Predictive Value of an Early Amplitude Integrated Electroencephalogram and Neurologic Examination

WHAT'S KNOWN ON THIS SUBJECT: An early amplitude integrated electroencephalogram has been shown to be predictive of encephalopathy and short-term neurologic outcome among neonates with hypoxic-ischemic encephalopathy.

WHAT THIS STUDY ADDS: In a prospective study, the authors found that the amplitude integrated electroencephalogram background pattern at <9 hours did not significantly enhance the predictive value of stage of hypoxic-ischemic encephalopathy at <6 hours in predicting death and disability at 18 months.

AUTHORS: Seetha Shankaran, MD,[a] Athina Pappas, MD,[a] Scott A. McDonald, BS,[b] Abbot R. Laptook, MD,[c] Rebecca Bara, RN,[a] Richard A. Ehrenkranz, MD,[d] Jon E. Tyson, MD, MPH,[e] Ronald Goldberg, MD,[f] Edward F. Donovan, MD,[g] Avroy A. Fanaroff, MD,[h] Abhik Das, PhD,[b] W. Kenneth Poole, PhD,[b] Michele Walsh, MD, MS,[h] Rosemary D. Higgins, MD,[i] Cherie Welsh, MD,[j] Walid Salhab, MD,[k] Waldemar A. Carlo, MD,[l] Brenda Poindexter, MD,[m] Barbara J. Stoll, MD,[n] Ronnie Guillet, MD, PhD,[o] Neil N. Finer, MD,[p] David K. Stevenson, MD,[q] and Charles R. Bauer, MD,[r] for the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network

[a]Department of Pediatrics, Wayne State University, Detroit, Michigan; [b]Statistics and Epidemiology Unit, RTI International, Research Triangle Park, North Carolina; [c]Department of Pediatrics, Women and Infants' Hospital, Department of Pediatrics, Brown University, Providence, Rhode Island; [d]Department of Pediatrics, Yale University School of Medicine, New Haven, Connecticut; [e]Department of Pediatrics, University of Texas Medical School at Houston, Houston, Texas; [f]Department of Pediatrics, Duke University, Durham, North Carolina; [g]Department of Pediatrics, University of Cincinnati, Cincinnati, Ohio; [h]Department of Pediatrics, Case Western Reserve University, Cleveland, Ohio; [i]Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, Maryland; [j]Department of Pediatrics, Wake Forest University, Winston-Salem, North Carolina; [k]Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas, Texas; [l]Department of Pediatrics, University of Alabama, Birmingham, Alabama; [m]Department of Pediatrics, Indiana University School of Medicine, Indianapolis, Indiana; [n]Department of Pediatrics, Emory University School of Medicine, Atlanta, Georgia; [o]Department of Pediatrics, University of Rochester Medical Center, Rochester, New York; [p]Department of Pediatrics, University of California, San Diego, California; [q]Department of Pediatrics, Stanford University, Palo Alto, California; and [r]Department of Pediatrics, University of Miami, Miami, Florida

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abstract

OBJECTIVE: To examine the predictive validity of the amplitude integrated electroencephalogram (aEEG) and stage of encephalopathy among infants with hypoxic-ischemic encephalopathy (HIE) eligible for therapeutic whole-body hypothermia.

DESIGN: Neonates were eligible for this prospective study if moderate or severe HIE occurred at <6 hours and an aEEG was obtained at <9 hours of age. The primary outcome was death or moderate/severe disability at 18 months.

RESULTS: There were 108 infants (71 with moderate HIE and 37 with severe HIE) enrolled in the study. aEEG findings were categorized as normal, with continuous normal voltage ($n = 12$) or discontinuous normal voltage ($n = 12$), or abnormal, with burst suppression ($n = 22$), continuous low voltage ($n = 26$), or flat tracing ($n = 36$). At 18 months, 53 infants (49%) experienced death or disability. Severe HIE and an abnormal aEEG were related to the primary outcome with univariate analysis, whereas severe HIE alone was predictive of outcome with multivariate analysis. Addition of aEEG pattern to HIE stage did not add to the predictive value of the model; the area under the curve changed from 0.72 to 0.75 ($P = .19$).

CONCLUSIONS: The aEEG background pattern did not significantly enhance the value of the stage of encephalopathy at study entry in predicting death and disability among infants with HIE. *Pediatrics* 2011; 128:e112–e120

For the past 30 years, term infants with encephalopathy because of hypoxia-ischemia (HIE) have been evaluated clinically with the Sarnat neurologic examination. This staging system is based on an initial examination at 12 to 24 hours of age, followed by daily evaluations until 6 days and every other day until hospital discharge.[1] The Sarnat stage of encephalopathy correlates well with neurodevelopmental impairment in infancy and childhood,[2–4] and scoring systems adapted from the Sarnat scoring system, including the Thompson score[5] and Miller score,[6] also have been shown to predict outcome.

The amplitude integrated EEG (aEEG) is a processed single-channel electroencephalogram that is compressed with regards to amplitude and time. It is rectified and smoothed and plotted semilogarithmically. An abnormal aEEG has been shown to be predictive of persistence of encephalopathy and impaired neurologic outcome when performed in the first few days of life.[7–11] A strong association between the early aEEG and neurodevelopmental outcome has been noted.[12]

Hypothermia initiated at <6 hours of age and continued for 72 hours in term infants with HIE reduces the risk of death and disability at 18 to 22 months[13,14] and improves neurologic outcome in survivors.[15] The window during which initiation of hypothermia has been studied is <6 hours of age.[16,17] Three of the published randomized controlled trials in which hypothermia has been evaluated as neuroprotection used stage of HIE as entry criteria,[13–15] and 2 of the trials used the additional criterion of an aEEG obtained at <6 hours of age.[13,15] Poor correlation has been noted between an early abnormal aEEG and outcome in 1 recent study,[18] and in another it has been noted that early abnormal aEEG may predict outcome for infants treated with normothermia but not hypothermia.[19] The objective of our study was to assess the predictive value of the aEEG performed at <9 hours on outcome at 18 to 22 months of age among infants with moderate or severe HIE eligible for whole body hypothermia. We chose 9 hours of age to allow time to achieve a steady state target temperature among infants who were cooled.[14] Cooling was not delayed to obtain the aEEG because aEEG was not used as a criterion for eligibility for cooling.

DESIGN AND METHODS

This observational prospective study was performed in the participating centers of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN). Infants at ≥36 weeks' gestation with severe acidosis and/or birth resuscitation at <6 hours of age were eligible for the NICHD randomized controlled trial (RCT) of whole body hypothermia for neonatal HIE.[14] After the trial, infants were eligible if the same criteria were met and an aEEG was obtained at <9 hours of age. Study enrollment was initiated in June 2001 and concluded in March 2006.

The neurologic examinations for evaluating for moderate or severe HIE were performed by certified physicians.[14] The certification process was as follows: each NRN site principal investigator (PI) was considered the gold standard examiner after orientation and review of the examination with the study subcommittee. Additional physician examiners reviewed the definitions of the components of the examination from the study manual of procedures and then performed neurologic examinations on 3 term infants, including 2 infants with abnormal findings, independent of the site PI and within 1 hour of the examination performed by the PI. A hard copy of the examinations was sent to the study data coordinating center at RTI International, Research Triangle Park, North Carolina. The study lead investigator (Dr Shankaran) compared the examinations of the physician examiners with the site PI, and a physician was certified if all 3 examinations achieved concordance with that of site PI regarding stage of HIE.

The aEEG was obtained by using the first prototype of the Moberg neonatal EEG monitor (Moberg Research, Inc, Ambler, PA) that has a portable system with an aEEG amplifier head box, a compact-sized computer, a flat-panel touch-screen display and an isolation transformer. The display includes a standard 8-channel display with an adjustable time scale, an amplitude scale, high and low filters, and an aEEG displayed as a numeric semilogarithmic scale with trends (graphics) of computed numeric values. A built-in educational program with a step-by-step guide for application of electrodes and obtaining the aEEG was developed. Training sessions were held for all research personnel to establish consistency in obtaining the aEEG. Four leads were used: reference, ground, and cerebral C3 and C4. The C3 and C4 locations were measured by using the modified international 10/20 electrode placement system. The site was marked with a nontoxic skin marking pencil, followed by application of Nu-Prep abrasive skin-stripping gel. Gold disk cup electrodes (Grass-Telefactor, West Warwick, RI) were filled with EEG paste, applied to the site, and secured with a thin strip of hypoallergenic tape. A turban of gauze was placed around the infant's head if needed. During the latter part of the study (after February 2004), an impedance check (≤10 kΩ) was available on the monitor. The recording period was 30 minutes. Clinical events such as seizures were not

recorded during the aEEG acquisition. The administration of medications (anticonvulsants, sedatives, or analgesics) were not recorded during or before the recording.

The aEEG recordings were archived on ORB or DVD-R disks sent to the data coordinating center. After completion of the study, the recordings were evaluated by a designated central reader (Dr Pappas) and a second reader (Dr Shankaran) experienced in evaluating aEEG recordings.[20] The predefined plan was that if consensus on the first 60 readings was high ($\kappa > 0.75$), then the designated central reader would continue to read the remaining recordings.

The aEEG background was classified as continuous normal voltage (CNV) with a maximum voltage of 10 to 50 μV and a minimum voltage between 5 and 10 μV; discontinuous normal voltage (DNV) with more periods of CNV and periods of intermittent low voltage above 5 μV; burst suppression (BS) with periods of very low voltage without variability (<5 μV) intermixed with bursts of higher amplitude (>25 μV); continuous low voltage (CLV) with continuous background and maximum voltage around or below 5 μV; or flat tracing (FT) with inactive background and very low voltage below 5 μV. CNV and DNV were defined as normal background aEEG, whereas BS, CLV, and FT were designated as abnormal background aEEG on the basis of the work of Toet et al.[9] Tracings with significant artifacts from electrical noise or movement interference that influenced the voltage and width of the entire tracing were excluded.

The primary outcome of this study was death or moderate/severe disability at 18 months of age.[14] Neurologic and developmental evaluations were performed by certified examiners trained for interobserver reliability who were unaware of cooling status or aEEG readings. Moderate disability was defined as a Mental Development Index (MDI) score of 70 to 84 and either a Gross Motor Function Classification System (GMFCS) level of 2, hearing impairment with no amplification, or persistent seizure disorder at 18 months. Severe disability was defined as any of the following: MDI $<$ 70; GMFCS level 3 to 5 (corresponding to moderate/severe cerebral palsy); hearing impairment that required hearing aids; or blindness. The study was approved by the institutional review board at participating centers, and parental informed consent was obtained for study participation. The follow-up component of the study ended in October 2008.

STATISTICAL ANALYSIS

Data were analyzed to evaluate whether the maternal and infant characteristics were similar between the infants who participated as part of the RCT (enrolled June 2001 to May 2003) and those who were enrolled after the RCT (June 2003 to March 2006). Similar comparisons were made between infants who were included in the study sample and those excluded because of a lack of information on the primary outcome. Comparisons between groups were performed by using χ^2 or Fisher's exact test for the categorical variables and t tests for continuous variables. The relationship between the stage of HIE or aEEG background and the primary outcome was tested by using Fisher's exact test. Values for sensitivity, specificity, positive predictive value (PPV), negative predictive value, and area under the curve (AUC) were calculated.

Multivariate logistic regression analysis was performed to assess the relationship between aEEG background and primary outcome, adjusting for level of encephalopathy and cooling status; an additional regression model added aEEG within 6 hours as a covariate. The interaction effects with cooling also were evaluated.

RESULTS

There were 140 infants enrolled in this study; an additional 41 infants, enrolled at participating sites, were excluded at the time of aEEG readings because their aEEG studies were noted to have been obtained after 9 hours of age. Among the 140 infants, aEEG readings were missing for 10 infants (both on the computer disks and on the backup monitor), and 13 recordings were technically unsatisfactory because of artifacts. Among the 117 infants with usable aEEG readings, 9 were lost to follow-up at 18 to 22 months of age, leaving 108 infants with aEEG obtained at $<$9 hours of age and complete primary outcome data in the study group. The aEEG was obtained at 6.3 $\pm$ 1.4 hours (mean $\pm$ SD) among all study infants.

Maternal and neonatal characteristics were compared between the infants enrolled during the RCT ($n = 46$) and those enrolled after the RCT ($n = 62$) (Table 1). Neonatal and maternal characteristics were comparable between groups except that a higher percentage of women were married and the frequency of uterine rupture was higher among the group of infants enrolled in RCT compared with the group enrolled after the RCT.

Staging of encephalopathy using Sarnat criteria at $<$6 hours of age among the 108 study infants revealed that 37 (34%) infants had severe HIE and 71 (66%) infants had moderate HIE (Fig 1). At 18 months of age, 1 infant (noted with "a" in Fig 1) did not have a follow-up examination to distinguish between moderate or severe disability; this infant was reported to have cerebral palsy, developmental and language delay, seizures since discharge, and blindness with some functional vision. The primary outcome of death or

TABLE 1 Infants Enrolled During the RCT Versus Infants Enrolled After the RCT

	RCT	After RCT	Total
Maternal characteristics, N (%)	46 (100)	62 (100)	108 (100)
Race			
Black	14 (30)	18 (29)	32 (30)
White	14 (30)	21 (34)	35 (32)
Other	18 (39)	23 (37)	41 (38)
Maternal age, y	28 ± 6 (N = 46)	27 ± 6	27 ± 6
Married[a]	28 (64)	24 (39)	52 (50)
Median gravida	3	2	2
Median parity	2	2	2
Any pregnancy complications[b]	14 (30)	27 (44)	41 (38)
Any intrapartum complications[c]	40 (87)	50 (81)	90 (83)
Emergency cesarean delivery	33 (72)	40 (65)	73 (68)
Neonatal characteristics, N (%)	46 (100)	62 (100)	108 (100)
Outborn	17 (37)	27 (44)	44 (41)
Male gender	23 (50)	39 (63)	62 (57)
Apgar score ≤ 5			
At 5 min	39 (87)	49 (82)	88 (84)
At 10 min	31 (74)	37 (74)	68 (74)
Birth weight, g	3368 ± 655	3448 ± 649	3414 ± 649
Intubation in delivery room	43 (93)	56 (90)	99 (92)
Continued resuscitation at 10 min	42 (91)	61 (98)	103 (95)
Time to spontaneous respiration ≥10 min	30 (68)	31 (55)	61 (61)
Cord blood			
pH	6.9 ± 0.2 (N = 34)	6.9 ± 0.2 (N = 51)	6.9 ± 0.2 (N = 85)
Base deficit	18.0 ± 8.0 (N = 30)	18.6 ± 8.0 (N = 41)	18.4 ± 7.9 (N = 71)
Seizures	22 (48)	26 (42)	48 (44)
Moderate encephalopathy	28 (61)	43 (69)	71 (66)
Severe encephalopathy	18 (39)	19 (31)	37 (34)
Anticonvulsants at baseline	20 (51)	26 (58)	46 (55)
Analgesics at baseline	8 (20)	14 (30)	22 (26)
Cooling	23 (50)	34 (55)	57 (53)
Age at initiation of cooling, h	4.8 ± 1.0 (N = 23)	4.4 ± 1.6 (N = 32)	4.5 ± 1.4 (N = 55)

[a] $P < .05$.

[b] Includes chronic hypertension, antepartum hemorrhage, thyroid disease, and diabetes.

[c] Includes fetal heart rate decelerations, cord prolapse, uterine rupture, maternal pyrexia, shoulder dystocia, and maternal hemorrhage.

moderate/severe disability occurred in 53 (49%) infants; 30 of 37 (81%) of infants with severe HIE had the primary outcome, and 23 of 71 (32%) of infants with moderate HIE had the primary outcome; the ability to predict the primary outcome among those with severe HIE compared with moderate HIE had the following: sensitivity, 0.57 (30 of 53); specificity, 0.87 (48 of 55); PPV, 0.81 (30 of 37); and negative predictive value, 0.68 (48 of 71); $P < .0001$.

Among the 108 infants, the aEEG at <9 hours of age was read as normal for CNV (n = 12) and DNV (n = 12) and abnormal for BS (n = 22), CLV (n = 26), and FT (n = 36) (Fig 1). The reliability of 60 readings between the 2 readers was 0.91 (κ coefficient). The relationship of an abnormal aEEG background at <9 hours of age and the primary outcome is noted in Table 2. The PPV of severe HIE (0.81) was higher than an abnormal aEEG (0.56), whereas the PPV of moderate HIE (0.32) was lower than that of an abnormal aEEG (0.56). The AUC between the neurologic examination of moderate/severe HIE and death/disability was 0.72 (95% confidence interval: 0.64–0.80). When the aEEG was added to the model, neurologic examination remained significant ($P < .0001$), whereas aEEG was not; the AUC did increase to 0.75 (95% confidence interval: 0.66–0.83), but it was not a significant increase in the AUC ($P = .19$).

The relationship of the background pattern of the aEEG among cooled infants (n = 57) and noncooled infants (n = 51) and among those with aEEG obtained before 6 hours (n = 45) and those obtained between 6 and 9 hours of age (n = 63) with the primary outcome is noted in Table 2.

The relationship of aEEG background, stage of encephalopathy, and hypothermia on primary outcome by multivariate logistic regression analysis is noted in Table 3. The odds ratio (95% confidence interval) for primary outcome increased with severe HIE compared with moderate HIE 9.2 (95% confidence interval: 3.2–26.5). Cooling decreased the risk of the primary outcome (odds ratio: 0.3 [95% confidence interval: 0.1–0.8]). There were no interactions between cooling and aEEG or cooling and stage of HIE (data not shown).
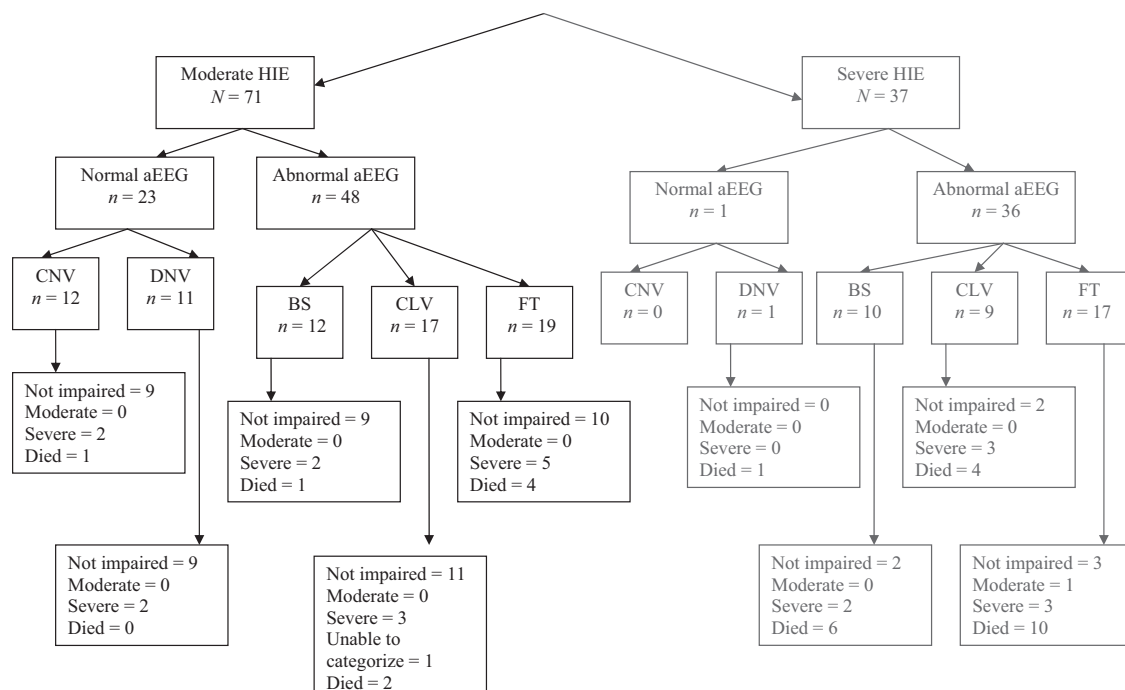
Moderate HIE
N = 71

Severe HIE
N = 37

Moderate HIE → Normal aEEG (n = 23), Abnormal aEEG (n = 48)

Normal aEEG n = 23 → CNV n = 12, DNV n = 11

CNV n = 12 →
Not impaired = 9
Moderate = 0
Severe = 2
Died = 1

DNV n = 11 →
Not impaired = 9
Moderate = 0
Severe = 2
Died = 0

Abnormal aEEG n = 48 → BS n = 12, CLV n = 17, FT n = 19

BS n = 12 →
Not impaired = 9
Moderate = 0
Severe = 2
Died = 1

CLV n = 17 →
Not impaired = 11
Moderate = 0
Severe = 3
Unable to categorize = 1
Died = 2

FT n = 19 →
Not impaired = 10
Moderate = 0
Severe = 5
Died = 4

Severe HIE → Normal aEEG (n = 1), Abnormal aEEG (n = 36)

Normal aEEG n = 1 → CNV n = 0, DNV n = 1

DNV n = 1 →
Not impaired = 0
Moderate = 0
Severe = 0
Died = 1

Abnormal aEEG n = 36 → BS n = 10, CLV n = 9, FT n = 17

BS n = 10 →
Not impaired = 2
Moderate = 0
Severe = 2
Died = 6

CLV n = 9 →
Not impaired = 2
Moderate = 0
Severe = 3
Died = 4

FT n = 17 →
Not impaired = 3
Moderate = 1
Severe = 3
Died = 10

FIGURE 1
Stage of encephalopathy, amplitude integrated EEG, and primary outcome..

TABLE 2 Relationship of Predictors to Primary Outcome

	Primary Outcome		Total	Sensitivity	Specificity	PPV	Negative Predictive Value
	No	Yes					
aEEG <9 h old[a]				0.89	0.33	0.56	0.75
Abnormal aEEG	37	47	84				
Normal aEEG	18	6	24				
Total	55	53	108				
aEEG <6 h old[b]				0.85	0.48	0.57	0.80
Abnormal aEEG	13	17	30				
Normal aEEG	12	3	15				
Total	25	20	45				
aEEG 6–9 h old				0.91	0.20	0.56	0.67
Abnormal aEEG	24	30	54				
Normal aEEG	6	3	9				
Total	30	33	63				
Moderate HIE				0.78	0.38	0.38	0.78
Abnormal aEEG	30	18	48				
Normal aEEG	18	5	23				
Total	48	23	71				
Severe HIE				0.97	0.00	0.81	0.00
Abnormal aEEG	7	29	36				
Normal aEEG	0	1	1				
Total	7	30	37				
Cooled infants[c]				1.00	0.30	0.51	1.00
Abnormal aEEG	23	24	47				
Normal aEEG	10	0	10				
Total	33	24	57				
Non-cooled infants				0.79	.36	0.62	0.57
Abnormal aEEG	14	23	37				
Normal aEEG	8	6	14				
Total	22	29	51				

[a] P = .01.
[b] P = .03.
[c] P < .01.

DISCUSSION

In this study we prospectively evaluated the predictive value of a 30-minute aEEG obtained at <9 hours of age among infants with moderate or severe HIE, with death or disability at 18 months of age. We found that the PPV of severe HIE was higher than that of an abnormal aEEG, but the PPV of moderate HIE was lower than that of an abnormal aEEG. An abnormal aEEG background was not independently associated with death or disability in the logistic regression analysis.

Our study differs from earlier aEEG studies regarding patient characteristics for study entry, time of acquiring aEEG recordings, monitors used, and definition and duration of neurologic or developmental outcome.[5–7] In 1999, al Naqeeb et al[10] evaluated amplitude in the aEEG among 40 infants with suspected birth asphyxia and noted that suppressed and moderately abnormal amplitude predicted poor outcome (defined as neuromotor abnormalities and/or optimality score < 20 and/or

TABLE 3 Logistic Regression for Primary Outcome

	P	Odds Ratio	95% Confidence Interval
Covariates			
Abnormal background	.15	2.33	0.73–7.37
Severe HIE	<.0001	9.20	3.19–26.55
Cooling	.02	0.33	0.13–0.83
Covariates with age at aEEG added			
Abnormal background	.17	2.28	0.71–7.31
Severe HIE	<.0001	9.12	3.15–26.37
Cooling	.02	0.32	0.12–0.83
aEEG within 6 h	.82	1.12	0.44–2.86

Max-rescaled $R^2 = 0.34$; $C = 0.79$.

general quotient < 85) of infants at 18 to 24 months of age. The aEEG recordings in the study were performed between 2 hours and 21 days, with a median age of 18 hours, whereas those in the current study were all performed at <9 hours of age.

The more recent studies in which aEEG has been evaluated at <6 hours and neurodevelopmental outcome include the retrospective study by van Rooij et al in 2005[21] in which 190 aEEG recordings were evaluated among 160 infants. These researchers did not evaluate the predictive ability of an early aEEG; they noted that the recovery of the background pattern within 24 hours was associated with a lower rate of disability (defined as death, cerebral palsy, or developmental quotient < 85) at 2 years. Shany et al [22] in 2006 reported on 39 infants with HIE; BS pattern at 3 hours and low voltage plus BS pattern at 6 hours were associated with poor outcome (developmental score < 79 or cerebral palsy). The authors speculate that background pattern was more sensitive than voltage measurements.

The CoolCap RCT[11] tested for selective head-cooling with mild systemic hypothermia after neonatal encephalopathy enrolled neonates if the aEEG at <6 hours was read by trained site investigators as moderately or severely abnormal amplitude using the al Naqeeb voltage criteria.[10] Infants with normal or mildly abnormal aEEG ($n = 16$) were

enrolled if there was a seizure pattern on the aEEG. The aEEG was obtained with the Lectromed monitor using a single channel with biparietal electrodes. At 18 months of age, the aEEG amplitude and presence of seizures were independently associated with unfavorable outcome (GMFCS level 3–5, Bayley MDI < 70, or bilateral cortical visual impairment).[23,24]

The predictive value of early and serial aEEG recordings on neurodevelopmental outcome of infants with HIE who were either cooled or maintained at normothermia has been published recently. In the study by Thoresen et al,[19] the PPV of an abnormal aEEG pattern at 3 to 6 hours of age was 84% for the normothermia group and 59% for infants who received hypothermia ($n = 23$ for whole body cooling and $n = 20$ for selective head cooling). In our study also, the PPV of an abnormal aEEG in predicting outcome was higher among noncooled infants (62%) than cooled infants (51%).

The results of our study reveal associations between the aEEG and outcome that are not as strong as those of previous studies of early aEEG and neurologic or developmental outcome. One reason is that our study did not include any infants with no/mild encephalopathy. Other explanations for differences among these studies in the predictive value of the aEEG are that the frequency response curves used in generating aEEG recordings differ among

manufacturers.[25] The location of the electrodes was central in our study and bi-parietal in the CoolCap and majority of the European studies. Recently it has been noted that the aEEG is influenced by electrode location and inter-electrode space. The amplitude may be higher in the C3–C4 than the P3–P4 location.[25] We excluded readings with significant artifacts that affect the entire tracing. It has been noted that artifacts occurred in 12% of 200 hours of recording time from a representative sample of 20 infants with neonatal encephalopathy.[26] In previous studies the rate of artifacts has not been documented among the aEEG recordings that were analyzed,[9,21,24] while other studies have performed recordings for several hours[8,21] or evaluated selected high quality sections from recordings.[10,11,18] Similar to some previous studies,[8,10,11] we did not have access to clinical information; information on cooling or the raw EEG during readings were also not available.

The strengths of our study are that we have a prospective sample of infants with moderate or severe HIE at <6 hours with aEEG recordings obtained < 9 hours of age. We standardized the neurologic examination for staging of HIE and the method of obtaining the aEEG. Excellent reliability of readings by 2 observers was achieved before the central reader evaluations. The 18-month outcome data acquisition was also standardized regarding duration of follow-up and definitions of outcome.

The weaknesses of this study are the limitations of the equipment used, including our inability to assess impedance during the initial part of the study, the brevity of the recordings, and inability to evaluate the raw EEG. We did not examine serial aEEG evaluations,[19,27,28] sleep-wake cycles,[29] or clinical events such as seizures or administration of anticonvulsants, seda-

tives, or analgesics during or before the aEEG recording. The influence of these medications on the aEEG remains unclear; the aEEG background may be dampened by overdose of phenobarbital[30] or midazolam administration.[31] Hypothermia leads to accumulation of levels of sedatives[32] that may affect the aEEG. As with all cooling studies, this is an unmasked study regarding cooling treatment.

CONCLUSIONS

We have demonstrated that the early aEEG did not add to the predictive value of death and disability among infants with moderate or severe HIE. Currently none of the NICHD NRN centers use the aEEG for eligibility criteria for clinical cooling or ongoing research trials. An objective marker of the presence of the severity of HIE should continue to be sought, and caution is advised if aEEG alone is used as a screening tool in selecting candidates for neuroprotective interventions.

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