Amplitude-Integrated Electroencephalography Improves the Identification of Infants with Encephalopathy for Therapeutic Hypothermia and Predicts Neurodevelopmental Outcomes at 2 Years of Age

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Objectives To examine whether using an amplitude-integrated electroencephalography (aEEG) severity pattern as an entry criterion for therapeutic hypothermia better selects infants with hypoxic-ischemic encephalopathy and to assess the time-to-normal trace for aEEG and magnetic resonance imaging (MRI) lesion load as 24-month outcome predictors.

Study design Forty-seven infants meeting Norwegian therapeutic hypothermia guidelines were enrolled prospectively. Eight-channel EEG/aEEG was recorded from 6 hours until after rewarming, and read after discharge. Neonatal MRI brain scans were scored for summated (range 0-11) regional lesion load. A poor outcome at 2 years was defined as death or a Bayley Scales of Infant-Toddler Development cognitive or motor composite score of <85 or severe hearing or visual loss.

Results Three severity groups were defined from the initial aEEG; continuous normal voltage (CNV; n = 15), discontinuous normal voltage (DNV; n = 18), and a severe aEEG voltage pattern (SEVP; n = 14). Any seizure occurrence was 7% CNV, 50% DNV, and 100% SEVP. Infants with SEVP with poor vs good outcome had a significantly longer median (IQR) time-to-normal trace: 58 hours (9-79) vs 18 hours (12-19) and higher MRI lesion load: 10 (3-10) vs 2 (1-5). A poor outcome was noted in 3 of 15 infants with CNV, 4 of 18 infants with DNV, and 8 of 14 infants with SEVP. Using multiple stepwise linear regression analyses including only infants with abnormal aEEG (DNV and SEVP), MRI lesion load significantly predicted cognitive and motor scores. For the SEVP group alone, time-to-normal trace was a stronger outcome predictor than MRI score. No variable predicted outcome in infants with CNV.

Conclusions Selection of infants with encephalopathy for therapeutic hypothermia after perinatal asphyxia may be improved by including only infants with an early moderate or severely depressed background aEEG trace. *(J Pediatr 2017;■■:■■-■■).*

Following large randomized trials of therapeutic hypothermia for full-term infants with moderate or severe hypoxic-ischemic encephalopathy (HIE),[1] in 2010 the International Liaison Committee on Resuscitation recommended that therapeutic hypothermia should become standard care.[2,3] Subsequently, there has been a significant reduction in HIE-related mortality and neurologic impairment in early childhood.[3-9]

In the first 3 large, randomized studies of therapeutic hypothermia,[5,8,10] 2 main selection criteria for receiving therapeutic hypothermia were similar and included a combination of early clinical and physiological criteria as well as neurologic criteria describing the level of consciousness and reflexes. The National Institute of Child Health and Development trial[8] used more comprehensive neurologic criteria[8] than the CoolCap (Brain-Cooling for the Treatment of Perinatal Hypoxic-Ischemic Encephalopathy)[10] and TOBY (TOtal Body hYpothermia: A Study

aEEG	Amplitude-integrated EEG
BSID-III	Bayley Scales of Infant and Toddler Development, 3rd edition
CNV	Continuous normal voltage
DNV	Discontinuous normal voltage
EEG	Electroencephalography(ic)
GMFCS	Gross motor functional classification score
HIE	Hypoxic-ischemic encephalopathy
MRI	Magnetic resonance imaging
SEVP	Severe aEEG voltage pattern
TTNT	Time-to-normal trace

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of Treatment for Perinatal Asphyxia)[5] trials. The CoolCap and TOBY trials used an additional third criterion based on the degree of electroencephalographic (EEG) voltage depression assessed from the amplitude-integrated EEG (aEEG) trace. It is not clear whether fulfillment of all 3 criteria (physiological, neurologic, and aEEG) should be used to identify infants for therapeutic hypothermia to indicate that the brain is affected by, or at risk of, encephalopathy after moderate or severe perinatal asphyxia. Correct identification of infants with encephalopathy is important because the effect of therapeutic hypothermia in infants without signs of moderate or severe encephalopathy has not been tested in clinical trials. It is not known whether cooling is beneficial, ineffective, or even harmful to infants who are unwell after birth but not encephalopathic or who present in poor condition at birth but have a normal aEEG.

To investigate the importance of using aEEG criteria to select infants for therapeutic hypothermia, we studied a cohort of infants treated with therapeutic hypothermia in whom early EEG and aEEG were recorded but not analyzed before discharge. The aims of this study were 2-fold: first, to examine whether using aEEG data better selects infants for therapeutic hypothermia than physiological and neurologic examination criteria alone and second, to examine whether ≥1 early biomarkers, for example, time to recovery to normal background EEG trace (time-to-normal trace [TTNT]), brain lesion load determined from early magnetic resonance imaging (MRI), or other biochemical measures correlate with 2-year cognitive and motor outcomes.

Methods

Full-term newborn infants with perinatal asphyxia treated with therapeutic hypothermia were enrolled prospectively from a single center (Ullevål Neonatal Intensive Care Unit, Oslo University Hospital, Oslo, Norway) from January 1, 2010 to December 31, 2011. Fifty-three neonates were treated with whole body cooling for 3 days as standard of care under the Norwegian National Guidelines for therapeutic hypothermia.[11] In 3 infants, consent to partake in the study was not obtained, and 3 others were excluded owing to congenital myotonia (n = 1), cooling for <72 hours (n = 1), and lack of a satisfactory aEEG recording (n = 1). Of the 47 infants included, 23 were outborn. The Norwegian therapeutic hypothermia guidelines are based on the TOBY registry protocol[4] and use physiological and neurologic selection criteria but not the aEEG criterion. EEG and aEEG were recorded as described elsewhere in this article and analyzed offline after patient discharge.

Physiological criteria for therapeutic hypothermia were gestational age ≥36 weeks and ≥1 of (a) Apgar score ≤5 at 10 minutes, (b) need for respiratory support 10 minutes after birth, (c) pH <7.00, or (d) base excess ≤-16 mmol/L in any blood sample within 60 minutes of birth. Neurologic criteria were reduced level of consciousness and ≥1 of 4 signs: (1) reduced muscle tone, (2) abnormal eye or tendon reflexes, (3) weak or absence of sucking reflex, or (4) clinical seizures. From these criteria, infants were classified into three severity grades, I, II, and III according to Sarnat and Sarnat.[12] Four infants were reclassified retrospectively (**Table I**) based on available information.

Ethics approval was obtained from the Regional Committee for Medical and Health Research, South-Eastern Norway and given by the Scientific Committee of Oslo University Hospital. Written parental consent was obtained for publishing clinical and outcome data.

Nineteen of the 24 patients born at our facility and 22 of 23 infants born elsewhere were intubated before transport and ventilated throughout the period of therapeutic hypothermia. The target range for $PaCO_2$ was set at 45-60 mm Hg during therapeutic hypothermia. Hypotension was treated if the mean blood pressure was <40 mm Hg for >20 minutes. All infants were sedated with morphine. Passive cooling was started as soon as perinatal asphyxia was suspected and active cooling was started in the cooling center after 155 minutes for infants born at our facility and 336 minutes for infants elsewhere. The mean time to reach target temperature was 176 vs 344 minutes, respectively.

The cooling system was a whole-body, servo-controlled, water-circulated jacket (CritiCool MTRE, Yavne, Israel) programmed to maintain the rectal temperature at 33.5°C for 72 hours.[13] Rewarming was carried out at a rate of ≤0.5°C per hour until the rectal temperature reached 37.0°C. To prevent hyperthermia after rewarming, the cooling jacket and rectal probe were retained for ≥4 hours after normothermia was achieved.[14]

The EEG/aEEG was monitored from the start of active cooling until after rewarming (78-84 hours) using an 8-channel EEG (NicoletOneTMversion 5.2, Carefusion, San Diego, California). Eight EEG disposable stick-on scalp electrodes (Blue Sensor BRS-50 K AmbuTM ECG electrode; Medicotest A/S, Ølstykke, Denmark) were used in a reduced montage following the International 10-20 system.[15] The expert undertaking the main off-line aEEG/EEG analyses[16] was not involved in clinical care. A single channel cross-brain aEEG trace (from central electrodes C3-P3) was derived and displayed at 6 cm/hour paper speed on a semilogarithmic scale for the assessment of aEEG background pattern classification. This single channel was also run as an EEG to describe episodes of EEG seizures down to a resolution of 10-second epochs. The 8-channel EEG recording was read for the whole recording period for all patients. The aEEG background voltage and pattern were assessed every hour from the start of recording to 12 hours after birth. From 12 to 24 hours, assessments were made in 6-hour intervals (at 6-12, 12-18, and 18-24 hours) followed by 12 hours (24-36, 26-48, 48-66, 66-72) until the start of rewarming when data from every second hour was recorded.

The classification of the first aEEG pattern observed after starting monitoring was the "most severe pattern" seen during the first 30 minutes of recording. The aEEG traces from these 30 minutes were classified for background voltage[17] and descriptive pattern.[18,19] The aEEGs were categorized as continuous normal voltage (CNV), discontinuous normal voltage (DNV), and a combined third group named severe aEEG voltage pattern (SEVP), including burst suppression, low voltage, or a flat trace. An electrographic seizure was defined as an

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Table I. Clinical and 2-year outcome data in CNV, DNV, and SEVP aEEG groups

	CNV (n = 15)	DNV (n = 18)	SEVP (n = 14)	CNV vs DNV	DNV vs SEVP
Gestational age (wk)	39.7 (38.0-41.1)	40.4 (38.9-41.1)	39.6 (38.6-39.9)	NS	NS
Birth weight (kg)	3.08 (2.72-3.74)	3.56 (3.15-3.89)	3.40 (3.15-3.67)	NS	NS
Resuscitation					
CPR during resuscitation	4	3	11	NS	.001
Adrenalin during resuscitation	1	0	8	NS	.001
Physiological criteria					
Apgar scores at 10 minutes	5 (5-6)	5 (4.3-6)	4 (1-6.3)	NS	NS
pH, first hour	6.89 (6.86-6.99)	6.99 (6.87-7.11)	6.91 (6.83-7.09)	NS	NS
Base excess, first hour (mmol/L)	17.9 (13.6-19.2)	17.6 (11.93-20.23)	15 (12.3-18.9)	NS	NS
Ventilation at 10 min	11	15	13	NS	NS
Neurologic criteria					
HIE grade I (mild)	2	1	1	NA	NA
HIE grade II (moderate)	12	14	6	NA	NA
HIE grade III (severe)	1	3	7	NA	NA
Clinical data					
Lactate ≤5 mmol/L*	8.1 (4.4-12.3)	4.1 (2.4-13.2)	8.38 (6.3-22.7)	NS	.037
Troponin T at 72 h	59 (39-77)	96 (54-144)	119 (58-469)	NS	NS
LDH at 72 h	756 (617-1118)	745 (570-1580)	740 (594-1547)	NS	NS
Duration of inotropy (h)	0 (0-33)	27 (0-76)	44 (11-79)	NS	NS
Short-term neurology					
TTNT (h) for SEVP group	NA	NA	18.5 (12-56)	NA	NA
Seizure prevalence	1/15 (7)	9/18 (50)	14/14 (100)	.05	.002
MRI lesion load 0-11	1 (0-2)	1 (1-2.8)	2.5 (1.3-9)	NS	.059
2-year outcomes					
Deaths	0	0	3	NS	.09
Neurodevelopmental evaluations (n)	15	17	9		
Cognitive composite score (n = 41)	95 (92.5-100)	100 (90-105)	90 (62.5-98.8)	NS	.034
Cognitive score 70-84	2	2	1		
Cognitive score <70	0	0	1		
Motor composite score (n = 41)	91 (85.5-95.5)	88 (83.5-97)	82 (50.5-89.5)	NS	.093
Motor score 70-84	2	4	3		
Motor score <70	0	0	2		
Seizures on AEDs	0	1	0	NA	NA
Cerebral palsy	0	1	2	NA	NA
Individual cognitive/motor scores for CP		a) 95/85	a) 70/46 b) 60/64		
Poor outcome (survivors)	3	4	5	NS	.02
Individual cognitive/motor score for poor outcome	a) 95/82 b) 80/94 c) 80/79	a) 90/76 b) 85/82 c) 80/79 d) 75/79	a) 100/82 b) 95/82 c) 85/79 d) 70/46 e) 60/64		
Poor outcome	3 (20)	4 (22)	8 (57)	NS	.02
Good outcome	12 (80)	14 (78)	6 (43)		

AED, antiepileptic drug; *CPR*, cardiopulmonary resuscitation; *LDH*, lactate dehydrogenase; *NA*, not applicable; *NS*, not significant.
Data are presented as the number (%) with each characteristic or the median (IQR).
*Duration in hours when lactate has decreased to ≤5 mmol/L.

evolving repetitive, stereotyped waveform with a definite onset, peak, and end, lasting for ≥10 seconds of raw EEG.[20,21] Status epilepticus was defined as a period of continous or repetitive ictal activity lasting 30 minutes or longer.[20]

Moderate (DNV) or severely depressed background voltage (burst suppression, low voltage, or flat trace) for ≥30 minutes within 6 hours (range 2-12) of birth, or nonconvulsive seizure activity on any background voltage pattern (including CNV) were criteria for therapeutic hypothermia in prior trials.[17,19] The time taken for the aEEG to recover from an SEVP pattern to at least a DNV pattern was defined as the TTNT. Antiepileptic drugs were used for clinical seizures. The antiepileptic drug protocol prescribed phenobarbital 20 mg/kg as first-line treatment, followed by a second dose, then midazolam and lidocaine. A clinical EEG was occasionally requested and read by clinical neurophysiologists. The continuous aEEG/EEG monitoring was first read after discharge by an external collaborator.

Cerebral MRI was performed on postnatal days 4-5 and 10-11.[22] The later scan was used for analysis, if available. Two infants who died were never scanned. Four infants (1 died) only had early scans. Two independent experts assessed the MRI scans for quality, anatomy, injury pattern, hemorrhage, and evidence of venous sinus thrombosis.[22] The Rutherford scoring system was used[23] with separate scores for basal ganglia and thalami, white matter, and cortex on a scale of increasing injury severity of 0-3, and for the posterior limb of the internal capsule on a scale of 0-2. A total injury score was calculated giving a range from 0 (no lesions) to 11 (maximum lesion load). We also applied a binary MRI score for poor and good outcome to our dataset developed for the nested TOBY study.[19]

Table II. Predictors of BSID-III scores

Models	B	Std Error	t	Sig
Cognitive score, dependent variable for combined DNV and SEVP group, survivors (R = 0.828, n = 29)*				
Constant	104.262	2.106	49.514	.000
MRI (0-11)	–3.375	0.475	–7.104	.000
Excluded variables, none to enter with significance of <.100				
Motor score, dependent variable for combined DNV and SEVP group, survivors (R = 0. 649, n = 29)*				
Constant	96.932	3.048	31.798	.000
MRI (0-11)	–3.154	0.688	–4.593	.000
Excluded variables, none to enter with significance of <.100				
Cognitive score, dependent variable, SEVP group only, survivors (R = 0.939, n = 11)*				
Constant	106.697	2.261	47.183	.000
Time to normal trace (h)	–0.641	.074	–8.609	.000
Excluded variables, none to enter with significance of <.100				
Motor score, dependent variable, SEVP group only, survivors (R = 0.796, n = 11)*				
Constant	101.975	5.694	17.908	.000
Time to normal trace (h)	–0.712	0.163	–4.36	.001
Excluded variables, none to enter with significance of <.100				

*These regressions were also run including the 3 that died in the SEVP group, allocating them a numeric value 1 point lower than the subjects testable. This did not change the order by which the variables entered the regression but strengthened the model.

Serial plasma glucose, lactate (the duration in hours after birth before the plasma lactate decreased to ≤5 mmol/L), lactate dehydrogenase at 72 hours,[24] serum cardiac troponin T, cardiopulmonary resuscitation, and adrenalin during resuscitation and seizure variables were used in the exploratory analysis.

At 2 years, a clinical neuropsychologist administered the Bayley Scales of Infant and Toddler Development, 3rd edition (BSID-III)[25] and a pediatric neurologist performed a neurologic examination[26]; neither was involved in the neonatal care and both were blinded to the MRI and EEG results.

Eight parents did not speak a Scandinavian language and no interpreter was used. Because this might affect the language scores, only cognitive and motor data were included in the final analysis.[27] A gross motor functional classification score (GMFCS) was assigned for those children with cerebral palsy. A GMFCS level of 3-5 was defined as a poor motor outcome and <3 as a good outcome. Cognitive and motor composite scores of ≥85 were considered normal.[28,29] Children with cognitive or motor scores of 70-84 were considered to have moderate delays. Severe delay was defined as a cognitive or motor score of <70. For the binary analysis, a good outcome was defined as cognitive and motor scores of ≥85 without vision or hearing impairment. A poor outcome was defined as death or ≥1 of cognitive or motor scores of <85, a GMFCS of 3-5, or severe vision or hearing impairment. In some analyses, infants who died were assigned a value 1 unit lower than the lowest a survivor could get on the BSID-III (55 for cognition scale score), for example a 54. The corresponding lowest value for BSID-III motor score is 45 for a survivor, so 44 was used for the infant with MRI who died.

Statistical analyses were performed using SPSS 23 (SPSS, Chicago, Illinois). Demographic and clinical data were summarized at baseline as the median (IQR). Two group comparisons were undertaken with either the Mann-Whitney, Wilcoxon, or Kolmogorov-Smirnov tests. Tables of 2 × 2 were analyzed with the 'N-1' χ^2 test.[30] $P < .05$ was considered significant.

Multiple stepwise linear regression analyses were performed to explore the ability of early biomarkers to predict BSID-III cognitive or motor outcomes at 2 years. Independent variables were birth weight, number of antiepileptic drugs used, time (hours) for plasma lactate to decrease to ≤5 mmol/L, number of hours with inotropic support, lactate dehydrogenase levels at 72 hours, MRI lesion load, and TTNT (only applicable for the SEVP group) (**Table II**). The distributions of the residuals were always inspected for outliers, which were not found. Treatment criteria for therapeutic hypothermia (pH, BE, Apgar score, need for ventilator support at 10 minutes after birth, HIE grading, and aEEG pattern at 6 hours) were not used in the regression analyses. Infants who never regained a normal trace after rewarming were allocated 78 hours in the regression analysis.

Results

Table I shows the demographic, baseline, clinical, and outcome variables for the 47 included infants, divided into 3 severity groups based on their initial aEEG pattern. Fifteen infants had CNV (normal), 18 had DNV (moderately abnormal), and 14 had SEVP (severely abnormal) aEEG patterns.[17,18] The median start time of aEEG monitoring for the whole cohort was 6 hours. The aEEG was applied earlier in the CNV (median 4 hours) than the DNV (7 hours) and SEVP (6 hours) groups, because more CNV were born at our facility (born at our facility/born elsewhere ratio 11/4) compared with DNV (7/11) and SEVP (5/9).

Because EEG abnormalities were required for enrollment into the CoolCap and TOBY trials, the 15 infants with CNV

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would not have met the entry criteria for cooling in those trials.[5,10] Using the HIE categories from the TOBY trial,[5] 11 of the 47 infants included in the study had severe HIE (HIE grade III) of whom 8 had a poor outcome and 32 had moderate HIE (HIE grade II) of whom 7 had a poor outcome and 4 had mild (HIE grade I), all with a good outcome.

There were no differences between the CNV, DNV, or SEVP groups in the physiological criteria, except that significantly more infants with SEVP received cardiopulmonary resuscitation, including adrenalin, compared with infants with CNV and infants with DNV (**Table I**). Clinical variables assumed to be related to organ failure rather than encephalopathy were not different between infants with CNV and infants with DNV, except that there were no infants with a supplemental oxygen requirement in the CNV group and the serum cardiac troponin T was higher in the SEVP than in the DNV group.

The occurrence of any seizures (both clinical and EEG) was significantly lower in the CNV than the DNV group (**Table I**). Compared with the other 2 aEEG groups, the SEVP group showed more signs of abnormal brain function with a longer median TTNT, a greater proportion of infants with any seizures compared with DNV, and greater MRI lesion load (**Table I**).

Forty-one infants had neurodevelopmental assessments at a median age of 24[21,22,24-27,31] months. Their neurodevelopmental outcomes are presented in **Table I**. Overall, 15 infants had a poor outcome, including 3 who died. Three infants developed cerebral palsy, 2 with a quadriplegic pattern (GMFCS 4 or 5) and both with BSID-III scores of <70. One of these 2 infants needed bilateral hearing aids. In the entire cohort, no infants were visually impaired. One infant (DNV group) had a hemiplegic pattern (GMFCS 1) with BSID-III scores of >84 and was classified as having a good outcome. Only 1 child, without cerebral palsy but with BSID-III scores of <85 (DNV group), had seizures requiring regular anti-epileptic drugs at 2 years of age. Outcome details for individual surviving children with poor outcomes in the 3 aEEG groups are given in **Table I**.

Table II shows the results of the stepwise linear regression analyses for potential predictors of 2-year BSID-III cognitive and motor scores. MRI lesion load (range 0-11) showed a strong negative association with cognitive scores ($P = .001$); for each point increase in MRI lesion load score, the cognitive score decreased by 3.38 points. TTNT can only be analyzed in infants who start with a poor trace (SEVP) and TTNT showed a strong negative association with both cognitive and motor scores in this group. The BSID-III motor score decreased by 6.41 points for every 10 hours of increased duration in TTNT in the SEVP group. TTNT was significantly longer in infants with SEVP with a poor outcome (58.5 hours; IQR 9-79) compared with infants with a good outcome (18 hours; IQR 12-19; $P = .03$). There were no predictors of cognitive or motor outcomes in the CNV group.

The correlation between the BSID-III cognitive score at 2 years of age and the MRI lesion load score for infants who had a DNV or SEVP aEEG pattern 6 hours after birth is displayed in the **Figure**. There was a significant linear relationship between the cognitive and MRI scores for the infants who had either a DNV or SEVP aEEG pattern at 6 hours after birth; higher MRI lesion scores were associated with lower cognitive scores (**Figure**, A $r^2 = 0.35$ for infants with DNV and $r^2 = 0.72$ for infants with SEVP). The **Figure**, B shows the corresponding data for the CNV group only, showing no relationship between cognition score at 2 years and the MRI score ($r^2 = .06$). The **Figure**, C shows the relationship between TTNT and BSID-III motor score in the SEVP group: the longer the TTNT, the lower the BSID-III motor score.

In the TOBY nested substudy,[23] 131 of 325 infants undergoing therapeutic hypothermia or standard care (normothermia) had MRI scans examined and a binary MRI scoring system predicting poor outcome at 18 months was proposed if there was ≥1 of the following 4 regional MRI severity scores: basal ganglia and thalami of 2, basal ganglia and thalami of 3, posterior limb of the internal capsule of 2, or white matter of 3. When applied to the group with aEEG abnormalities in our study, the nested TOBY score only predicted 4 of 8 infants correctly to have a poor outcome and 14 of 20 infants to have a good outcome. Thus, the positive predictive value for poor outcome was 50% (4 of 8) and the negative predictive value for poor outcome was 70% (14 of 20), with a specificity of 78% (4 of 18) and a sensitivity of 40% (4 of 10).

Twenty-four of the 47 infants had both clinical or EEG seizures between birth and the end of rewarming; 1 was in the CNV group, 9 in the DNV group, and 14 in the SEVP group (**Table I**). All infants with clinical seizures received anti-epileptic medication. Of the 14 with clinical seizures only, 11 occurred before aEEG monitoring started and in the remaining 3 the seizures were not verified on offline EEG. Ten infants (7 with a clinical correlate) had EEG seizures diagnosed offline, which were classified as single, repetitive, or status epilepticus. Of the 6 infants with status epilepticus, 3 had a good outcome (1 from the DNV group and 2 from the SEVP group) and 3 had a poor outcome (all from the SEVP group). The median duration (full range) was 19 hours (12-20) for the good and 75 hours (48-80) for the poor outcomes groups; the median duration (full range) was 5 hours (0.6-7) and 6 hours (6-28 hours), respectively, regarding outcome. The presence of seizures, when entered into the stepwise regression, did not improve outcome prediction.

Discussion

The first 3 large, randomized, controlled trials of therapeutic hypothermia[5,8,10] included infants with moderate or severe, but not mild, encephalopathy. These trials used similar entry criteria except that the presence of a depressed aEEG as a marker of encephalopathy was not used in the National Institute of Child Health and Development trial as an entry criterion. Presently, centers outside the United States, particularly those who initiate therapeutic hypothermia without recording an aEEG, do not use the strict neurologic criteria developed for the National Institute of Child Health and Development cooling protocol, but apply the less strict neurologic criteria developed for the CoolCap and TOBY trials. Our findings suggest that this practice is likely to over-recruit infants for therapeutic

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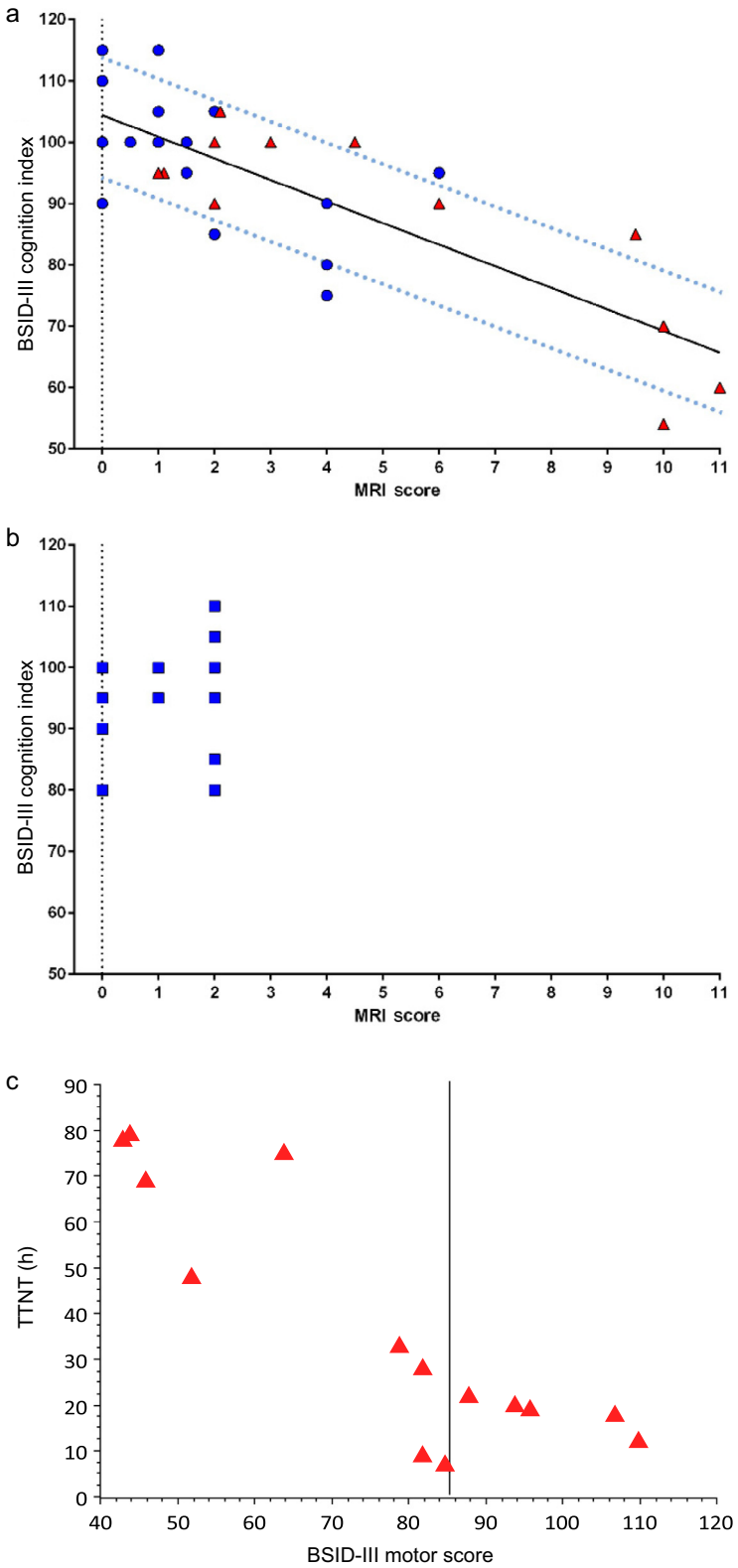

Figure. **A,** BSID-III cognitive score versus MRI lesion load for infants with aEEG abnormalities; DNV (circles) and SEVP (triangles) for 27 of the 32 infants (2 died without MRI, 3 missing BSID-III). The figure shows the line of regression ± 1 SD. **B,** BSID-III cognitive score versus MRI lesion load for infants with CNV aEEG findings. There was no relation between cognition and MRI score. **C,** BSID-III motor score versus TTNT for infants with SEVP.

FLA 5.4.0 DTD ■ YMPD9150_proof ■ May 23, 2017

hypothermia. The 15 infants in this study with CNV met the Norwegian guidelines for therapeutic hypothermia but would not have met the CoolCap/TOBY aEEG criteria. This means that 1 in 3 infants in our cohort did not have an abnormal aEEG that would have qualified for therapeutic hypothermia in the CoolCap/TOBY trials. We found no differences in the physiological criteria between the CNV and DNV groups. However, only the DNV and SEVP groups, not the CNV group, had clinical findings associated with measures of abnormal brain function: seizure burden, increased MRI lesion load, and prolonged TTNT (for SEVP only).

Previously, we published comparable aEEG data from the United Kingdom.[31] In the UK cohort, 43 infants were treated with therapeutic hypothermia and 31 with normothermia using the CoolCap/TOBY protocol, including the aEEG entry criterion. Experienced investigators, who introduced the aEEG prediction method to neonatology, read the traces retrospectively.[18,19] As in our current study, some of the infants from the UK study (8/43; 18%) were cooled despite having a normal aEEG pattern at entry on retrospective analysis. The incidence of poor outcomes differs between the UK study and our current Norwegian study; in the UK cohort, 41% of infants had a poor outcome (including 23% mortality) and, in our cohort, 30% of the infants had a poor outcome (6.3% mortality). This difference is best explained by different distributions of aEEG severity at entry; in the UK cohort, 37% of the infants had the less severe CNV or DNV patterns compared with 70% of the infants in our study. In the SEVP group (burst suppression, low voltage, and flat traces), however, the relative morbidity and mortality were very similar; there were 27 such infants in the UK study with 10 survivors with good outcomes, 7 survivors with poor outcomes, and 10 deaths. In the current study, 14 infants had SEVP with 6 survivors with good outcomes, 5 survivors with poor outcomes, and 3 deaths. We speculate that uniformly evaluating the aEEG pattern at entry for therapeutic hypothermia would allow more accurate comparisons of outcomes between different studies because the baseline findings of normal, moderate, or severe patterns could be identified.

Our second aim was to examine whether data from the aEEG readings of TTNT correlated with outcome at 2 years assessed using the BSID-III. We used cognitive and motor scores as separate outcome markers in the 32 infants with an abnormal aEEG. Using multiple stepwise linear regressions for these patients, MRI lesion load was the only factor that correlated significantly with the cognitive and motor scores (**Table II**). For the SEVP group, TTNT was the best predictor for cognitive and motor scores. TTNT has also the advantage of being determined from an early bedside examination giving robust information during the therapeutic hypothermia period.

When running the same multiple stepwise regressions on the CNV group only, no variable predicted outcome. Both aEEG and EEG are useful tools for assessing seizures during therapeutic hypothermia. It is documented that the incidence of neonatal seizures has not changed in the cooling era, but overall seizure burden has been reduced. Neonatal seizures are often nonconvulsive.[32,33] Using a fetal sheep model of neonatal HIE, Gunn et al[34] have suggested that seizures occurring during therapeutic hypothermia do not injure the brain to the same extent as seizures during normothermia. This, in addition to our small and mild cohort, may be the reason why we did not find a different degree of injury in those who had evidence of any seizures compared with those who did not. However, if TTNT or MRI were not in the regression analysis, the duration of status epilepticus was the strongest outcome predictor in the SEVP group.

The predictive value for outcome of cerebral MRI is thought to not be affected by therapeutic hypothermia.[35] The positive predictive value for poor outcome in a nested substudy of the TOBY trial was 76% and 74% in the cooled and noncooled groups, respectively.[23] In our smaller cohort, however, the TOBY scoring system did not predict binary poor outcome, the positive predictive value being 50%. No other prospective study has tested and published the predictive value of the nested TOBY Rutherford scoring system. One of the reasons for the discrepancy noted in our study may be that the overall injury was milder in our study, even after exclusion of the 15 infants with a normal aEEG at entry. Other scoring systems of MRI severity within the first 2 weeks after birth have predicted outcome at 1-3 years in both cooled and noncooled infants.[23,36-38] However, as with the TOBY scoring system used here, these other protocols need to be verified in clinical cohorts unrelated to the infants in whom the scores were developed.

There are limitations to this small cohort study, particularly that there were relatively few infants with severe injury. Clinical neurology scoring at entry grading the level of encephalopathy into mild, moderate, or severe categories showed that the 4 infants with mild HIE who were entered into the study all had a normal outcome. We did not use the language domain of the BSID-III examination because several children came from families that did not speak Norwegian. This approach is similar to comparable outcome studies.[29,39]

In this cohort of infants treated with therapeutic hypothermia, early MRI pathology correlated well with 2-year cognitive outcome and, for the SEVP group, the time it took for the aEEG to regain a normal background voltage (TTNT) correlated with motor outcome. Additionally, previously reported MRI criteria did not predict poor outcome, which suggests that MRI scores developed in 1 study may not directly translate to other infant cohorts.

In the first hypothermia trials, all infants were warmed to 37°C within 30 minutes of birth and cooling was first started by 4-5 hours of age. Currently in many centers, infants are resuscitated with room air, passive cooling is started early, and hypocapnia, hypoglycemia, and stress are minimized. The combination of these factors, not only therapeutic hypothermia, may contribute to reduced rates of morbidity and mortality.

Our data are a reminder that infants who are considered for therapeutic hypothermia should show signs of encephalopathy. There may be possible harm from subjecting a newborn who would not have qualified for therapeutic hypothermia in the clinical trials to 3 days of intensive care and potentially risky procedures. Because the effects of cooling in the absence of overt encephalopathy are not known, the results of our study suggest

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that aEEG depression may be an important selection requirement in addition to the physiological and neurologic examination criteria to prevent overtreatment and ensure that only those infants who are suitable for therapeutic hypothermia are cooled. ■

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