ORIGINAL ARTICLE

Association of cerebral activity with MRI scans in infants with neonatal encephalopathy undergoing therapeutic hypothermia

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Abstract

We aimed to correlate amplitude-integrated EEG (aEEG) in neonatal hypoxic ischemic encephalopathy (HIE) with early magnetic resonance imaging (MRI). In this retrospective study, 32 neonates over 35 weeks' gestation with moderate/severe HIE who were treated with hypothermia were included. Early MRI scans and daily aEEG background were categorized to mild/normal, moderate, and severely abnormal. Time to sleep cycling was noted on aEEG. Mantel-Haenszel test for trends was used to explore associations between aEEG and MRI and outcome. LOESS regression was used for exploring the association of cycling with MRI scores. MRI was normal/mildly abnormal in 20 (63%) infants; in 9 (28%), moderately abnormal; and in 3 (9%), severely abnormal. Twenty-seven (84%) infants s urvived. MRI severity score was significantly associated with aEEG background score on the third and fourth days of life ($p < 0.01$). An increase in the MRI severity score was noted if sleep cycling appeared after the fifth day of life.

Conclusions: Depressed aEEG at the third and fourth days of life and appearance of cycling beyond the fifth day of life are associated with cerebral MRI abnormalities and may be associated with increased risk of abnormal outcome.

What is known:
• *Since therapeutic hypothermia has been shown to change long-term outcome, amplitude-integrated EEG in infants with hypoxic ischemic neonatal encephalopathy soon after birth have a limited predictive power for long-term outcome in treated infants.*
• *Brain MRI after therapeutic hypothermia in the above infants has a significant predictive value for long-term outcome*

What is new:
• *Background amplitude-integrated EEG activity depression at the age of 3 and 4 days and delay of appearance of cycling activity are associated with worse MRI scores and may be predictive of worse long-term outcome*

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Abbreviations

aEEG Amplitude-integrated electroencephalography
CP   Cerebral palsy
HIE   Hypoxic ischemic encephalopathy
MRI   Magnetic resonance imaging
NICU Neonatal intensive care unit

Background

Moderate-to-severe neonatal hypoxic ischemic encephalopathy (HIE) has an incidence of 1.2/1000 live births in our medical center (local data base). This incidence is similar to that reported in the last decade of the last century [1, 2] but higher than recent data from the last decade reporting 0.4/1000 [3, 4].

Due to the high risk of adverse neurodevelopmental outcome of infants with HIE, the predictive values of amplitude-integrated EEG (aEEG) [5–7], conventional EEG [8, 9], evoked potentials [10, 11], magnetic resonance imaging (MRI) [10–14], and physical examination [7] have been assessed throughout the years. With the advent of therapeutic hypothermia for HIE, prediction of prognosis by early markers faces new challenges [15–17].

aEEG is a continuous limited channel (mostly one to two channels) cerebral function monitoring technique that was adapted for the intensive care environment [18, 19] and is increasingly used in neonatal intensive care units (NICUs) worldwide for the purpose of assessing cerebral activity and seizures in high-risk neonates. Before therapeutic hypothermia became standard of care, different studies demonstrated that aEEG background patterns during the first hours after birth [5–7] as well as later appearing aEEG indices such as cycling [20] and normalization of background pattern [21] were associated with outcome. However, in the most recently published studies, aEEG in the first hours after birth in infants treated with therapeutic hypothermia for HIE has a lower predictive value [15, 16, 22, 23].

Cerebral MRI scans of infants who have suffered from HIE reveal different patterns of injury (deep gray matter (i.e., basal ganglia) and watershed area injury) depending on the time, severity, and duration of insult. Deep gray matter injury with various degree of accompanying white matter injury has been linked to peripartum sentinel events and the severity of imaging findings has been found to be correlated with outcome [24]. Watershed area injury has been linked to brief episode of cerebral hypoperfusion, not severe enough to cause frank infarction or widespread necrosis [25], and its severity is correlated to gestational age and cognitive outcome [26]. Highlighted areas of ischemic injury identified in diffusion-weighted imaging (DWI) performed early after birth have also been shown by to be associated with outcome [14] and are even more accurate if combined with spectroscopy measures of lactate to N-acetyl aspartate ratio (> 0.25) [13, 27]. Also,

MRI injury scores in infants treated with therapeutic hypothermia for HIE correlated with long-term neurodevelopmental outcome [28–30].

We hypothesize that aEEG soon after completion of therapeutic hypothermia is correlated to findings in early brain MRI in infants with neonatal encephalopathy.

Our primary objective was to compare an aEEG severity score at specific time periods after birth with an early MRI severity score. Secondary objectives were to assess whether there is a relationship between the time of normalization of cerebral function and brain MRI findings and compare MRI and aEEG severity scores with long-term outcome.

Patients and methods

This was a retrospective cohort study.

**Study population** Neonates born between August 2008 and September 2014 with neonatal HIE.

Inclusion criteria Infants born after 35 weeks of gestation, diagnosed with moderate-to-severe HIE, that were monitored with aEEG for the first 4 days of life, treated with hypothermia, and had an early brain MRI (before hospital discharge).

Exclusion criteria Infants diagnosed with cerebral malformations/hemorrhage/infection, inborn error of metabolism, genetic disorder, and other conditions that could have led partially or entirely to encephalopathy.

Hypoxic ischemic encephalopathy For the purpose of the study, HIE was determined if:

1. A sentinel event occurred around birth (e.g., prolapsed of cord, abruption of the placenta, uterus rupture) or a pathologic fetal monitoring with either a 5-min Apgar score < 5, cord pH < 7.0, cord blood base excess > 15 mmol/L, or a prolonged resuscitation (with positive pressure ventilation) took place after birth
2. Encephalopathy was determined either clinically or by depressed brain activity on aEEG or by aEEG seizures. (The presence of either elevated troponin or elevated liver function tests or elevated creatinine or presence of blood in urine was sought to confirm that a hypoxic ischemic event had taken place)

   a. Clinical encephalopathy was defined as either depressed consciousness, generalized hypotonia, or depressed neonatal reflexes according to the Sarnat classification [31]

Fig. 1 Classification of aEEG background: **a** continuous with sleep cycling, **b** discontinuous, **c** burst suppression, **d** isoelectric
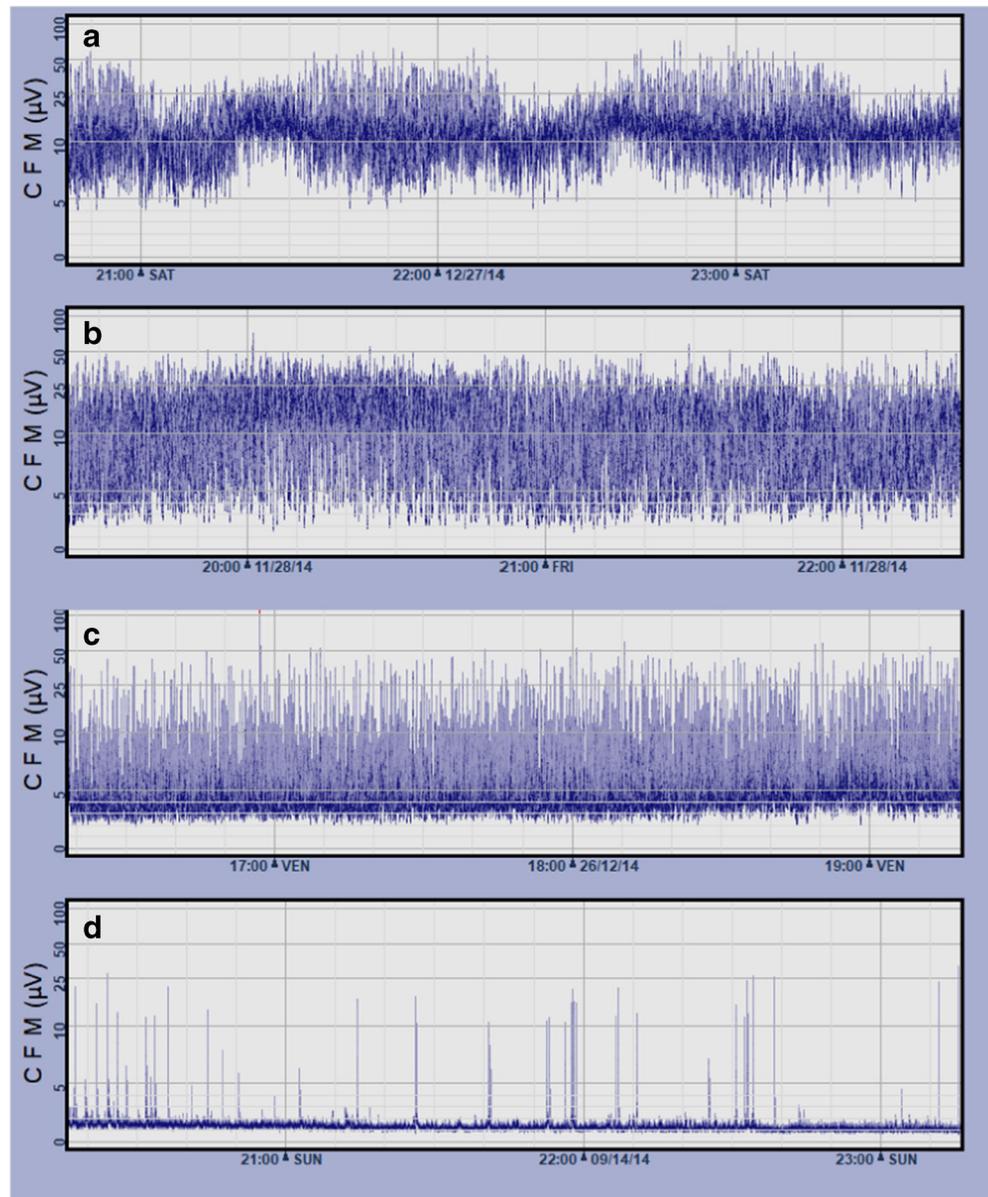

Data retrieval Neonates participating in the study were identified from the local computerized NICU register of all aEEG monitored infants. Neonates at risk of moderate or severe HIE after birth are routinely screened and monitored with aEEG as part of our local NICU protocol and treated with hypothermia for 72 h if the above criteria for HIE are met. After institution of normothermia, aEEG is recorded for a further 24 h and if possible until sleep cycling appears. MRI scans are performed according to availability of the scanner as soon as infants are stable for transport normothermic. Data from medical files were retrieved. MRI scans and aEEG recording were reassessed and the assessors were blinded to the degree of HIE and to the findings in each modality (i.e., MRI/aEEG).

Medical records The following data were retrieved from the medical records:

– Events around delivery, Apgar scores, cord pH, sentinel events
– Resuscitation data
– Need for respiratory support and use of antiepileptic drugs
– Survival at discharge
– Survival postdischarge
– Long-term outcome
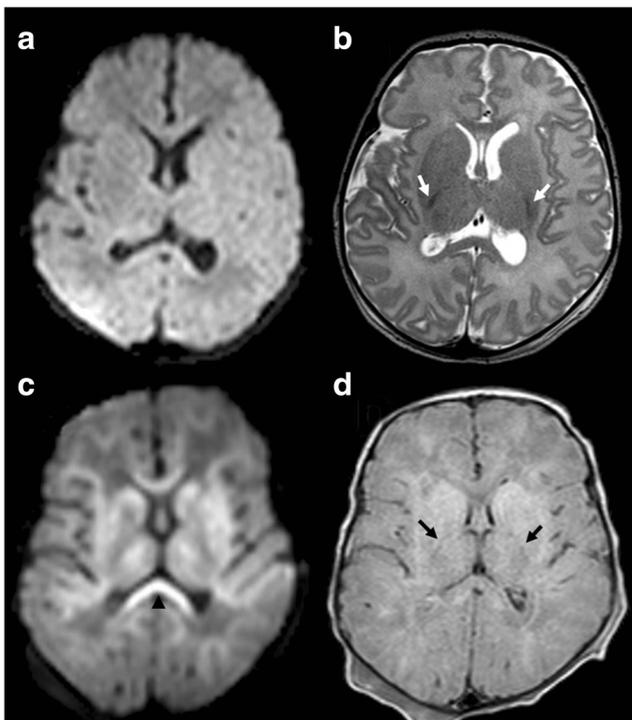
Fig. 2 MRI scans from two infants in the study: Upper panels (**a** and **b**): 42 weeks' gestation infant born through thick meconium, resuscitated after birth, Apgar score 3, 5, and 8 at 1, 5, and 10 min, respectively. Cord pH 6.8. Suffered from moderate encephalopathy. Sleep cycling on aEEG appeared on the fourth day of life. MRI scan was done at the age of 7 days. **a** Diffusion-weighted axial image with no abnormalities. **b** T1-weighted image, note the posterior limb of the internal capsule (white arrows). Overall score of this infant was 0 (low MRI severity score). Lower panels (**b** and **c**): 38 weeks' gestation infant born by emergency Cesarean section due to abruption of the placenta. Resuscitated after birth, Apgar scores 1, 1, and 1 at 1, 5, and 10 min, respectively. Cord pH 6.98. Suffered from severe encephalopathy. Sleep cycling never appeared. MRI scan was done at the age of 5 days. **c** Diffusion-weighted axial image: note the bilateral restriction in the thalamus, basal ganglia, temporal white matter, and corpus callosum (black arrowhead). **d** T2-weighted image, note the reversed signal intensity in the posterior limb of the internal capsule (black arrows), abnormal signal intensity of the white matter, the thinning of the cortical mantel, and lack of normal sulci. Overall score of this infant was 9 (high MRI severity score). The infant died at the age of 7 days due to extensive brain damage and multiorgan failure.

Long-term outcome Neurodevelopmental outcome and survival after discharge were retrieved from the hospital admission-transfer-discharge system connected in real time to the national database via the ministry of interior. The system records all deaths, hospitalizations, outpatient visits, medications, and problems lists. Outcome was categorized as unfavorable if death or cerebral palsy (CP) or mental retardation was noted in the record, otherwise it was categorized as favorable.

Amplitude-integrated EEG One channel aEEG recordings were acquired with the CFM 6000 (Olympic/Natus) [18, 19]. aEEG recordings were evaluated by IM (neonatologist with over 15 years of neuromonitoring experience) according to the

dominant pattern present in the following time intervals: first 6 h of life, 6–12 h, 12–24 h, every 24 h until the end of the recording or up to 120 h. Background activity during each time interval was assessed according to Hellstrom-Westas et al. classification [32] as: continuous (Fig. 1a), discontinuous (Fig. 1b), burst suppression (Fig. 1c), low voltage or isoelectric (Fig. 1d). Initiation of cycling on any background in the aEEG was noted (Fig. 1a) as well as presence or absence of seizures.

aEEG background was categorized into two or three categories as follows:

Two categories:

1. Normal/near normal: continuous or discontinuous background
2. Abnormal: burst suppression, low voltage or isoelectric background

Three categories:

1. Normal/near normal: continuous or discontinuous background
2. At risk/moderately abnormal: burst suppression background
3. Severely abnormal: low voltage or isoelectric background

Cohen's kappa statistics comparing IM and ES (neonatologist with more than 20 years of experience with aEEG) was performed using random aEEG time interval segments, one for each infant. The agreement was in the high range: 0.859 for the two category scores and 0.709 for the three category scores.

Early life MRI MRI performed in infants with HIE routinely includes at least the following sequences: 3D-T1W, axial T2W, BOLD or SWI, and DWI/ADC. The first MRI of the infant was scored according to a modified grading from Rutherford et al. [28] (Fig. 2 and Table 1) by IS who is a board-certified neuroradiologist with more than 15 years of experience in neonatal brain imaging. The scoring is based on grading abnormalities in the basal ganglia and thalami, posterior limb of the internal capsule, corpus callosum, white and gray matter, brain stem, and cerebellum. Each area was scored according to Table 1 in the above four MRI sequences and the highest (worst) score was generated for each area. MRI findings were categorized as follows:

Normal or mildly abnormal (0):	Total score < 4, no area scoring 2 or above allowed
Moderate (1):	Total score 4–8, no area scoring 3
Severe (2):	Total score > 8

Table 1 Modified Rutherford score

Score	0	1	2	3
White matter	Normal	Abnormal signal in periventricular white matter	Abnormal signal extending to subcortical regions or focal punctate lesions/infarcts	Severe widespread abnormal signal, overt infarct or hemorrhage
Gray matter	Normal	Abnormal signal intensity, including highlighting in no more than 2 regions	Abnormal signal intensity, including highlighting in 3 regions	Abnormal signal intensity, including highlighting in more than 3 regions
Basal ganglia	Normal	Focal abnormal signal intensity	Multi-focal abnormal signal intensity	Widespread abnormal signal intensity
Posterior limb of internal capsule (PLIC)	Normal	Reduced/asymmetrical signal intensity	Reversed or abnormal signal intensity bilaterally	Abnormal signal intensity extending outside the PLIC
Corpus callosum	Normal	Focal signal abnormality in no more than two sites	Extensive signal abnormalities	
Cerebellum	Normal	Focal signal abnormality in no more than two sites	Multifocal signal abnormalities in no more than two sites	Severe widespread abnormal signal, overt infarct or hemorrhage
Brain stem	Normal	Abnormal signal restricted to the pyramids	Loss of anatomical details, excessive differentiation between anterior and posterior pons, mild/focal areas of abnormality, mild asymmetries	Widespread abnormal signal intensity, abnormal myelination, marked asymmetries

Data analysis and statistical considerations

Clinical data is presented as mean/median/percentage with standard deviation/range as appropriate.

Each aEEG time interval was assessed separately for association of the degree of cerebral activity depression with the MRI score categories using Mantel-Haenszel test for trends. As seven-time intervals were assessed, we used the Bonferroni correction for multiple comparisons and significance was set to $p < 0.007$. Associations of long-term outcome with MRI and aEEG were similarly assessed.

In order to explore the association between the time-to-cycling appearance and the MRI severity score, a non-parametric LOESS regression was used. In two infants, no cycling developed during aEEG recording and they were omitted from this analysis.

Results

During the study period, 50 infants that fulfilled the inclusion criteria for moderate-to-severe neonatal encephalopathy were treated with hypothermia. In 18 (36%), an MRI scan was not performed before discharge due to unavailability ($n = 15$) or death ($n = 3$). In the final analysis, 32 infants were included. Cohort characteristics are presented in Table 2. Twenty-three (72%) of the infants were male. Seven (22%) infants were delivered vaginally, 7 (22%) underwent vacuum extraction, and 18 (56%) were delivered via Cesarean section. In 17 (53%), a sentinel event was reported (i.e., placental abruption, prolapse of cord, uterine rupture etc.). Resuscitation at birth included intubation in 24 (75%) of the infants and 19 (59%) were still intubated at the end of the resuscitation. Nine (28%) infants needed chest compressions during the immediate resuscitation. Median Apgar score was 3, 6, and 7 at 1, 5, and 10 min, respectively. Median age at the initiation of therapeutic hypothermia was 6 h (interquartile range 2–6; in 4 infants, hypothermia was initiated after 6 h of age due to late diagnosis). Seizure activity was confirmed with aEEG in 25 (78%) of the infants though 29 (91%) were treated at least once with anti-epileptic drugs.

All infants were monitored with aEEG. Thirty (94%) developed cycling activity during the recording (median age 2.44 days, IQR 1.53–3.96) (Fig. 3). The distribution of aEEG patterns during the different time intervals after birth is presented in Table 3.

MRI scans were performed at a median age of 7 (range 5–20) days. In twenty (63%), infants the MRI severity score was graded as 0; in 9, (28%) it was graded as 1; and in 3 (9%), it was graded as 2 (Table 4). Five (16%) infants died: one infant at 7 days of age after withdrawal of care, 3 in infancy (1, 3, and 4 years of age) due to causes related to HIE (CP with mental retardation), and 1 died to due to systemic disease (hypophosphatasia) at the age of

Table 2 Infants characteristics

Demographic data	
Male	23 (72%)
Delivery room data	
Delivery mode, vaginal/vacuum/CS, *n* (%)	7 (22%), 7 (22%), 18 (56%)
Sentinel event, *n* (%)	17 (53%)
Umbilical cord pH (*n* = 29) (mean ± SD)	6.9 ± 0.19
Apgar 1 (*n* = 31) median (IQR)	3 (2–4)
Apgar 5 (*n* = 31) median (IQR)	6 (3–7)
Apgar 10 (*n* = 24) median (IQR)	7 (5–8)
Intubation at delivery room, *n* (%)	24 (75%)
Chest compression at the delivery room, *n* (%)	9 (28%)
Ventilation at the end of resuscitation at delivery room, *n* (%)	19 (59%)
First pH after resuscitation at the delivery room (mean ± SD)	7.15 ± 0.16
Hospitalization data	
Assisted ventilation after admission, *n* (%)	26 (81%)
Duration of assisted ventilation (*n* = 28) (median, IQR)	31 (1.25–72) hours
Seizures diagnosed with aEEG (*n* = 32)	25 (78%)
Anti-epileptic drugs, *n* (%)	29 (91%)
Age of start of active hypothermia (*n* = 29) (median, IQR)	6 (2–6)
Cycling during aEEG recording, *n* (%)	30 (94%)
Time to sleep cycling (*n* = 30)[a] (mean days, IQR)	2.44 (1.53–3.96)
MRI data	
Age in days at first MRI, median (range)	7 (5–20)
MRI grading 0/1/2 (*n*)	20 (63%)/9 (28%)/3 (9%)
Outcome	
Survival	27 (84%)
Survival without severe neurodevelopmental sequel[b] *n* (%)	18 (56%)

[a] Two infants did not develop cycling after more than 7 days of monitoring

[b] Sequels: death, cerebral palsy, mental retardation

Fig. 3 Kaplan-Meir curve of the percentage of infants developing sleep cycling according to age in days
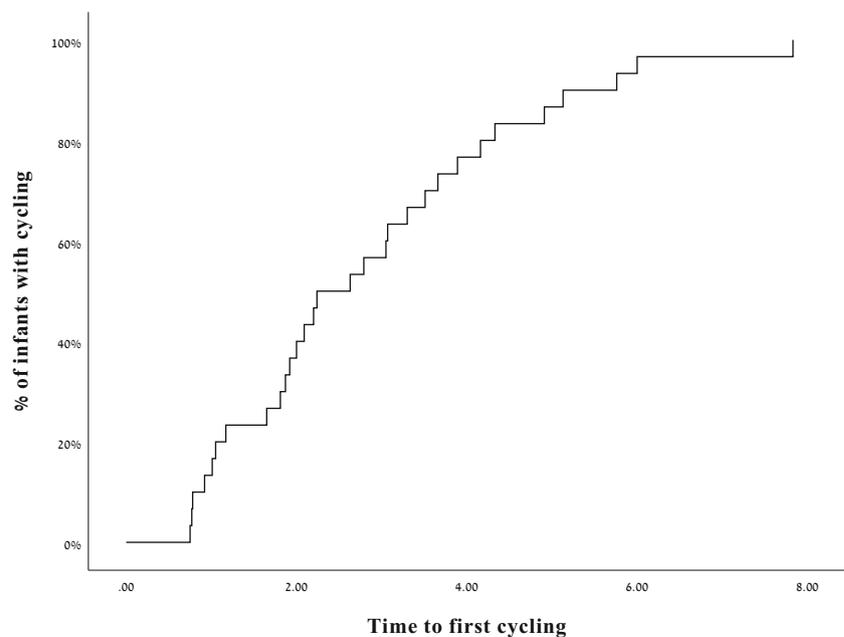
Table 3 Distribution of the different aEEG patterns during the different time intervals after birth

Pattern	Time interval						
	0–6 h	6–12 h	12–24 h	24–48 h	48–72 h	72–96 h	96–120 h
N	27	30	31	31	31	32	27
Isoelectric	0	0	1	1	1	1	0
Low voltage	7	9	8	4	1	0	1
Burst suppression	16	9	10	10	9	7	5
Discontinuous	3	11	10	15	15	14	6
Continuous	1	1	2	1	5	10	15

7 months. Three children were diagnosed with severe CP, four with mental retardation, and two with CP and mental retardation. Eighteen (56%) children were not diagnosed with severe CP or mental retardation and considered with favorable outcome; of them, 16 (89%) had a low score on MRI ($p = 0.004$ for the association of the MRI severity score with outcome).

MRI severity score was significantly associated with aEEG background in the third and fourth days of life (Table 5), though the association with the two-category score only trended to be significant. At those time intervals, all infant with severe MRI score had a depressed aEEG while, of the infants with normal/slightly abnormal MRI score, only 15% at the third day of life and 16% at the fourth day of life had a depressed aEEG (Table 6).

No significant associations were found between aEEG background and outcome.

LOESS regression analysis for the association of the appearance of sleep cycling with the MRI severity score is presented in Fig. 4 and suggests an increase in the MRI severity score if cycling appears beyond the age of 4 days.

Discussion

The main findings of this study include the association between depressed aEEG background activity and worse MRI severity category at the third and fourth days of life and the

increase in the MRI severity score if sleep cycling does not develop after the age of 4 days, i.e., more than 24 h after termination of therapeutic hypothermia.

aEEG has been used in the context of neonatal encephalopathy as an adjunct bedside tool for the assessment of the degree of encephalopathy and was also found to have a predictive value of later neurodevelopmental outcome soon after birth. As therapeutic hypothermia for HIE was found to have clear effect on the outcome of infants with neonatal encephalopathy, it became clear that depressed aEEG soon after birth may have a reduced sensitivity for predicting poor neurodevelopmental outcome. Several studies assessed its prognostic value in infants with HIE treated with therapeutic hypothermia and a recent meta-analysis [33]; pooling nine of these studies demonstrated that despite a depressed aEEG activity at 6 h of age, outcome may still be normal. Unlike our findings, a persistently depressed aEEG activity at the age of 48 h was associated with adverse long-term outcome in the meta-analysis.

Padden et al. [34] explored the correlation of background aEEG patterns with early MRI in a small cohort ($n = 38$) at two time points: at the beginning of the aEEG recording and at its end (at an approximate of 72 h), and found a significant

Table 4 Distribution of MRI severity score across the different cerebral structures

Structure	Score			
	0	1	2	3
PLIC	17	9	6	
BG	23	4	2	4
WM	21	3	3	5
Cortex	21	8	1	3
CC	20	9	2	1
Cerebellum	28	4		
Brain stem	32			

BG basal ganglia, *CC*, corpus callosum, *PLIC* posterior limb of internal capsule, *WM* white matter

Table 5 Association of aEEG severity score with MRI severity score

CFM time interval	aEEG (3 categories) p value for trends	aEEG (2 categories) p value for trends
0–6 h ($n = 27$)	0.581	0.515
6–12 h ($n = 30$)	0.137	0.280
12–24 h ($n = 31$)	0.050	0.186
24–48 h ($n = 31$)	0.075	0.514
48–72 h ($n = 31$)	0.008	0.025
72–96 h ($n = 32$)	0.003	0.010
96–120 h ($n = 27$)	0.207	0.557

MRI severity score (modified Rutherford score): 0: Normal/mildly abnormal, 1: Moderately abnormal, 2: Severely abnormal

aEEG (3 categories): 1. Normal/near normal, 2. Moderately abnormal, 3. Severely abnormal

aEEG (2 categories): 1. Normal/near normal, 2. Abnormal

p value is significant if it is < 0.007

Table 6 Number (%) of infants with abnormal aEEG per MRI severity score

MRI severity score	0–6 h (n = 27) p = 0.515	6–12 h (n = 30) p = 0.280	12–24 h (n = 31) p = 0.186	24–48 h (n = 31) p = 0.514	48–72 h (n = 32) p = 0.025	72–96 h (n = 30) p = 0.010	96–120 h (n = 27) p = 0.816
0	17/19 (89%)	11/20 (55%)	10/20 (50%)	9/20 (45%)	3/20 (15%)	3/19 (16%)	4/16 (25%)
1	5/7 (71%)	5/8 (63%)	7/8 (88%)	4/8 (50%)	2/8 (25%)	2/8 (25%)	2/8 (25%)
2	1/1 (100%)	2/2 (100%)	2/3 (66%)	2/3 (60%)	3/3 (100%)	3/3 (100%)	1/3 (33%)

MRI severity score (modified Rutherford score): 0: Normal/mildly abnormal, 1: Moderately abnormal, 2: Severely abnormal

aEEG (2 categories): 1. Normal/near normal, 2. Abnormal

p value is significant if it is < 0.007

correlation to MRI injury score only in infants that were not cooled ($n = 21$) as opposed to infants that were cooled ($n = 17$) unlike our finding that found an association with the MRI severity score at this age. Besides their small sample size, their study differed from ours in the short time interval that they assessed while we considered the predominant background pattern during each time interval.

Massaro et al. [35] in a study of 75 infants with neonatal encephalopathy that were cooled found that the longer the aEEG was depressed (burst suppression, low voltage of isoelectric), the higher the odds for adverse outcome (death, significant abnormal neurological exam at discharge or severe global, cortical or deep gray matter injury on brain MRI) with increasing specificity. They also found that if by the fourth day of life infants did not develop aEEG cycling, they were more likely to have an abnormal short-term outcome. Though, all infants in this cohort were

cooled as in our study, the outcome parameters used included death and abnormal neurological exam, while our study focused on the MRI scoring as a proxy of outcome and this may be the reason why they found significant associations of severely depressed aEEG with outcome throughout the first 4 days of life, while in our cohort, this association was significant only in the third and fourth days of life. Similar to our study, infants that did not develop cycling by the fourth day of life were more likely to have an abnormal outcome.

In another study by Weeke et al. [36] in 26 cooled infants, conventional EEG background activity at 36 and 48 h was significantly associated with neurodevelopmental outcome ($p = 0.009$ and $p = 0.029$, respectively) and with severity of brain injury in MRI ($p = 0.002$ and $p = 0.018$, respectively). Though, in this study, conventional EEG and a modified Barkovich MRI classification (that included diffusion MRI and posterior limb of internal capsule

Fig. 4 LOESS regression analysis
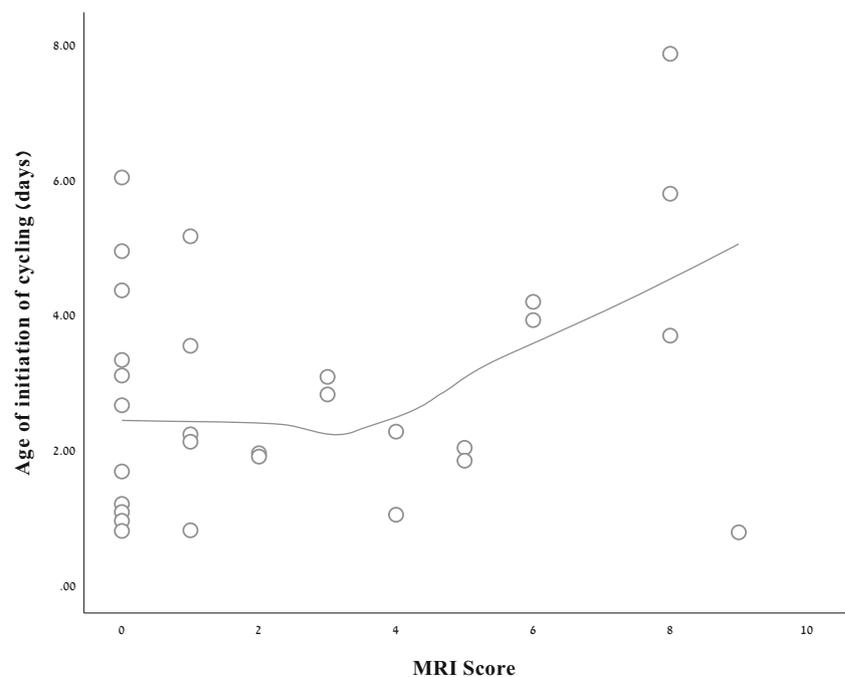
evaluation) were used, the time interval of the significant association of cerebral activity with MRI was similar to our findings. Dunne et al. [37] assessed in 49 infants with neonatal encephalopathy the predictive value of an aEEG computerized discontinuity index for an abnormal cerebral MRI outcome using Rutherford et al. [28] criteria. In their study, a higher mean discontinuity and a higher seizure burden were associated with a more severely abnormal MRI scans with a specificity of 94% and 97% and a sensitivity of 53% and 41% at 24 and 48 h, respectively. Both aEEG continuity index and MRI predicted outcome in 88% of the cohort at the age of 2 years. Though, in this study, both the assessment of cerebral function and MRI scans were different, the time frame of 24 and 48 h associated with abnormal MRI scans was similar to ours.

The strength of this study relates to the availability of most of the aEEG recordings soon after birth up to at least 24 h after cessation of therapeutic hypothermia.

Weaknesses include the retrospective design of the study and the relatively small cohort. Another weakness is the lack of MRI data in 18 infants that were not scanned, but as this data is missing, due to unavailability of the scanner and not to the severity of HIE, we do not think that it would have altered the results.

Another weakness is the outcome data that did not rely on a formal neurodevelopmental examination. Thus, though the outcome was significantly associated with MRI, it was not associated with the aEEG data, even at the time intervals that aEEG was significantly associated with the MRI. This discrepancy may be related to the higher predictive value of the MRI, the small cohort, but also to inaccuracy of the outcome data itself.

Conclusions

aEEG background has a significant association after the first 2 days of life with MRI abnormalities that are known to be related to abnormal neurodevelopmental outcome. This finding is corroborated by other studies. Together with the finding that delayed appearance of cycling is associated with abnormal MRI scans, it may be useful for assessing infants with neonatal encephalopathy in the first days of life before MRI results are available. However, caution should be used in making decisions (e.g., withdrawal of care or cessation of therapeutic hypothermia) based solely on aEEG without clinical and imaging corroboration as there are infants with depressed aEEG that have a favorable outcome and infants with normal/near normal aEEG with unfavorable outcome. Our findings maybe also useful for the early assessment of new neuroprotective agents.

Compliance with ethical statements

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