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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

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Abstract

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.

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Keywords

neonatal seizures; whole-body hypothermia; neurodevelopmental outcome; hypoxic-ischemic encephalopathy

Neonatal seizures are a common problem, affecting 1 to 4/1000 live term births.[1–4] Of the approximately 4 000 000 live births annually in the United States, there are 3700 to 15 000 term infants with neonatal seizures each year. Neonatal seizures are often associated with serious underlying etiologies such as hypoxic-ischemic encephalopathy, intracranial hemorrhage, strokes, or sepsis.[5] As a result, the natural history of infants with neonatal seizures, particularly seizure recurrence and longer-term neurodevelopmental outcome, is not easily separated from the primary etiology of seizures.[1,2,6–10]

The combined morbidity and mortality rate of term infants with seizures can be as high as 35% to 60%,[6,9,11] depending on the etiology of the seizure. Infants with neonatal seizures can develop cerebral palsy, developmental delay, and/or epilepsy. Hypoxic-ischemic encephalopathy is a common etiology of neonatal seizures,[12,13] and when both are present, the outcome is generally poor. Whether the seizures themselves have an independent impact on the immature neonatal brain and are responsible for additional damage or whether the seizures represent another manifestation of the existing brain injury is still a subject of debate.[5] However, given the available animal data, it appears that the addition of seizures can have further detrimental effects.[14,15] In a recent study, clinical neonatal seizures in the setting of birth asphyxia were noted to be associated with worse neurodevelopmental outcome, independent of the severity of hypoxic-ischemic brain injury.[16]

In term asphyxiated infants enrolled in a clinical trial of selective head-cooling for neonatal encephalopathy, the presence of neonatal seizures at the time of enrollment in the trial was associated with poor outcome at 18 months.[17] However, the impact of clinical seizures during the entire neonatal hospital course on outcome during therapeutic hypothermia has not been evaluated. In the National Institute of Child Health and Human Development Neonatal Research Network clinical trial of systemic hypothermia in hypoxic-ischemic encephalopathy,[18] over 60% of the study participants were reported to have had clinical seizures. The data collected during the trial provided the opportunity to examine the effect of hypothermia on clinical seizures and the effect of clinical neonatal seizures on later development. After the National Institute of Child Health and Human Development Trial was published, investigators at each of the participating sites were invited to submit proposals to test hypotheses that could be evaluated using the prospectively collected randomized controlled trial data. All proposals were reviewed by the Hypothermia Trial Subcommittee of the National Institute of Child Health and Human Development Neonatal Research Network and approved following revisions. We performed a secondary analysis of the Neonatal Research Network whole body hypothermia trial data,[18] to assess whether neonatal seizures in this cohort had additional impact on the primary outcome of death or moderate/severe disability.

Methods

Following National Institute of Child Health and Human Development Neonatal Research Network guidelines, a proposal to analyze data in the Neonatal Research Network database collected for the whole body hypothermia trial was submitted by investigators at one of the participating sites (J.M.K., R.G.) to the Hypothermia Study Subcommittee to investigate the possible association between the presence or absence of clinical seizures and long-term outcome in this population. The proposal was reviewed and accepted by the study PI (S.S.)

and members of the Neonatal Research Network Hypothermia Subcommittee. The Data Coordinating Center for the National Institute of Child Health and Human Development Neonatal Research Network is RTI International, Research Triangle Park, North Carolina. Data previously entered into the database that had been evaluated for accuracy and completeness were analyzed according to the proposed protocol by RTI biostatisticians on the Hypothermia Subcommittee (S.A.M. and W.K.P.). Except for the statisticians, the authors of the study did not have direct access to either the database or the primary data and remained blinded as to study arm.

Study participants were infants of at least 36 weeks' gestation with moderate to severe encephalopathy who were enrolled in the Neonatal Research Network whole body hypothermia trial. Eligibility criteria included: pH < 7.0 or base deficit > of 16 mmol/L in the first hour of life. If the blood gas was missing or had pH between 7.01 and 7.15 or base deficit between 10 and 15.9 mmol/L in first hour, additional criteria were required. These included a history of an acute perinatal event and either a 10-minute Apgar score of 5 or less or need for assisted ventilation for more than 10 minutes. Once they were determined to be eligible by these physiologic criteria, the infants were examined by certified physician examiners for signs of encephalopathy, defined as the presence of 1 or more signs in at least 3 of the following 6 categories[18]: level of consciousness, spontaneous activity, posture, tone, primitive reflexes (suck or Moro), and autonomic nervous system (pupils, heart rate, or respiration). Infants who had moderate or severe encephalopathy or documented seizures were randomized to whole body hypothermia (at 33.5°C for 72 hours, followed by slow rewarming) or control groups. All surviving infants were followed to 18 months of age and neurological and cognitive outcome evaluations were performed by certified trained examiners masked to intervention status. Study data forms and a manual of procedures were developed by the Hypothermia Trial Subcommittee and approved by the National Institute of Child Health and Human Development Steering Committee. A training session for site principal investigators, follow-up investigators, and research nurses was held before study initiation. The parent study was approved by the institutional review board at each site. Data collection was performed daily prospectively by trained research nurses and data transmitted on a weekly basis to the data coordinating center.

We evaluated the association between the presence of clinical neonatal seizures recorded at any time during the hospitalization and the following: (1) the combined outcome, death or moderate or severe disability at 18 months; (2) the Bayley Mental Development Index at 18 months; and (3) Bayley Mental Development Index < 70 at 18 months. Clinical seizures were documented as subtle (ocular deviation, sucking, lip smacking), swimming, rowing, or bicycling movements that could be tonic/clonic, localized, multifocal, or generalized. The management of seizures was not standardized and was based on usual care at each individual participating center. The maternal and neonatal characteristics of those infants with clinical seizures and those without seizures were also compared.

Study Definitions

The following study definitions were applied. *Neonatal seizures*: The presence of clinical neonatal seizures in subjects was recorded at 5 time intervals during the study enrollment, enrollment to 24 hours, 25 to 48 hours, 49 to 72 hours, and 73 hours until discharge. Most seizures were identified clinically by the attending physician. The presence of seizures was documented in the Neonatal Research Network database according to the criteria in the manual of operations for the whole body hypothermia study by experienced research nurses with the oversight of the site principal investigators. The nurses reviewed the patient records of each infant in the study at randomization, every 24 hours of study intervention, and at discharge, and coded seizures if documented in the bedside chart or in the medical record. The confirmatory electroencephalograms (EEGs) were not required as part of the research

protocol. For the purposes of these analyses, infants were classified as having clinical neonatal seizures if seizures were documented at any time during the study. This definition is therefore simply one of presence or absence of seizures during the entire neonatal hospital stay and does not fully capture the severity or timing of the neonatal seizures. *Moderate and severe disability*: Cognitive outcome was assessed using the Bayley Scales of Infant Development II. Severe disability was defined as any of the following: Bayley Mental Development Index score > 2 standard deviations (SD) below the mean score (ie, < 70), a Gross Motor Function Classification System level 3 to 5 (indicative of moderate or severe cerebral palsy); hearing impairment requiring hearing aids; or blindness. Moderate disability was defined as a Mental Development Index 1 to 2 SD below the mean (ie, 70–84) in addition to one or more of the following: a Gross Motor Function Classification System grade of level 2, hearing impairment with no amplification, or a persistent seizure disorder at 18 months of age.

Statistical Methods

Multivariate analyses using logistic regression for the combined outcome (death or moderate or severe disability) or linear regression (Bayley Mental Development Index) included treatment effects, severity of encephalopathy (moderate or severe), and the presence of neonatal seizures. We examined the association between neonatal seizures and death or moderate or severe disability, neonatal seizures and Bayley Mental Development Index, and the interaction between hypothermia treatment and neonatal seizures. Logistic regression analyses with neonatal seizures as the outcome and with treatment and severity of encephalopathy as covariates were used to test the association between neonatal seizures and severity of encephalopathy. All data were analyzed using SAS® software, version 9.1. All study results and manuscript drafts were critically reviewed by the Neonatal Research Network Hypothermia Trial Subcommittee.

Results

Of the 208 subjects (102 hypothermia, 106 control), 127 were reported to have had seizures during the course of the hypothermia trial. Among these 127 infants with clinical seizures, 94 had seizures by the time of study enrollment, and an additional 26, 4, and 2 infants had seizures noted by 24, 48, and 72 hours, respectively. At the time of neonatal intensive care unit discharge, 1 additional infant was noted to have had seizures during the hospitalization. Data on occurrence of clinical seizures was missing among 20 infants by discharge (including 17 deaths). The clinical characteristics of the 127 infants with seizures at anytime during the hospitalization were compared with the 81 infants who were not reported to have had seizures during the hospitalization. There were no significant differences in gestational age or birth weight; however, more infants with seizures were born to African American mothers, were outborn, had a lower Apgar score at 10 minutes, had time to spontaneous respiration > 10 minutes, needed continued resuscitation at 10 minutes, had lower cord pH and higher base deficit, were classified as having severe encephalopathy, and received anticonvulsants as compared to infants without seizures (Tables 1 and 2). At the time of study initiation, 44% of hypothermia infants and 57% of control infants had seizures ($P = .09$).

The outcomes among infants with and without clinical seizures are noted in Table 3. In the univariate analyses (with no correction for multiple testing), there was a higher proportion of infants with either death or disability or Bayley Mental Development Index < 70 among infants with clinical seizures. However, these outcomes could also be seen independently in those with severe hypoxic-ischemic encephalopathy. The proportion of severe hypoxic-ischemic encephalopathy infants was higher in the seizure group than in the seizure-free group (44% versus 21%, $P < .001$). Multivariate logistic regression modeling was then

performed to control for the effects of hypothermia treatment and severity of hypoxicischemic encephalopathy (Tables 4–6). The effects of neonatal seizures on later outcome were not significant in the regression models controlling for hypothermia treatment or severity of hypoxic-ischemic encephalopathy, suggesting that neonatal seizures do not appear to exert an independent risk for later adverse outcomes in this cohort.

Discussion

This secondary analysis of the National Institute of Child Health and Human Development Neonatal Research Network whole body hypothermia study cohort[18] did not identify an independent effect of clinical neonatal seizures on later outcomes. These findings suggest that neonatal seizures do not exert an impact independent of the underlying degree of encephalopathy.

Our study appears to challenge what has been a prevailing, though controversial, concept that neonatal seizures exert an added deleterious effect on the newborn brain independent of the degree of encephalopathy. Animal models of neonatal seizures show that seizures are associated with poor developmental outcomes.[14,15] Yet, in humans, it is still unclear if this association has more to do with the etiology of seizures than the seizures themselves.[5,6,9,11,17] Studies of neonatal seizures typically include infants with a variety of etiologies, including perinatal asphyxia, sepsis/meningitis, and central nervous system hemorrhage. By using the trial cohort of encephalopathy presumably due to hypoxia-ischemia, we had a more homogeneous group of term infants presenting with neonatal encephalopathy, as well as information characterizing the severity of encephalopathy.

Our study was limited by several factors. As EEG recordings were not required as part of the study, we relied on clinical recognition of electrographic seizures, our analysis is confounded by imprecise ascertainment. EEG recordings were not required as part of the protocol. The use of antiepileptic drugs and sedation can have interfered with the diagnosis of clinical seizures. A high percentage of infants without clinical seizures received anticonvulsants, based on the usual care of severe encephalopathy at the centers. Assessment of underlying etiology of seizures, in addition to hypoxic-ischemic encephalopathy, that can be secondary (ie, hypoglycemia, hypocalcemia, or hyperglycemia) was not part of the research protocol. We did not have access to magnetic resonance imaging data on the study infants.[16] The sample size was relatively small and when this secondary analysis was proposed, it was predicted to have 80% power to detect a 50% increase in adverse outcomes in the seizure group. However, despite being “under-powered,” our study was able to control for critical covariates—hypothermia treatment and severity of initial encephalopathy—that are hypothesized to affect later neurodevelopmental outcome more than the presence of seizures. The definition of neonatal seizures used in this study was problematic and did not allow for assessment of relative seizure duration or severity. The case report forms relied on reported clinical seizures, so it is not surprising that there is wide variability in the rate (and probably methodology) of seizure diagnosis by center. This reflects the current wide variability in local practices in diagnosing and managing of neonatal seizures.[19]

While this study suggests that the presence of neonatal seizures cannot cause added harm in the setting of neonatal encephalopathy, understanding the true impact of neonatal seizures will require, continuous EEG monitoring within a cohort of infants homogeneous in the severity and etiology of underlying encephalopathy. However, they certainly are not a good prognostic sign as pointed out by the abnormal Bayley Mental Development Index, severe and moderate hypoxic-ischemic encephalopathy, and the increase in death and disability. Therefore, more careful characterization (duration, type, responsiveness to therapy) can be useful in prognosis. In addition, a treatment trial can require more effective anti-seizure

medications than are currently available. Until these studies can be performed, we cannot determine whether aggressive treatment of neonatal seizures will improve long-term neurodevelopmental outcome.

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Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Dr. Abhik Das (DCC Principal Investigator) and Mr. Scott McDonald (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

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Table 1

Maternal Characteristics of Infants With Seizures at Any Time (n = 127) Versus Infants With No Seizures (n = 81)

Maternal characteristics	Seizures (n = 127)	No seizures (n = 81)	Total (N = 208)
Race, n (%)*			
Black	51 (40)	21 (26)	72 (35)
White	47 (37)	25 (31)	72 (35)
Other	29 (23)	35 (43)	64 (31)
Maternal age, y, mean ± SD	27.2 ± 6.3	27.4 ± 5.8	27.3 ± 6.1
Married, n (%)[a]	64 (51) (n = 125)	51 (65) (n = 78)	115 (57) (n = 203)
Gravida, median	2	2	2
Parity, median	2	1	2
Complications of pregnancy, n (%)			
Chronic hypertension	14 (11)	12 (15)	26 (13)
Antepartum hemorrhage	17 (13)	13 (16)	30 (14)
Thyroid disease	2 (2)	0 (0)	2 (1)
Diabetes	11 (9)	6 (7)	17 (8)
Intrapartum complications, n (%)			
Fetal heart rate decelerations[a]	97 (77) (n = 126)	56 (69)	l53 (74) (n = 207)
Cord prolapse	25 (20)	12 (15)	37 (18)
Uterine rupture	19 (15)	10 (12)	29 (14)
Maternal pyrexia[a]	9 (7) (n = 126)	12 (15)	21 (10) (n = 207)
Shoulder dystocia[a]	13 (10) (n = 126)	7 (9)	20 (10) (n = 207)
Maternal hemorrhage	11 (9)	3 (4)	14 (7)
Labor, h, mean ± SD†	11.3 ± 9.1 (n = 66)	13.5 ± 8.8 (n = 39)	12.1 ± 9.0 (n = 105)
Rupture of membranes, h, mean ± SD†	6.2 ± 11.7 (n = 115)	5.5 ± 7.6 (n = 73)	5.9 ± 10.3 (n = 188)
Emergency cesarean delivery	95 (75)	57 (70)	152 (73)

* Significant at $P < .05$ (Fisher exact test for categorical variables, t test for continuous variables).

[a] Numbers are reported in parentheses where data are incomplete.

Table 2

Neonatal Characteristics of Infants With Seizures at Any Time (n = 127) Versus Infants With No Seizures (n = 81)

Neonatal characteristics	Seizures (n = 127)	No seizures (n = 81)	Total (N = 208)
Outborn, n (%)*	69 (54)	24 (30)	93 (45)
Male gender, n (%)	73 (57)	44 (54)	117 (56)
Apgar scores ≤ 5, n (%)			
At 5 min[a]	119 (94) (n = 126)	70 (86)	189 (91) (n = 207)
At 10 min*[a]	104 (87) (n = 119)	50 (69) (n = 72)	154 (81) (n = 191)
Birth weight, g, mean ± SD	3340 ± 595	3435 ± 681	3377 ± 630
Gestational age, wks, mean ± SD	38.9 ± 1.6	38.9 ± 1.7	38.9 ± 1.6
Length, cm, mean ± SD[a]	50.9 ± 3.1 (n = 119)	50.7 ± 3.2 (n = 79)	50.8 ± 3.1 (n = 198)
Head circumference, cm, mean ± SD[a]	34.2 ± 1.8 (n = 121)	34.1 ± 2.0 (n = 79)	34.1 ± 1.9 (n = 200)
Intubation in delivery room	122 (96)	73 (90)	195 (94)
Continued resuscitation at 10 min*	123 (97)	72 (89)	195 (94)
Time to spontaneous respiration ≥ 10 min†	94 (78) (n = 120)	46 (60) (n = 77)	140 (71) (n = 197)
Cord blood			
pH, mean ± SD*†	6.8 ± 0.2 (n = 80)	6.9 ± 0.2 (n = 65)	6.9 ± 0.2 (n = 145)
Base deficit, mean ± SD*[a]	20.6 ± 7.5 (n = 67)	17.5 ± 7.7 (n = 57)	19.2 ± 7.7 (n = 124)
Moderate encephalopathy*[a]	70 (56) (n = 126)	64 (79)	134 (65) (n = 207)
Severe encephalopathy*[a]	56 (44) (n = 126)	17 (21)	73 (35) (n = 207)
Anticonvulsants*[a]	74 (61) (n = 122)	9 (13) (n = 67)	83 (44) (n = 189)

*Significant at $P < .05$ (Fisher exact test for categorical variables, t test for continuous variables).

[a]Numbers are reported in parentheses where data are incomplete.

Table 3

Stage of Encephalopathy, Treatment, and Outcomes Among Infants With and Without Neonatal Seizures

	Seizures (n = 127)	No seizures (n = 81)	*P* value*
Number	127	81	
Hypothermia treatment	56 (44%)	46 (57%)	.09
Death or disability	78 (62%)	32 (40%)	.003
Moderate HIE	70 (56%)	65 (79%)	<.001
Severe HIE	56 (44%)	17 (21%)	
MDI	75 ± 23 (n = 83)	81 ± 15 (n = 55)	.07
MDI < 70	33 (40%)	1 1 (20%)	.02

Abbreviations: HIE, hypoxic-ischemic encephalopathy; MDI, Bayley Mental Development Index.

No correction for multiple testing.

**P* values are from Fisher exact test for categorical variables, or *t* test for MDI.

Table 4

Association of Neonatal Seizures and Death or Moderate or Severe Encephalopathy

Covariates	Odds ratio and 95% CI	*P* value
Seizures	1.76 (0.94–3.29)	.08
Hypothermia treatment	0.52 (0.28–0.95)	.03
Severe HIE	5.29 (2.67–10.51)	<.001

Abbreviations: CI, confidence interval; HIE, hypoxic-ischemic encephalopathy.

Table 5

Linear Regression Model for MDI

Covariates	Estimate	*P* value
Seizures	−3.26	.37
Hypothermia treatment	4.61	.18
Severe HIE	−8.89	.03

Abbreviations: HIE, hypoxic-ischemic encephalopathy; MDI, Bayley Mental Development Index.

Table 6

Logistic Regression Model for MDI < 70

Covariates	Odds ratio and 95% CI	*P* value
Seizures	1.93 (0.83–4.48)	.13
Hypothermia treatment	0.55 (0.26–1.19)	.13
Severe HIE	3.01 (1.27–7.13)	.01

Abbreviations: CI, confidence interval; HIE, hypoxic-ischemic encephalopathy; MDI, Bayley Mental Development Index.