hajnal BL, Vigneron D, Sola A, Partridge JC, Allen F, et al. Prediction of neuromotor outcome in perinatal asphyxia: evaluation of MR scoring systems. *AJNR Am J Neuroradiol*. 1998; 19(1):143–9. [PubMed: 9432172]
32. Rutherford M, Ramenghi LA, Edwards AD, Brocklehurst P, Halliday H, Levene M, et al. Assessment of brain tissue injury after moderate hypothermia in neonates with hypoxic-ischaemic encephalopathy: a nested substudy of a randomised controlled trial. *Lancet Neurol*. 9(1):39–45. [PubMed: 19896902]

33. Bennet L, Dean JM, Wassink G, Gunn AJ. Differential effects of hypothermia on early and late epileptiform events after severe hypoxia in preterm fetal sheep. *J Neurophysiol.* 2007; 97(1):572–8. [PubMed: 17093117]
34. Bjorkman ST, Miller SM, Rose SE, Burke C, Colditz PB. Seizures are associated with brain injury severity in a neonatal model of hypoxia-ischemia. *Neuroscience.* 166(1):157–67. [PubMed: 20006975]
35. Connell J, Oozeer R, de Vries L, Dubowitz LM, Dubowitz V. Clinical and EEG response to anticonvulsants in neonatal seizures. *Arch Dis Child.* 1989; 64(4):459–64. [PubMed: 2730114]
36. Rafay MF, Cortez MA, de Veber GA, Tan-Dy C, Al-Futaisi A, Yoon W, et al. Predictive value of clinical and EEG features in the diagnosis of stroke and hypoxic ischemic encephalopathy in neonates with seizures. *Stroke.* 2009; 40(7):2402–7. [PubMed: 19478219]
37. Williams CE, Gunn AJ, Mallard C, Gluckman PD. Outcome after ischemia in the developing sheep brain: an electroencephalographic and histological study. *Ann Neurol.* 1992; 31(1):14–21. [PubMed: 1543346]
38. Rutherford M, Ramenghi LA, Edwards AD, Brocklehurst P, Halliday H, Levene M, et al. Assessment of brain tissue injury after moderate hypothermia in neonates with hypoxic-ischaemic encephalopathy: a nested substudy of a randomised controlled trial. *Lancet Neurol.* 2010; 9(1):39–45. [PubMed: 19896902]

Table 1

Clinical characteristics for 56 newborns with hypoxic-ischemic encephalopathy treated with therapeutic hypothermia, with and without electrographic seizures.

	EEG Seizures N = 17	No EEG seizures N = 39	P
Male sex	11 (64%)	17 (44%)	0.1
Gestational age, <i>weeks</i>	39.7 ($\pm$ 1.4)	39.1 ($\pm$ 1.4)	0.1
Birth weight, <i>grams</i>	3268 ($\pm$ 652)	3356 ($\pm$ 637)	0.6
Median Apgar score			
5 minutes	2 (0, 6)	3 (0, 8)	0.04
Blood gas within 60 minutes of birth			
pH	6.96 ($\pm$ 0.2)	6.98 ($\pm$ 0.2)	0.8
Base excess	-18 ($\pm$ 9)	-15 ($\pm$ 7)	0.2
Cardiac massage	8 (47%)	13 (34%)	0.3
Time to therapeutic temperature (hours)	4.1 ($\pm$ 2.0)	5.4 ($\pm$ 2.0)	0.03
Phenobarbital load prior to onset of EEG monitoring	2 (11%)	7 (16%)	0.7
Maximum encephalopathy score	6 (4, 6)	5 (3, 6)	0.0001
Day of life at MRI	4 (4, 8)	5 (4, 14)	0.07
Died prior to hospital discharge	4 (25%)	1 (3%)	0.01

Variables listed as mean ($\pm$ SD), median (range) or N(%).

Table 2

Initial background EEG for newborns with hypoxic-ischemic encephalopathy treated with therapeutic hypothermia with and without electrographic (EEG) seizures.

EEG Background	EEG Seizures N = 17	No EEG Seizures N= 39
Normal	1 (6%)	17 (44%)
Excessively discontinuous	3 (18%)	15 (38%)
Depressed and undifferentiated	4 (24%)	1 (3%)
Burst suppression	5 (29%)	3 (8%)
Extremely low voltage	4 (24%)	3 (8%)

* Variables listed as median (range) or N (%).

Table 3

Seizure characteristics for 17 newborns with hypoxic-ischemic encephalopathy treated with therapeutic hypothermia by severity of magnetic resonance imaging injury.

	Moderate-Severe Injury N = 10	Minimal-No Injury N= 7	P
Age at seizure onset, <i>hours</i>	18 (14, 62)	12 (10,16)	0.001
Clinical correlate	6 (60%)	4 (57%)	0.6
Status epilepticus	5 (50%)	0	0.04
Multifocal onset seizures	2 (22%)	0	0.3
Seizure resolution with single loading dose (20mg/kg) of phenobarbital	3 (30%)	7 (100%)	0.004

* Excludes status epilepticus. Variables listed as median (range) or N (%).

Table 4

Magnetic resonance imaging characteristics for 56 newborns with hypoxic-ischemic encephalopathy treated with therapeutic hypothermia, with and without

	Seizures N = 17	No seizures N = 39	P
Moderate-severe <i>injury</i>	10 (59%)	10 (26%)	0.02
<i>Pattern of Injury</i>			
Normal	5 (29%)	17 (46%)	0.5
Watershed predominant	7 (41%)	15 (38%)	
Basal ganglia/thalamus predominant	5 (29%)	7 (18%)	
Cortical injury	10 (59%)	12 (31%)	0.05
Near total injury	5 (29%)	2 (5%)	0.01

Variables listed as N(%).

Table 5

Descriptive seizure and MRI characteristics in 17 newborns with hypoxic-ischemic encephalopathy treated with therapeutic hypothermia by pattern of injury.

A. EEG Seizures With Moderate-Severe Injury					
	Age at 1st EEG recorded seizure (hrs)	Number of seizures (clinical correlate/total)	Seizure localization	Medications	MRI
<i>Watershed Predominant</i>					
1	62.3	14/15	Bifrontal	Phenobarbital 20mg/kg	Bilateral anterior watershed injury
2	15.0	0/SE	L→R Hemi	Phenobarbital 40mg/kg	Bilateral L>R anterior and posterior watershed injury
3	26.0	4/12	L Central→Temporal	Phenobarbital 50mg/kg; fosphenytoin 20mg/kg	Bilateral anterior watershed injury R caudate body injury
4	17.6	2/SE	R Occipital	Phenobarbital 30mg/kg	Anterior and posterior watershed injury with additional cortical involvement
5	16.8	2/2	R occipital L centrottemporal	Phenobarbital 20mg/kg	Anterior and posterior watershed injury
<i>Basal Ganglia/Thalamus Predominant</i>					
6	14.1	0/SE	R→L Central→Temporal L→R Central	Phenobarbital 40mg/kg	Abnormal signal in the thalamus and lentiform nuclei
7	19.0	0/6	L→R Central L Central L→R Frontal L→R Frontal→central	Phenobarbital 30mg/kg	Abnormal signal in the thalamus, lentiform nuclei and peritolandic cortex
<i>Near Total Injury</i>					
8	17.2	2/SE	<i>Multifocal</i>	Phenobarbital 40mg/kg	Extensive injury to the thalamus, basal ganglia

A. EEG Seizures With Moderate-Severe Injury					
	Age at 1st EEG recorded seizure (hrs)	Number of seizures (clinical correlate/total)	Seizure localization	Medications	MRI
9	24.0	2/14	L Frontal→central L→R Frontal→central	Phenobarbital 30mg/kg	and cortex Extensive injury to the thalamus, basal ganglia and cortex
10	21.7	0/SE	<i>Multifocal</i> R→L Occipital R Occipital Occipital→Frontal→temporal R Frontal→central L→R Frontal→central L→R Hemispheric	Phenobarbital 40mg/kg; levetiracetam 20mg/kg	Extensive injury to the thalamus, basal ganglia and cortex

B. EEG seizures with no-minimal injury					
	Age at 1st recorded EEG seizure (hrs)	Number of seizures (clinical correlate/total)	Seizure localization	Medications	MRI
<i>Normal</i>					
11	12.5	0/3	R Occipital	Phenobarbital 20mg/kg	Normal
12	12.1	1/5	Central	Phenobarbital 20mg/kg	Normal
13	11.2	2/2	Bihemispheric	Phenobarbital 20mg/kg	Normal
14	11.3	1/1	L Frontal→Central	Phenobarbital 20mg/kg	Normal
<i>Watershed Predominant</i>					
15	13.5	0/1	R Occipital	Phenobarbital 20mg/kg	L Anterior watershed injury
16	15.8	1/6	L→R Occipital	Phenobarbital 20mg/kg	L Posterior watershed injury

B. EEG seizures with no-minimal injury					
	Age at 1st recorded EEG seizure (hrs)	Number of seizures (clinical correlate/total)	Seizure localization	Medications	MRI
17	9.7	0/10	L → R Occipital	None	Bilateral anterior watershed injury

L left; R right; SE status epilepticus