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Risk factors for EEG seizures in neonates treated with hypothermia

A multicenter cohort study

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ABSTRACT

Objective: To assess the risk factors for electrographic seizures among neonates treated with therapeutic hypothermia for hypoxic-ischemic encephalopathy (HIE).

Methods: Three-center observational cohort study of 90 term neonates treated with hypothermia, monitored with continuous video-EEG (cEEG) within the first day of life (median age at onset of recording 9.5 hours, interquartile range 6.3–14.5), and continued for >24 hours (total recording 93.3 hours, interquartile range 80.1–112.8 among survivors). A pediatric electroencephalographer at each site reviewed cEEGs for electrographic seizures and initial EEG background category.

Results: A total of 43 (48%) had electrographic seizures, including 9 (10%) with electrographic status epilepticus. Abnormal initial EEG background classification (excessively discontinuous, depressed and undifferentiated, burst suppression, or extremely low voltage), but not clinical variables (including pH <6.8, base excess \leq -20, or 10-minute Apgar \leq 3), was strongly associated with seizures.

Conclusions: Electrographic seizures are common among neonates with HIE undergoing hypothermia and are difficult to predict based on clinical features. These results justify the recommendation for cEEG monitoring in neonates treated with hypothermia. *Neurology*® 2014;82:1239–1244

GLOSSARY

ACNS = American Clinical Neurophysiology Society; **aEEG** = amplitude-integrated EEG; **cEEG** = continuous video-EEG; **HIE** = hypoxic-ischemic encephalopathy.

Neonatal seizures are common,^{1–4} are often caused by hypoxic-ischemic encephalopathy (HIE),⁵ and may be harmful to the developing brain.^{6–10} Though therapeutic hypothermia may lower the risk of electrographic seizures among neonates with HIE,^{11,12} the incidence remains high, estimated at 30% to 95%.^{11,13,14}

In 2011, the American Clinical Neurophysiology Society (ACNS) recommended that all neonates at high risk for brain injury, including those with neonatal encephalopathy, be monitored with continuous video-EEG (cEEG) to evaluate suspicious clinical events or to assess for the presence of subclinical seizures.¹⁵ In spite of these recommendations, access to cEEG remains limited at many centers, since application and interpretation require specialized equipment and training, and many centers lack access altogether or must limit use of cEEG to those patients considered at highest risk for seizures. One common paradigm is to monitor neonates who display clinical seizures, though evidence suggests that clinicians are poor at clinically distinguishing seizures from nonseizure events,^{16,17} and most seizures in newborns lack a clear clinical correlate.^{18–20}

We aimed to identify risk factors for electrographic seizures among neonates who were treated with therapeutic hypothermia and monitored according to guidelines from the ACNS.

Editorial, page 1200

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METHODS This was a retrospective multicenter cohort study. Participating institutions were The Children's Hospital of Philadelphia, Children's National Medical Center, and the University of Michigan C.S. Mott Children's Hospital. Neonates were treated with whole-body therapeutic hypothermia according to National Institute of Child Health and Human Development eligibility criteria and protocol.²¹ All 3 sites monitor patients who undergo therapeutic hypothermia using cEEG from the time of admission and through rewarming. Consecutive cooled patients were included as study subjects if cEEG was initiated within the first day of life and continued for ≥ 24 hours. Enrollment periods were as follows: center 1, May 2006 to January 2008; center 2, March 2008 to January 2010; and center 3, January 2011 to December 2012. Data from a subset of subjects were previously reported.¹⁴ Clinical data were extracted from electronic medical records and bedside charts by a child neurologist at each center. A sentinel event was defined as a placental abruption, uterine rupture, cord rupture, cord knot, or tight nuchal cord. Study data were collected and managed using REDCap (Research Electronic Data Capture) tools hosted at the University of California, San Francisco.²²

Subjects at each center were monitored using conventional video-EEG. A trained technologist applied surface electrodes according to the international 10 to 20 system, modified for neonates. Monitoring was initiated as part of routine care and according to institutional clinical guidelines as soon as possible after admission to the intensive care nursery (median age at onset of EEG 9.5 hours of life, interquartile range 6.3–14.5), and was maintained throughout the duration of therapeutic hypothermia and rewarming (median duration of EEG recording 93.3 hours among survivors, interquartile range 80.1–112.8).

A neurophysiologist with experience in neonatal EEG at each site reviewed the archived full-length video-EEG recordings to evaluate for the presence of electrographic seizures and electrographic status epilepticus. 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 μV .^{23,24} Electrographic status epilepticus was defined as continuous electrographic seizure lasting at least 30 minutes, or recurrent electrographic seizures for at least 50% of 1–3 hours of recording time.^{24,25} EEG background at the onset of recording was evaluated for at least 1 hour of recording and classified into 1 of 4 patterns: (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, bursts of activity separated by interburst intervals with amplitude $\geq 5 \mu\text{V}$ and $< 25 \mu\text{V}$ for at least 2 seconds, and with no state changes; (3) severely abnormal, depressed and undifferentiated, with persistently low-voltage background activity with amplitude between 5 μV and 15 μV and without normal features, burst suppression, invariant and unreactive pattern of bursts of paroxysmal activity with mixed features but no age-appropriate activity and alternating with periods of marked voltage attenuation with amplitude $< 5 \mu\text{V}$, or extremely low voltage, invariant and unreactive pattern, with amplitude $< 5 \mu\text{V}$ or with no discernible cerebral activity; (4) electrographic status epilepticus at the onset of recording.

Clinical and electrographic seizures were treated with medications according to institutional guidelines and at the discretion of the treating physician. None of the study centers used prophylactic phenobarbital.

Standard protocol approvals, registrations, and patient consents. The Committee on Human Research or Institutional

Review Board at each institution approved the study, including waiver of consent.

Statistical analysis. Statistical analyses were performed using Stata 11.2 software (Stata Corp., College Station, TX). Continuous data were dichotomized and χ^2 and Fisher exact tests were used to compare categorical variables. All tests were 2-sided. Logistic regression analysis was used to examine the association between risk factors and presence of electrographic seizures. In cases where a clinical risk factor was not documented in the patient chart, it was considered as not present. We considered a p value < 0.05 significant.

RESULTS Patient population. A total of 109 term neonates were treated with therapeutic hypothermia during the study period, and 90 met inclusion criteria. Subjects were excluded as follows: 2 were studied as part of a late-onset cooling trial and hypothermia was not initiated within the first 6 hours of life; in 14 subjects, cEEG monitoring was initiated only after 24 hours of life; in 2 subjects, initial cEEG recording could not be interpreted; and in 1 subject, cEEG was discontinued prior to 24 hours of life. The clinical characteristics of the subjects at each center are presented in table 1.

Electrographic and clinical seizures. Overall, 43 of 90 subjects (48%) had electrographic seizures (range by institution 33%–71%, $p = 0.01$): 6% with only 1 or 2 seizures throughout the recording period, 32% with > 2 seizures, and 10% with electrographic status epilepticus. The range of patients with a higher seizure burden (> 2 seizures or status epilepticus) was 33% to 48% across institutions ($p = 0.2$). Electrographic seizure onset occurred at a median of 19.9 hours of life (interquartile range 16.7 hours–26.3 hours). Six subjects (7%) were in electrographic status epilepticus at the onset of recording. Only 4 of those with electrographic seizures (4% of the entire study population) had seizure onset de novo during rewarming.

Clinical seizures were suspected in 44 of 90 subjects (49%) prior to the onset of EEG monitoring. Of these, 35 (78%) received phenobarbital therapy. Half of subjects with clinically suspected seizures prior to monitoring had electrographic seizures ($n = 22$), while 46% ($n = 21$) of those without clinical seizures prior to onset of monitoring had electrographic seizures (relative risk 1.1, 95% confidence interval 0.7–1.7, $p = 0.7$). There was no difference in risk of electrographic seizures among those who received phenobarbital prior to cEEG monitoring.

Risk factors for electrographic seizures. In the unadjusted analysis, the risk of electrographic seizures was higher among subjects with an abnormal EEG background. None of the perinatal clinical resuscitation variables predicted electrographic seizure

Table 1 Clinical characteristics of 90 neonates treated with therapeutic hypothermia for hypoxic-ischemic encephalopathy at 3 academic medical centers

| | Overall (n = 90) | Center 1 (n = 43) | Center 2 (n = 24) | Center 3 (n = 23) | p Value |
|---|---------------------|----------------------|----------------------|----------------------|---------|
| Gestational age, wk | 39.1 ± 1.5 | 38.8 ± 1.5 | 39.1 ± 1.4 | 39.4 ± 1.3 | 0.3 |
| Emergent cesarean | 58 (64) | 26 (60) | 16 (67) | 16 (70) | 0.8 |
| Sentinel event | 44 (49) | 22 (51) | 12 (50) | 10 (43) | 0.9 |
| 10-minute Apgar ≤3 | 35 (39) | 15 (35) | 7 (29) | 13 (57) | 0.1 |
| Chest compressions | 43 (48) | 17 (40) | 7 (29) | 19 (83) | <0.0005 |
| First pH ≤ 6.8 | 20 (22) | 14 (33) | 3 (13) | 3 (13) | 0.08 |
| First base excess ≤ -20 | 46 (51) | 23 (53) | 11 (46) | 12 (52) | 0.8 |
| Decreased or absent responsiveness on initial examination | 79 (88) | 38 (88) | 19 (79) | 22 (95) | 0.2 |
| Clinical seizures prior to monitoring | 44 (49) | 23 (53) | 11 (46) | 10 (43) | 0.7 |
| Age at therapeutic temperature, h | 4.7 ± 1.6 | 5.1 ± 1.1 | 4.7 ± 2.3 | 4.1 ± 1.6 | 0.06 |
| Deceased prior to discharge | 16 (18) | 8 (19) | 5 (21) | 3 (13) | 0.8 |
| Length of stay among survivors, d | 13 (9, 24) | 13 (9, 27) | 10 (7, 21) | 15.5 (8.5, 30) | 0.2 |

Data are presented as n (%), mean ± SD, or median (interquartile range).

occurrence (table 2). Presence of a perinatal sentinel event, degree of encephalopathy, and age at achieving therapeutic temperature for hypothermia were also not significantly associated with electrographic seizures. Initial EEG background pattern was electrographic status epilepticus in 6 subjects. Among the remaining subjects, initial EEG background was strongly associated with risk of seizures (and the risk persisted after adjusting for all clinical risk factors plus treatment center, $p < 0.0001$): the more severely abnormal the background pattern, the higher the risk for electrographic seizures. Furthermore, the higher risk of seizures among subjects with abnormal EEG background was independent of treatment with antiseizure medications prior to initiation of the EEG recording. Though subjects with excessively discontinuous and severely abnormal EEG background at the onset of recording were at highest risk (70% and 63%, respectively), 12% of subjects with a normal initial EEG background pattern had EEG seizures. Among subjects with EEG seizure onset during rewarming, the background was severely abnormal in 3 (75%), and normal in the remaining subject. The predictive value of an abnormal initial EEG background for electrographic seizures is presented in table 3.

DISCUSSION Prior to the widespread use of therapeutic hypothermia, HIE was reported as the most common cause of neonatal seizures.³ Despite reports of reduced seizure burden among neonates treated with hypothermia,^{11,12} our multicenter data suggest that electrographic seizures remain common and are difficult to predict based on clinical features alone. EEG background at the onset of cEEG recording

was most closely associated with risk of EEG seizures, with the highest risk among those with the most severely abnormal background pattern. Conversely, none of the perinatal clinical variables predicted electrographic seizures.

Our results are in keeping with single-center studies performed prior to the widespread use of therapeutic hypothermia. In a study of 49 term infants with perinatal asphyxia, as in our study, early cEEG monitoring was more accurate for predicting EEG seizures than either the clinical risk factors at birth or degree of acidosis.²⁶ In a second study, a heterogeneous group of 51 neonates risk for seizures (including 30 with perinatal asphyxia) were examined with EEG recordings starting at a mean age of approximately 24 hours of life and found to have a very high association between initial EEG background and electrographic seizures.²⁷ The less robust association between abnormal EEG and seizures in our cohort may be related to the difference in study population, effect of hypothermia or sedating medications on EEG background, or potential protective effect of hypothermia.

Our results support the recommendation that cEEG monitoring be implemented for all neonates who are treated with therapeutic hypothermia for HIE,¹⁵ rather than targeted subgroups, such as those with clinical seizures or depressed mental status. We found that the risk of electrographic seizures was similar among subjects with and without premonitoring clinical seizures, as well as those with normal or hyperalert mental status as compared to those with depressed or unresponsive mental status.

Increasingly, centers across North America and Europe are implementing cEEG monitoring for neonates

Table 2 Risk factors for electrographic seizures among 90 neonates treated with therapeutic hypothermia for hypoxic-ischemic encephalopathy

| | N | EEG seizure, n (%) | Relative risk (95% CI) | p |
|---------------------------------------|----|--------------------|------------------------|----------|
| Emergent cesarean | | | | |
| Yes | 58 | 26 (45) | 0.8 (0.5-1.3) | 0.5 |
| No | 32 | 17 (53) | — | |
| Chest compressions | | | | |
| Yes | 43 | 24 (56) | 1.3 (0.9-2.1) | 0.1 |
| No | 47 | 19 (40) | — | |
| 10-minute Apgar ≤3 | | | | |
| Yes | 35 | 19 (54) | 1.2 (0.8-1.9) | 0.3 |
| No | 55 | 24 (43) | — | |
| First pH < 6.8 | | | | |
| Yes | 20 | 10 (50) | 1.1 (0.6-1.8) | 0.8 |
| No | 70 | 33 (47) | — | |
| First base excess ≤ -20 | | | | |
| Yes | 46 | 24 (52) | 1.2 (0.8-1.8) | 0.2 |
| No | 44 | 19 (43) | — | |
| Initial examination | | | | |
| Normal | 4 | 2 (50) | — | 0.3 |
| Hyperalert | 5 | 3 (60) | 1.5 (0.1-21.3) | |
| Depressed | 50 | 19 (38) | 0.6 (0.1-4.7) | |
| Unresponsive | 29 | 17 (59) | 1.4 (0.4-15.8) | |
| Initial background^a | | | | |
| Normal | 34 | 4 (12) | — | <0.00005 |
| Excessively discontinuous | 20 | 14 (70) | 17.5 (4.2-72.1) | |
| Severely abnormal | 30 | 19 (63) | 13.0 (3.5-46.6) | |

Abbreviation: CI = confidence interval.

^aStatus epilepticus at the onset of recording in 6 subjects who were dropped from this analysis.

with encephalopathy.^{28,29} Many centers are adopting modified montages, such as 2- or 3-channel amplitude-integrated EEG (aEEG), which has lower sensitivity and specificity for seizure detection than conventional video-EEG.³⁰⁻³³ Whether the increased

Table 3 Predictive value of excessively discontinuous or severely abnormal EEG background for electrographic seizures among 84 neonates treated with therapeutic hypothermia for hypoxic-ischemic encephalopathy

| | % | 95% CI |
|---------------------------|----|---------|
| Positive predictive value | 66 | 51%-79% |
| Negative predictive value | 88 | 73%-97% |

Abbreviation: CI = confidence interval.

Excludes 6 subjects with status epilepticus at the onset of recording.

accuracy of gold-standard full-montage video-EEG is clinically relevant is not known.

Though this study is strengthened by multicenter data, a large cohort size, gold-standard cEEG monitoring according to guidelines set out by the ACNS,¹⁵ and EEG review by pediatric neurophysiologists with experience in neonatal EEG, it is not without limitations. First, 3 separate pediatric neurophysiologists evaluated the EEG recordings without use of a consensus scoring system. Interrater differences are unlikely to have affected our primary result—that EEG background is associated with seizures among neonates treated with therapeutic hypothermia. However, misclassification of the outcome may have led to bias toward the null hypothesis and limited our ability to detect a difference among less robust predictors. Second, the lack of association with clinical risk factors may be related to limitations in clinical medical record documentation at each site or limited sample size. Nonetheless, we are able to determine that there is not a strong association between clinical risk factors and electrographic seizures. Third, subjects were enrolled over different study periods at the 3 centers, which may lead to heterogeneity within the study group, but again, should not affect the primary results. Fourth, we did not evaluate EEGs for elements such as normal named patterns, excessive abnormal sharp waves, degree of burst suppression, evolution of EEG background, or other more subtle EEG patterns, which may be useful for further refining risk of seizures. Finally, our data were insufficient to study additional perinatal risk factors such as maternal disease, placental abnormalities, and fetal causes (e.g., intrauterine growth retardation), findings that may further help to stratify the risk of seizures in this population.

Across 3 North American institutions, electrographic seizures were common among neonates treated with hypothermia and were difficult to predict based on clinical history alone. These findings justify the recommendation by the ACNS that EEG monitoring be used to detect electrographic seizures among neonates treated with hypothermia. Centers that have limited resources for prolonged conventional video-EEG could consider targeting neonates with moderate or severe initial EEG background abnormalities based on either early full-montage or an adapted montage such as single- or dual-channel aEEG, since these neonates are at highest risk. However, even neonates with normal initial EEG background may have electrographic seizures. Additional studies are warranted to further refine early EEG risk factors for seizures among neonates with HIE, as well as to determine the clinical impact of prolonged monitoring on medication use and long-term outcome.

AUTHOR CONTRIBUTIONS

H.C. Glass drafted and revised the manuscript for content, participated in study concept and design, planned and performed analysis and interpretation of data, performed statistical analysis, and approved the submitted manuscript. C.J. Wusthoff revised the manuscript for content, participated in study concept and design, assisted with interpretation of data, acquired data, and approved the submitted manuscript. R.A. Shellhaas revised the manuscript for content, assisted with interpretation of data, acquired data, and approved the submitted manuscript. T.N. Tsuchida revised the manuscript for content, participated in study concept and design, assisted with interpretation of data, acquired data, and approved the submitted manuscript. S.L. Bonifacio revised the manuscript for content, assisted with interpretation of data, and approved the submitted manuscript. M. Cordeiro revised the manuscript for content, assisted with interpretation of data, acquired data, and approved the submitted manuscript. J. Sullivan revised the manuscript for content, participated in study concept and design, assisted with interpretation of data, and approved the submitted manuscript. N.S. Abend revised the manuscript for content, participated in study concept and design, assisted with interpretation of data, acquired data, and approved the submitted manuscript. T. Chang revised the manuscript for content, participated in study concept and design, assisted with interpretation of data, acquired data, and approved the submitted manuscript.

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