Original Article

Seizures severity during rewarming can predict seizure outcomes of infants with neonatal hypoxic-ischemic encephalopathy following therapeutic hypothermia

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ABSTRACT

Background: The aim of this study was to examine the predictive value of amplitude-integrated electroencephalography (aEEG) on 12-month seizure outcomes of infants with neonatal hypoxic-ischemic encephalopathy (HIE) treated with therapeutic hypothermia.
Methods: We conducted this retrospective cohort study in a tertiary neonatal intensive care unit between May 2012 and September 2017. Neonates with HIE who received both therapeutic hypothermia (TH) and aEEG were enrolled.
Results: A total of 23 infants (14 boys, nine girls) with a mean gestational age of 38.9 weeks were enrolled. Fifteen (65%) infants had moderate HIE and eight (35%) had severe HIE according to modified Sarnat staging. The mean aEEG recording time was 107.5 h. Twenty (86.9%) infants had seizure activity during the first 24 h after cooling and 14 (60.8%) had seizure activity during the first 24 h after rewarming. At 12 months, five (21.7%) infants had poor seizure outcomes. Repetitive seizures or status epilepticus pattern during the first 24 h after rewarming, but not the first 24 h after cooling, were associated with the presence of epilepsy at 12 months ($p = 0.037$).
Conclusions: We identified a high incidence of electrographic seizures in infants with neonatal HIE treated with therapeutic hypothermia, and post-neonatal epilepsy in the children who

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survived after HIE. Repetitive seizures or status epilepticus pattern during the first 24 h after rewarming, but not in the first 24 h after cooling, were associated with the presence of epilepsy at 12 months.

At a glance of commentary

Scientific background on the subject

Post-neonatal epilepsy is a major medical problem in patients survived from perinatal hypoxic-ischemic encephalopathy (HIE). We have little information to know about who will suffer it at the beginning of hospital care. A tool with accurate prediction is urgently needed.

What this study adds to the field

Rebound seizures during rewarming period may be a significant clue for future seizure outcome. Via analyzing the seizure activities of amplitude-integrated electroencephalography (aEEG) during this critical period, we have found association with post-neonatal epilepsy. It could play a role of seizure outcome predictor.

Hypoxic-ischemic encephalopathy (HIE) affects 1 to 8 per 1000 live births in developed countries, and the incidence is even higher in undeveloped regions. HIE remains one of the major causes of neonatal mortality and morbidity [1], and approximately 15%—20% of patients die during the newborn period, with an additional 25% having long-term neurological deficits such as cerebral palsy, mental delay, and epilepsy [2]. Previous neonatal outcome studies have shown that seizures are powerful predictors of death or permanent neurodisability [3], and that more than half of neonatal seizures at term are attributable to HIE [4]. Therapeutic hypothermia (TH) has been shown to be beneficial for neonates with HIE, with a consistent reduction in death and neurological impairment [5,6]. However, most previous studies have focused on neurodevelopmental outcomes such as cerebral palsy, blindness, deafness, developmental delay and impaired motor function [7], and only a few studies have focused on the relationship between moderate and severe HIE and post-neonatal epilepsy [8,9].

Amplitude-integrated electroencephalography (aEEG) was first introduced in Sweden more than two decades ago, and it is currently used in multiple centers around the world [2]. As a monitor of cerebral function, aEEG is a reliable tool for monitoring both the background patterns and ictal activity of neonates with HIE compared with standard EEG [10]. In addition, aEEG has also been shown to be a strong outcome predictor even during the era of TH [11]. However, few studies have focused on the relationship between aEEG background and seizure activities and post-neonatal epilepsy in infants with neonatal HIE treated with TH. Thus, the aim of this study was to examine if the aEEG background can play a pivot role of seizure outcome predictor for neonatal HIE treated with TH.

Material and methods

Patient population

This was a retrospective cohort study using chart reviews of infants with neonatal HIE at the neonatal intensive care unit (NICU) of Chang Gung Children's Hospital between May 2012 and September 2017. At Chang Gung Children's Hospital, the eligibility criteria for TH in neonates with HIE are in accordance with the National Institute of Child Health and Human Development (NICHD) trial [12] with some modifications including gestational age > 35 weeks, evidence of acute perinatal events, and moderate to severe HIE (examination for encephalopathy according to modified Sarnat staging). Neonates who received both TH and aEEG monitoring for at least 72 h were enrolled [Fig. 1]. This study was approved by the Chang Gung Memorial Hospital Institutional Review Board.

Therapeutic hypothermia protocol

TH was commenced in the infants who fulfilled the eligibility criteria within 6 h of life. Affected neonates received whole body cooling to maintain an esophageal temperature at 33—34 °C for 72 h. They were then rewarmed slowly (≤0.5 °C/h) to 36.5 °C. An aEEG system (Olympic CFM™ 6000, Natus Medical, California, USA) was planned to use to monitor the background patterns and seizure activities during the whole TH period as long as the machine was available, even after rewarming till patients had no active issue about seizure. Antiepileptic drugs (AEDs) were prescribed if clinical or electrographic seizures were suspected. Phenobarbital was the first choice of drug to control seizures, and if the seizures could not be controlled with phenobarbital, levetiracetam was used. During the hypothermic period, physiologic variables and laboratory profiles were measured regularly.

Data collection

The medical records of the infants were systematically reviewed. Collected data included 1) demographic data, such as gender, gestational age, birth weight, and inborn/outborn; 2) event characteristics, such as history of resuscitation; 3) variables after resuscitation, such as Apgar scores at 1 and 5 min, first blood gas analysis, and aEEG recording; and 4) outcomes, including 12-month seizure outcomes and the duration of hospital stay. The aEEG recordings obtained from single-channel (P3—P4) aEEG monitors were retrospectively reviewed off-line during two time-epochs (first 24 h after cooling and 24 h after rewarming), and the background patterns and seizure activities were rated (by YJ Chen, JJ Lin). Background patterns
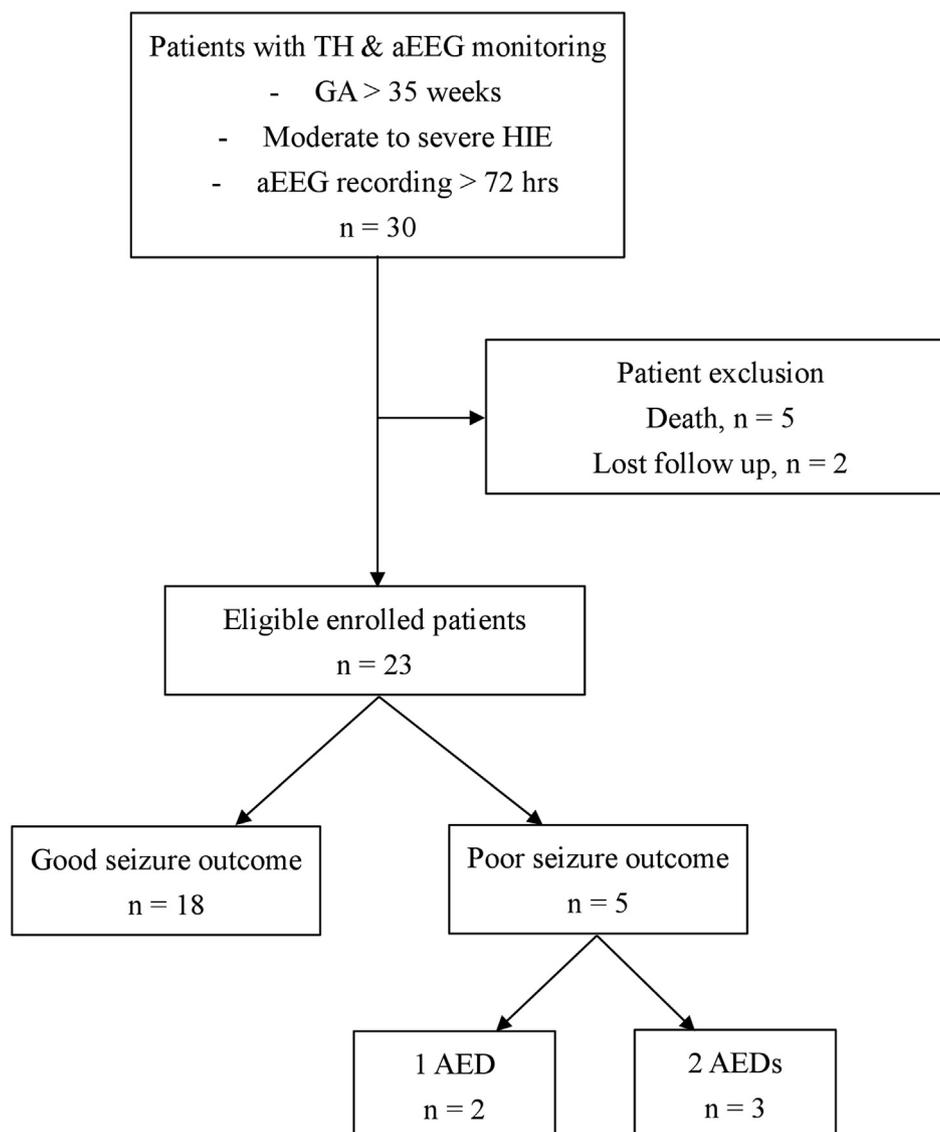
Fig. 1 Flow diagram of the study. Thirty asphyxiated newborns were admitted to our neonatal intensive care unit for therapeutic hypothermia during which aEEG was recorded. Five infants died within 6 months, and two were lost to follow-up. At 12 months of age, 18 infants (78%) had good seizure outcomes. Of the five infants (22%) with poor seizure outcomes, three took two kinds of antiepileptic drugs. Abbreviations used: TH: therapeutic hypothermia; aEEG: amplitude-integrated electroencephalography; GA: gestational age; HIE: hypoxic-ischemic encephalopathy; hrs: hours: AED: antiepileptic drug.

were classified using the method described by Thoresen [13]. The patterns were classified into two groups according to the most abnormal aEEG background present during the 24 h-epochs: 1) normal trace, including continuous normal voltage (CNV) and discontinuous normal voltage (DNV) and 2) abnormal trace, including burst-suppression (BS), low voltage (LV) and flat trace (FT) [Fig. 2]. Electrographic seizures were defined as repetitive, spike-wave patterns which repeated for more than 10 s. The epileptiform activity on aEEG will show characteristic pattern looking with increased amplitude during epileptic seizure activity and lower voltage in interictal period [10]. A seizure event was defined as the combination of typical aEEG waveforms and the corresponding raw EEG trace. Seizure activities were rated during the two time-epochs (first 24 h after cooling and 24 h after rewarming) due to the high possibility for clinical seizures. The events were classified into two groups according to the frequency of epileptic activity: 1) none and single seizure, and 2) repetitive seizures or status epilepticus. The events would be categorized into repetitive seizures if there were ≥ 3 discharges during 30-min period and status epilepticus if there was regular pattern of increased cortical activity with sawtooth pattern [10]. Seizure outcome was evaluated at 12 months of age and was defined as poor if there were unprovoked seizures with the regular usage of AEDs (regarded as post-neonatal epilepsy), and good if the infants were seizure free without the use of AEDs [Fig. 3].
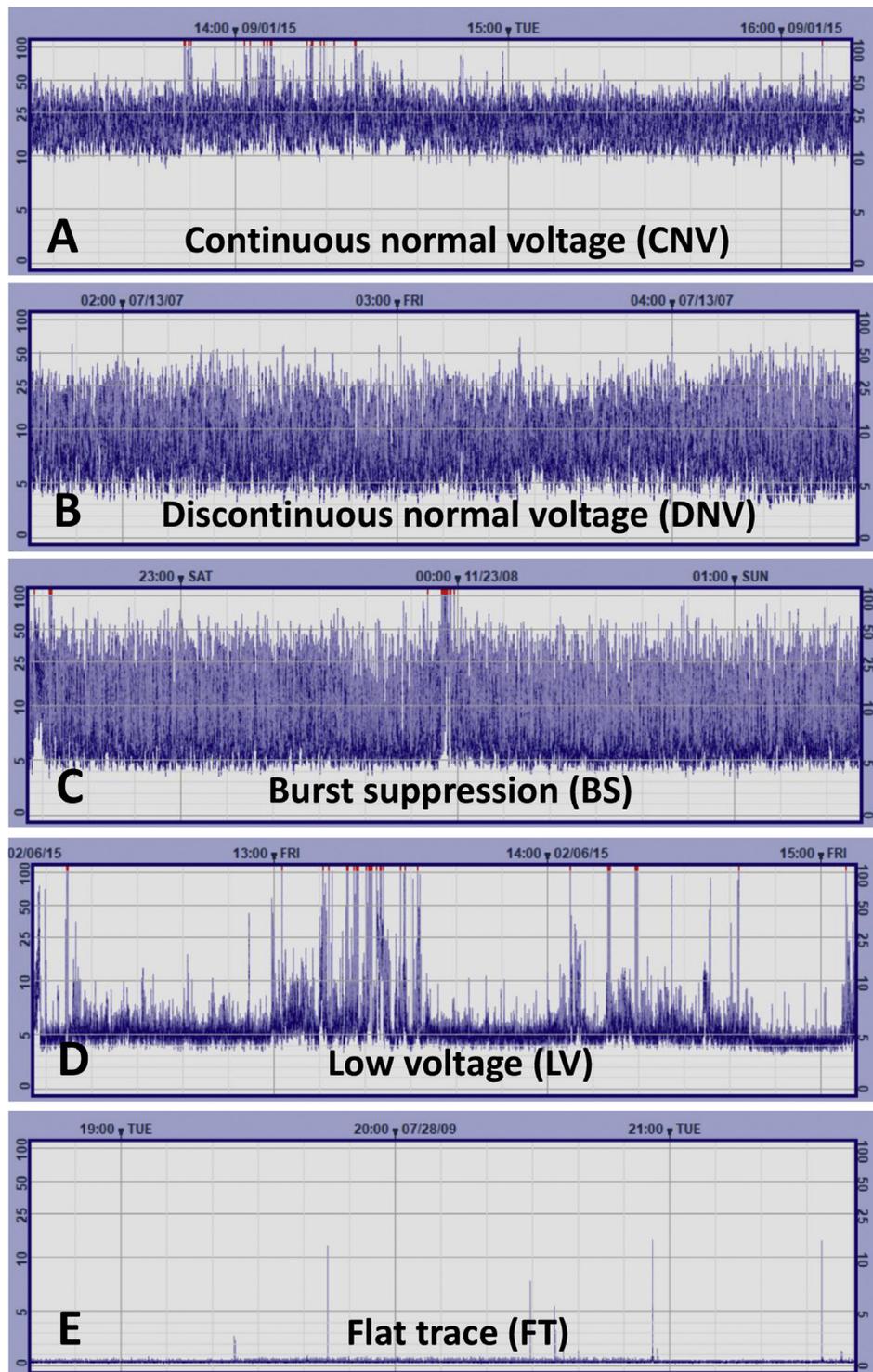
Fig. 2 aEEG background patterns of our infants (classified using the method described by Thoresen et al.). Panel A—B. Normal trace: (A) continuous normal voltage (CNV), (B) discontinuous normal voltage (DNV). Panel C—E. Abnormal trace: (C) burst-suppression (BS), (D) low voltage (LV), and (E) flat trace (FT).

Statistical analysis

Our main aim was to examine the predictive value of aEEG parameters on 12-month seizure outcomes in infants with neonatal HIE treated with TH. We compared aEEG background and seizure activities during two time-epochs (first 24 h after cooling and 24 h after rewarming) to 12-month seizure outcomes. The patient characteristics in each study group are represented as descriptive statistics, and the data are presented as median and interquartile range. Between-group differences were analyzed using the chi-square test or Fisher's exact test for categorical variables.
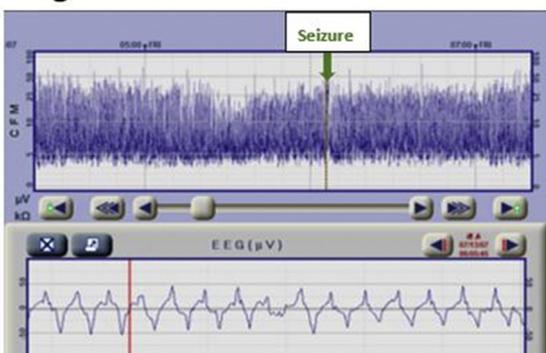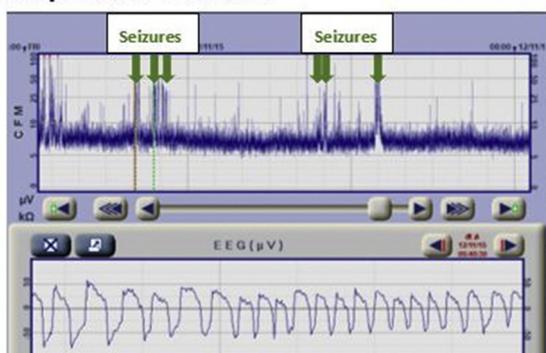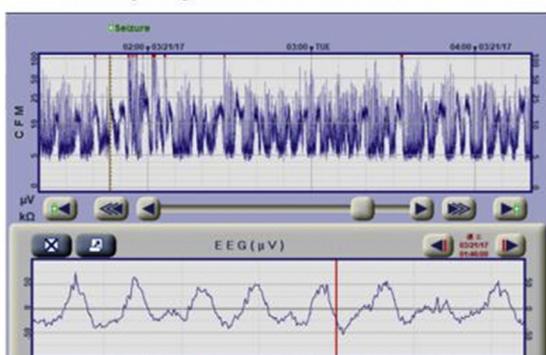
Fig. 3 The epileptiform activities on aEEG of our infants. Panel A. Single seizure. Panel B. Repetitive seizures. Panel C. Status epilepticus.

The Mann–Whitney U-test was used for comparing continuous variables because of small sample size for both groups. Statistical analysis was performed using SPSS Statistics version 21 (IBM, Armonk, NY). A two-sided p value < 0.05 was considered to indicate statistical significance.

Results

Patient profile

Thirty neonates who were admitted to the NICU of Chang Gung Children's Hospital for TH with aEEG monitoring between May 2012 and September 2017 were enrolled [Fig. 1]. Five infants died during the study period, mostly because their family decided to abandon treatment due to the grave prognosis. Another two infants were lost of follow-up. The remaining 23 neonates (14 boys, 61%) with a mean gestational age of 38.9 weeks were analyzed. Eighteen (78%) of these 23 infants were transferred to our NICU from the birth hospital for TH, and nine (39%) had resuscitation at birth. Among the 23 infants, the mean aEEG recording time was 107.5 h. The demographic data of the two seizure outcome groups are shown in [Table 1]. There were no significant differences between the two groups.

Variables during and after resuscitation and outcomes

Eight (35%) infants had evidence of severe encephalopathy (modified Sarnat stage III) before receiving TH, five (62.5%) of whom were in the good seizure outcome group. The baseline characteristics including 1-min and 5-min Apgar scores were similar between the two groups. Serum pH and base deficit levels immediately after resuscitation were also similar between the two groups, suggesting a similar severity of illness after resuscitation. At 12 months of age, 18 (78%) of the 23 infants had good seizure outcomes. Of the five infants (22%) in the poor seizure outcome group (post-neonatal epilepsy), three took two kinds of AEDs. The event characteristics during resuscitation and outcomes are listed in [Table 1].

Amplitude-integrated EEG pattern and 12-month seizure outcomes

Regarding the background patterns of aEEG records, six (26.1%) infants had normal continuous voltage, eight (34.8%) had discontinuous normal voltage, three (13%) had burst-suppression, five (21.7%) had low voltage, and one (4.4%) had a flat pattern during the first epoch. During the second epoch, five (21.7%) infants had normal continuous voltage, six (26.1%) had discontinuous normal voltage, 11 (47.8%) had burst-suppression, one (4.4%) had low voltage, and none (0%) had a flat pattern. The proportions of normal and abnormal traces between the two groups were similar during the first epoch. However, the proportion of normal traces in the good seizure outcome group was more than 2 times higher than that in the poor seizure outcome group during the second epoch, although the difference did not reach statistical significance [Table 2].

With regards to seizure activity as assessed by aEEG, 20 (86.9%) of the 23 infants had seizure activity, including four with a single seizure, 15 with repetitive seizures, and one with status epilepticus during the first epoch. All seizure activities were controlled with AEDs and hypothermia within 24 h after cooling. During the second epoch, 14 (60.8%) of the 23 infants had seizure activity, including two with a single seizure, eight with repetitive seizures, and four with status epilepticus. All of the five infants in the poor outcome group with post-neonatal epilepsy had electrographic repetitive seizures or status epilepticus during both time epochs. Repetitive seizures or status epilepticus pattern during the first 24 h after rewarming, but not the first 24 h after cooling, were associated with the presence of epilepsy at 12 months ($p = 0.037$) [Table 2].

Table 1 Characteristics of the 23 infants with neonatal hypoxic-ischemic encephalopathy treated with therapeutic hypothermia.

Demographic data	All infants (n = 23)	Good Sz outcome (n = 18)	Poor Sz outcome (n = 5)	p value
Male sex (%)	14 (61%)	10 (56%)	4 (80%)	0.611
Gestational age (weeks)	39 [38—39]	39 [38—40]	38.8 [38.4—39.6]	0.745
Birth weight (g)	3165 [2890—3410]	3141 [2875—3415]	3083 [2755—3249]	0.227
Outborn (%)	18 (78%)	14 (78%)	4 (80%)	1.000
Event Characteristics				
Resuscitation at birth (%)	9 (39%)	6 (33%)	3 (60%)	0.343
Variables after resuscitation				
Apgar score				
1 min	1 [1—4]	1.5 [1—4]	2.5 [1—4]	0.587
5 min	5 [3—7]	5 [3.3—7]	5 [3—7]	0.227
First blood gas				
pH	7.17 [7.08—7.31]	7.17 [7.09—7.31]	7.13 [7.08—7.27]	0.857
Base deficit (mmol/L)	16.1 [12.5—22.25]	16.25 [12.5—22.78]	16.05 [12.65—20.45]	1.000
Severe HIE	8 (35%)	5 (28%)	3 (60%)	0.297
aEEG recording time (H)	101.4 [90.8—117.9]	103.8 [92.3—118.1]	100.8 [90.5—121.7]	0.914
Outcomes				
Length of hospital stay (D)	27 [20.5—32]	27.5 [20.3—32.5]	24.5 [20.3—29.8]	0.199

Data are presented as number of infants (%), and median [interquartile range].
Abbreviations: HIE: hypoxic-ischemic encephalopathy; aEEG: amplitude-integrated electroencephalography; H: hours; D: days; Sz: seizure.

Discussion

HIE is a major risk factor for neonatal mortality and morbidity. Most previous studies have focused on neurodevelopmental outcomes such as the cerebral palsy, blindness, deafness, developmental delay and impaired motor function [7], and only a few studies have focused on the relationship between HIE and post-neonatal epilepsy [8,9].

Table 2 Correlations between background patterns and seizure activity of aEEG and 12-month seizure outcomes.

		Good Sz outcome (n = 18)	Poor Sz outcome (n = 5)	p value
Background patterns				
First epoch[a]	CNV	3 (16.7%)	3 (60%)	—
	DNV	8 (44.4%)	0 (%)	
	BS	3 (16.7%)	0 (%)	
	LV	3 (16.7%)	2 (40%)	
	FT	1 (5.6%)	0 (0%)	
First epoch[a]	I: Normal trace	11 (61.1%)	3 (60%)	1.000
	II: Abnormal trace	7 (38.9%)	2 (40%)	
Second epoch[a]	CNV	5 (27.8%)	0 (0%)	—
	DNV	5 (27.8%)	1 (20%)	
	BS	8 (44.4%)	3 (60%)	
	LV	0 (0%)	1 (20%)	
	FT	0 (0%)	0 (0%)	
Second epoch[a]	I: Normal trace	10 (55.6%)	1 (20%)	0.317
	II: Abnormal trace	8 (44.4%)	4 (80%)	
Seizure activity				
First epoch[a]	None	3 (16.7%)	0 (0%)	—
	Single seizure	4 (22.2%)	0 (0%)	
	Repetitive seizure	11 (61.1%)	4 (80%)	
	SE	0 (0%)	1 (20%)	
First epoch[a]	None + single Sz	7 (39%)	0 (0%)	0.272
	Repetitive Sz + SE	11 (61%)	5 (100%)	
Second epoch[a]	None	9 (50%)	0 (0%)	—
	Single seizure	2 (11.1%)	0 (0%)	
	Repetitive seizure	5 (27.8%)	3 (60%)	
	SE	2 (11.1%)	2 (40%)	
Second epoch[a]	None + single Sz	11 (61.1%)	0 (0%)	0.037*
	Repetitive Sz + SE	7 (38.9%)	5 (100%)	

aEEG: amplitude-integrated electroencephalography; Sz, seizure; CNV: continuous normal voltage; DNV: discontinuous normal voltage; BS: burst-suppression; LV: low voltage; FT: flat trace; SE: status epilepticus.
*p < 0.05: statistically significant.
[a] First epoch: first 24 h after cooling; Second epoch: first 24 h after rewarming.

In this study, we identified a high incidence of post-neonatal epilepsy (5/23, 21.7%) in our infants with HIE treated with TH. The diagnosis of post-neonatal epilepsy was made based on the broad definition of the International League Against Epilepsy (ILAE) as unprovoked seizures with the regular usage of AEDs [14]. Toet et al. reported that eight infants developed post-neonatal epilepsy (9.3%) among 86 survivors with moderate and severe HIE [8], whereas Pisani reported that only three of 30 infants (10%) with moderate and severe HIE developed post-neonatal epilepsy [15].

Our incidence of post-neonatal epilepsy was higher than these previous studies, probably due to widely diversity in enrolled subjects. The incidence of post-neonatal epilepsy depends both on the maturity of the infant and on the underlying etiology. We included a mixture of term and late preterm newborns with a gestational age of >35 weeks. In addition, there was a higher percentage (35%) of severe HIE in our study (vs. 2.3% in Toet's study and 16.6% in Pisani's study). Moreover, we excluded infants with <72 h of aEEG recording.

Amplitude-integrated EEG is the standard monitoring tool used to assess the trends of cortical electrical activity and detect electrographic seizures in neonates undergoing TH [16]. A systematic review showed that the maximum predictive reliability of aEEG background activity on neurodevelopmental outcomes was achieved at 72 h of life [17]. Another meta-analysis study concluded that a severely abnormal aEEG background persisting until or beyond the first 48 h of life predicted adverse neurodevelopmental outcomes [18]. However, no previous study has focused on the relationship between the background activity of aEEG and post-neonatal epilepsy. In this study, we did not find any significant correlations between the background patterns of aEEG during the two time epochs and the 12-month seizure outcomes [Table 2].

On the other hand, seizure burden during TH was associated with an abnormal outcome, including epilepsy. Kharoshankaya et al. reported that a high electrographic seizure burden in infants with moderate and severe HIE was significantly associated with abnormal outcomes at 24–48 months (including epilepsy diagnosed by a pediatric neurologist), independently of the severity of encephalopathy or treatment with hypothermia [19]. Weeke et al. also reported that the neurodevelopmental outcomes at 2 years including epilepsy were significantly associated with seizure burden in full-term infants with HIE ($p = 0.036$) [20]. With regards to the severity of electrographic seizures between the two time epochs (during cooling and rewarming), the poor outcome group had a higher seizure burden after discontinuation of cooling. In other words, more episodes of status epilepticus occurred during this period. Only a few studies have focused on the relationship between seizure activity in aEEG during the first 24 h after rewarming and post-neonatal epilepsy. In this study, the 12-month seizure outcomes were correlated with repetitive seizures or status epilepticus pattern during the first 24 h after rewarming, but not the first 24 h after cooling.

We chose two time periods (during cooling and rewarming) to evaluate seizure activities on aEEG based on reports that most clinical seizures occur during these periods [21]. Divyen et al. reported that seizures are common during cooling, particularly in the first 6–12 h after birth, with a significant rebound on the fourth day, coinciding with the rewarming period. This phenomenon of "rebound seizures" has been reported in other studies [16].

Several animal studies have reported that early hypoxia-ischemia in rat pups resulted in later seizures, and that the occurrence of later seizures was related to the severity of cerebral tissue injury [22,23]. In clinical studies, electrographic seizure burden in neonatal HIE has been associated with tissue injury on magnetic resonance imaging independently of aEEG background or markers of illness severity at birth [16]. Therefore, monitoring electrographic seizures and aggressive treatment to decrease seizure burden in neonatal HIE are very important [6].

Limitations

There are several limitations to this study. First, it was conducted at a single institution. Second, the sample size was relatively small. Third, the follow-up period was relatively short. Some of these children have a seizure-free period before developing epilepsy during pre-school/school age [24]. Fourth, the aEEG parameters were reviewed off-line, although during the actual TH period, the recordings were read by the physicians during ward rounds once or twice daily. Fifth, suspicious seizure episodes were mostly treated according to the clinical judgement of neonatologists during ward rounds and physicians would take aEEG as a reference. But, seizure in neonates might be missed by clinical observation along with single-channel aEEG monitoring. Zhang et al. reported that of 876 seizures confirmed by continuous EEG monitoring, 21% were detected by clinical observation, 44.4% by aEEG and 85.7% by aEEG plus C3/C4 raw EEG [25]. Therefore, combination of aEEG with continuous EEG monitoring offers more accurate diagnosis.

Conclusions

In this study, there was a high incidence of electrographic seizures in the infants with neonatal HIE treated with TH and post-neonatal epilepsy in those who survived after HIE. Repetitive seizures or status epilepticus pattern during the first 24 h after rewarming, but not during the first 24 h after cooling, were associated with the presence of epilepsy at 12 months.

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Conflicts of Interest

The authors have no conflicts of interest relevant to this article.

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