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The prognosis of brain magnetic resonance imaging injury pattern for outcomes of hypothermia-treated infants

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Abstract

Magnetic resonance imaging (MRI) can be a tool that allows the observation of structural injury patterns after cooling. The aim of this study was to determine the early pattern of brain injury in the MRIs of infants with hypoxic ischemic encephalopathy (HIE) after cooling and to search for any clinical factors related to abnormal MRI findings.

The study retrospectively recruited 118 infants who were treated with therapeutic hypothermia (TH) between 2013 and 2016.

Forty-three patients had normal brain MRI, and 75 had abnormal brain MRI findings. The TH-treated infants with abnormal brain MRI readings showed significantly more clinical seizures and the use of additional antiepileptic drugs (AEDs) than the normal MRI group. As a long-term outcome, more lesions in the basal ganglia and thalamus, posterior limb of internal capsule, or severe white matter lesions were associated with abnormal neurodevelopmental outcomes at 18 to 24 months of age.

A higher frequency of clinical seizures and AED use were related to abnormal brain injury on MRI. A significant risk for poor long-term outcomes was found in the abnormal brain MRI group.

Abbreviations: AED = antiepileptic drugs, aEEG = amplitude electroencephalogram, BE = base excess, BG = basal ganglia, CFM = cerebral function monitoring, CP = cerebral palsy, HIE = hypoxic–ischemic encephalopathy, MRI = magnetic resonance imaging, TH = therapeutic hypothermia.

Keywords: clinical factors, seizure, diffusion weighted magnetic resonance imaging, hypothermia, hypoxia-ischemia, seizures, long term outcomes

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What's known

- MRI has been a useful tool for the early detection of brain injury in infants with HIE.

What's new

- The abnormal brain MRI group showed significantly more clinical seizures and more use of additional antiepileptic drugs (AEDs) than the normal brain MRI group.
- More lesions in the basal ganglia and thalamus, posterior limb of internal capsule, or severe white matter lesions were deemed to be predictive of abnormal neurodevelopmental outcome at 18 to 24 months of age.

1. Introduction

Hypoxic–ischemic encephalopathy (HIE) after perinatal asphyxia is an important risk factor for morbidity and mortality in newborns and accounts for approximately 20% of the incidence of cerebral palsy (CP).[1,2] Other than CP, the neurodevelopmental sequelae of moderate-to-severe HIE often result in neuromotor disability accompanied by language, sensory, cognitive, or behavioral impairments. Currently, the best way to minimize the outcome of brain damage is to induce therapeutic hypothermia (TH), which is the only active treatment available for HIE. A recent systematic review reported that TH reduced mortality without an increase in major disability in survivors and improved both survival and development up to 18 to 24 months.[3] Furthermore, because the benefits of TH on survival and neurodevelopment outweigh the short-term adverse effects, broader inclusion of TH treatment for preterm (<35 weeks of gestation) and mild encephalopathic infants was suggested in some reviews.[4,5]

Early predictors of infants with HIE are reported as Apgar score, aEEG, Sarnat score, and magnetic resonance imaging (MRI).[4,6] These tools are vital for both decision-making and prognosis-prediction for TH. In particular, MRI is a primary short-term tool that allows the review of structural injury patterns after TH but can also serve as a predictor of long-term outcomes for neonatal infants with HIE. Brain lesions in the basal ganglia (BG) and thalamus in deep brain structures are considered severe acute hypoxic–ischemic insults that are often accompanied by abnormalities in the cortical and subcortical white matter. These lesions in deep brain structures and extended white matter may be categorized as a severe acute hypoxic–ischemic insult group[7] and are strongly associated with outcomes of cerebral palsy.[8]

The objective of this study was to categorize MRI patterns of injury in infants treated with TH (either selective head cooling or whole body cooling) after hypoxic ischemic insult between 2012 and 2016 at Seoul St. Mary's Hospital. The primary outcomes were the early patterns of injury in the MRIs of infants with HIE after TH treatment and clinical factors associated with abnormal MRI findings. The secondary outcome was to determine whether the abnormal brain MRI group was associated with neurodevelopmental disability at 18 to 24 months.

2. Methods

We included neonates who were treated with TH treatment in encephalopathic term or late preterm infants (≥35 weeks of gestation with birth weights ≥2000 g) between June 2013 and March 2016 at Seoul St. Mary's hospital, Catholic University of Korea. All infants experienced acute perinatal events (e.g., late or variable decelerations, cord prolapse, cord rupture, uterine rupture, maternal trauma, hemorrhage, or cardiorespiratory arrest). As soon as patients were stabilized, they were assessed for signs of intrapartum hypoxia and then for hypoxic encephalopathy as Sarnat stage ≥2. When they met these criteria, they were recruited for TH treatment within 6 hours of birth. The enrolled infants fulfilled 1 of the 2 parameters as previously described in the CoolCap, NICHD, European Trial, and TOBY trials[4–5,9–12]: pH of 7.0 or less or a base deficit >16 mmol/L and Apgar score 5 at 10 minutes or continued respiratory support at 10 minutes. The pH and base deficit were measured from the infant's arterial or venous gas within an hour of Neonatal intensive care unit admission. Cerebral function monitoring (CFM) (CFM, Natus Medical Inc., Seattle, WA) or video EEG was started as early as possible to detect any possible electrographic seizures. Infants presenting with clinical seizures or abnormal aEEGs were considered Sarnat stage ≥2, which was used to determine the infants with HIE eligibility for TH treatment. Seizures were clinically diagnosed by experienced neonatology staff as paroxysmal alterations in motor function and occasional autonomic function; this included clonic, tonic, and "subtle" seizure manifestations.[13] All TH infants were assessed using CFM or amplitude integrated EEG.[11] Moderate or severe voltage changes on amplitude-integrated encephalography or electrographic seizure waves were used to detect abnormal readings. Sarnat stages grades 1 to 3 before and after TH were monitored and recorded. Infants were randomly assigned to whole-body cooling (core esophageal temperature kept at 33.5 °C for 72 hours) or selective head cooling (core esophageal temperature kept at 34 °C for 72 hours).

After whole body cooling (Blanketrol III Hyper Hypothermia System, Cincinnati Sub-Zero, Cincinnati, OH) or selective head cooling (Olympic Medical Cool Care System, Olympic Medical, Seattle, WA), infants were rewarmed at a rate of 0.5 °C per hour. Brain MRI with MR diffusion was performed in all TH-treated infants (at least within 10 days of life) after they were rewarmed and extubated. This was due to MR diffusion changes disappearing after the first week of life.

We excluded infants with HIE who were older than 6 hours of birth at the time of assessment or those with major congenital abnormalities, syndromes, or metabolic diseases. Infants with birth weights ≤2000 g, gestational age ≤35 weeks of gestational age, overt bleeding, signs of infection, or those requiring ≥80% oxygen support, which may suggest persistent pulmonary hypertension, were also excluded.

The MRI was categorized according to patterns of structural injury. One independent radiologist was masked to the treatment and outcomes of the infants and reviewed the images for quality and acquired lesions. One specialized radiologist reviewed all images and classified them independently without knowing the clinical outcomes. The same radiologist assessed the early and later brain MRI scans and was blinded to the early results when reviewing the later scan. At corrected age of 18 to 24 months, infants who survived and returned for follow-up evaluations completed the cognitive, language, and motor composites of the Bayley Scales of Infant

and Toddler Development III. Children were considered to have a developmental delay if scores were below the test mean (scores of <84). Written informed parental consent was not obtained since this study was retrospectively reviewed. The study was approved by the Ethics Committee of Seoul St. Mary's Hospital, The Catholic University of Seoul, Korea.

2.1. Statistical analysis

Categorical variables were presented as percentages and frequencies and were compared using chi-squared statistics or Fisher exact *t* test. Continuous variables are presented as the means (±1 SD). These were expressed either as footnotes or notations next to the name of each continuous variable. All analyses were 2-tailed, with statistical significance defined as values of $P < .05$. Analysis of variance was performed when comparing the 3 different groups; however, log linear analysis was used to examine the relationship among categorical variables. Apgar scores were examined using the Kruskal–Wallis test since they were not normally distributed. All statistical analyses were performed with SPSS, version 19.0 (Statistical Package for the Social Sciences, SPSS-PC Inc., Chicago, IL).

3. Results

The study recruited 135 infants between 2013 and 2016. Of these infants, 2 died before further studies (e.g., brain images) were performed, and 15 infants were not followed for long-term neurological prognosis. As a result, 118 infants were enrolled in this study who received TH treatment; 43 (36%) had normal brain MRI findings, and 75 (64%) had abnormal MRI findings.

3.1. Primary outcome as MRI pattern of injury

Descriptive clinical characteristics for the TH-treated infants with outcomes of normal and abnormal brain MRI readings are presented in Table 1. The maternal and neonatal characteristics were not significantly different between the groups. Mean Apgar score at 1 minutes was significantly lower in the normal group; however, the mean Apgar score at 5 minutes between the 2 groups was not significant (Table 1). Short-term hospital outcomes were compared according to MRI findings (Table 2).

Table 1

Clinical characteristics of therapeutic hypothermia treated HIE group (n = 118).

	Normal MRI (n = 43)	Abnormal MRI (n = 75)	*P*-value
Gestational age, wk	39.73 ± 1.01	39.54 ± 1.34	.202
Birth weight, kg	3.27 ± 0.36	3.25 ± 0.45	.409
Male, n (%)	25 (51.8)	24 (60.0)	.780
Outborn, n (%)	14 (32.6)	14 (35.0)	.167
Mother age[a]	32.51 ± 3.79	33.05 ± 4.94	.562
Small for gestational age[b]	4 (9.3)	3 (7.5)	.957
Complications of pregnancy			
Fetal heart-rate deceleration	31 (72.1)	29 (72.5)	.200
Uterine rupture[b]	0 (0)	0 (0)	NA
Maternal pyrexia during labor[b]	3 (7.0)	4 (10.0)	.437
Maternal chorioamnionitis[b]	7 (16.3)	5 (12.5)	.676
Maternal hemorrhage[b]	1 (2.3)	0 (0)	NA
Emergency cesarean delivery	12 (27.9)	12 (30.0)	.943
Apgar score at 1 minute[a]	5.0 [2.0, 7.0]	6.0 [3.0, 7.0]	.036*
Apgar score at 5 minute[a]	7.0 [6.0, 9.0]	7.5 [6.0, 9.0]	.131
Apgar <5 at 10 minutes	9 (20.9)	6 (15.0)	.357
Ventilation by 10 minutes	43 (100.0)	36 (90.0)	NA
MAS, n (%)	7 (16.3)	5 (12.5)	.321
Surfactant use, n (%)	10 (23.3)	7 (17.5)	.808
PPHN, n (%)	4 (9.3)	3 (7.5)	.844
Initial pH[a]	7.28 ± 0.12	7.34 ± 0.92	.052
Initial BE[a]	8.54 ± 5.52	5.26 ± 3.39	.082
Sarnat stage on Day 1			.517
Stage 1	2 (4.7)	2 (5.0)	
Stage 2	35 (81.4)	32 (80)	
Stage 3	6 (14.0)	6 (15.0)	
LDH[a]	1,219.72 ± 496.54	1,148.77 ± 400.75	.541
CPK[a]	1042.58 ± 965.23	964.88 ± 716.47	.667
Age at cooling, hr[a]	3.12 ± 2.20	3.51 ± 1.81	.267
Cooling mode			.183
Whole body cooling	25 (58.1)	18 (45.0)	
Selective head cooling	18 (41.9)	18 (41.9)	
Ventilator care, days[a]	3.81 ± 3.73	3.4 ± 2.3	.828
Inotropic use, days[a]	2.4 ± 2.8	3.51 ± 108.8	.091
Sarnat stage on Day 4			.311
Stage 1	36 (83.7)	37 (92.5)	
Stage 2	6 (14)	2 (5.0)	
Stage 3	1 (2.3)	1 (2.5)	
MRI, day after birth[a]	7.1 ± 3.4	6.3 ± 2.7	.270

ANOVA test was performed when comparing the three different groups, however, log linear analysis was used to examine the relationship among categorical variables.

BE = base excess; CPK = creatine phosphokinase; HIE = hypoxic ischemic encephalopathy; hr = hour; LDH = lactate dehydrogenase; MAS = meconium aspiration syndrome; MRI = magnetic resonance imaging; PPHN = persistent pulmonary hypertension.

[a] Continuous variables: mean ± standard deviation.

[b] Fisher exact test.

* $P < .05$.

Table 2

Hospital outcomes of therapeutic hypothermia treated HIE infants (n = 118).

	Normal MRI (n = 43)	Abnormal MRI (n = 75)	*P*-value
Clinical seizure, n (%)	24 (55.8)	59 (78.7)	.047*
Seizure before TH[a]	1 (2.3)	8 (10.7)	.100
Seizure after TH[a]	3 (7.0)	10 (13.3)	.289
Electrographic seizure, n (%)	26 (60.5)	52 (70.7)	.325
Abnormal background	1 (2.3)	6 (8.0)	.413
Epileptic form	25 (58.1)	28 (37.3)	.520
Use of anticonvulsant agent, n (%)			
Use of AED			
One AED	18 (41.9)	40 (53.3)	
More than 2 AEDs	17 (39.5)	33 (44.0)	.007*
Phenobarbital use	35 (81.4)	70 (93.3)	.048*
Hospitalized days[b]	13.4 ± 5.7	13.9 ± 7.5	.206
Full feeding reached day[b]	8.23 ± 4.4	8.4 ± 5.0	.976
Complications			
Coagulation disorder[c]	18 (41.9)	25 (33.3)	.428
cardiovascular[d]	1 (2.3)	3 (4.0)	.147
PRC transfusion, n (%)	12 (27.9)	23 (30.37)	.461
Abnormal AEP, n (%)[a]	2 (4.7)	8 (10.8)	.088
Death, n (%)[a]	1 (2.3)	1 (1.3)	.598
Improved brain MRI on FU MRI	NA	71 (94.7)	NA

AED = antiepileptic drug; AEP = auditory evoked potential; FU = follow up; HIE = hypoxic ischemic encephalopathy; MRI = magnetic resonance imaging; PRC = packed red blood cell; TH = therapeutic hypothermia.

[a] Fisher exact test.

[b] Continuous variables: mean ± standard deviation.

[c] Coagulation disorder: prolonged PT and aPTT.

[d] Cardiovascular: bradycardia <70, persistent pulmonary hypertension and myocardial dysfunction.

* $P < .05$.

Table 3

MRI Grades according to brain lesions in HIE infants in relation to neurodevelopmental outcomes at 18–24 months (n = 118).

MRI findings	Normal (n = 83)	Abnormal neurodevelopment* (n = 35)	*P*-value
Normal	11 (14.5)	0 (0.0)	.001
Basal ganglia and thalami	6 (7.9)	18 (51.4)	.001
Posterior limb of internal capsule	1 (1.3)	7 (20.0)	.001
White matter	6 (17.1)	26 (34.2)	.001
Cortex	0 (0.0)	13 (17.1)	.001
Hemorrhage	19 (25.0)	4 (11.4)	.001

HIE = hypoxic ischemic encephalopathy; MRI = magnetic resonance imaging.
* Children were considered as abnormal neurodevelopment group an 18–24 months if scores of Bayley Scales of Infant and Toddler Development III were <85.

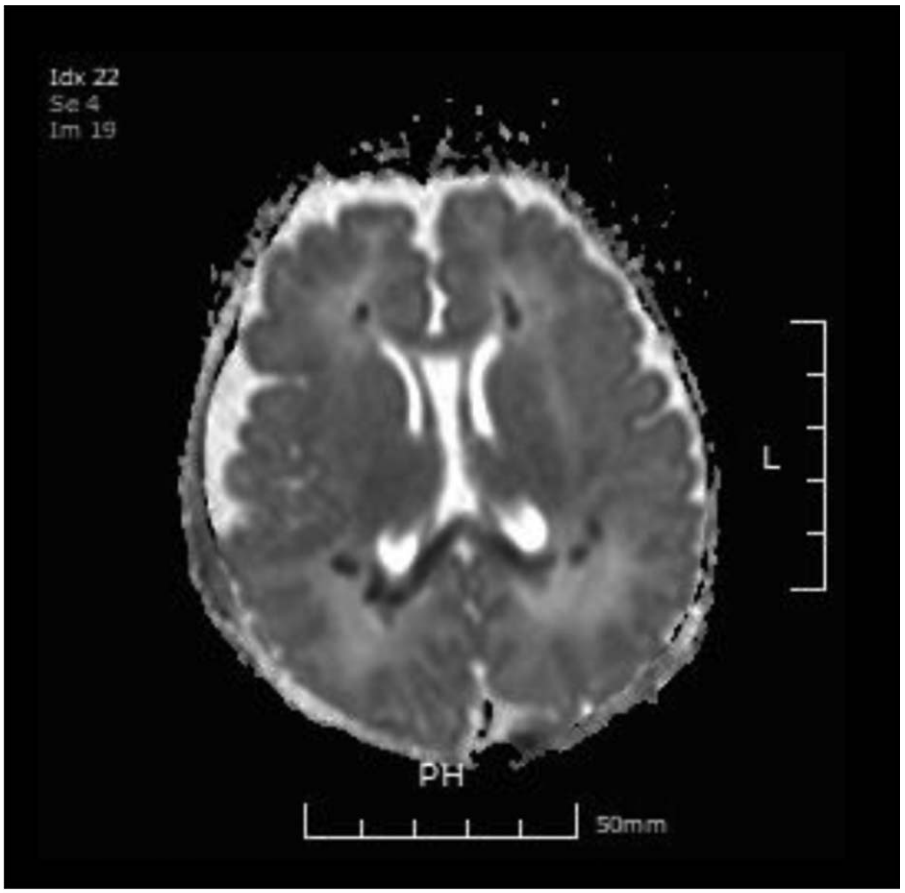
There was an approximately 78.7% frequency of clinical seizures and a 70% frequency of electrographic seizures among our TH-treated infants. When compared between groups, the abnormal brain MRI group showed significantly more clinical seizures (78.7% vs 55.8%, $P < .047$) and greater use of additional antiepileptic drugs (AED) than did the normal brain MRI group (53.3% vs 41.9%, $P < .007$) (Table 2). The mean hospitalization time was 14 days of age. Infants received full oral feeding at a mean of 8 days. The other hospital outcomes showed no significant difference between the 2 groups, including complications related to TH treatment and mortality rate.

3.2. Secondary outcome (follow-up at 18–24 months)

At 18 to 24 months, 118 infants survived, returned for follow-up evaluations, and completed the cognitive, language, and motor composites of the Bayley Scales of Infant and Toddler Development III. Children were considered to have developmental delay if scores were <84. More lesions in the basal ganglia and thalamus, posterior limb of internal capsule, or severe white matter lesions in brain scans were significantly associated with abnormal neurodevelopmental outcomes at 18 to 24 months of age (Table 3) (Figs. 1 and 2).

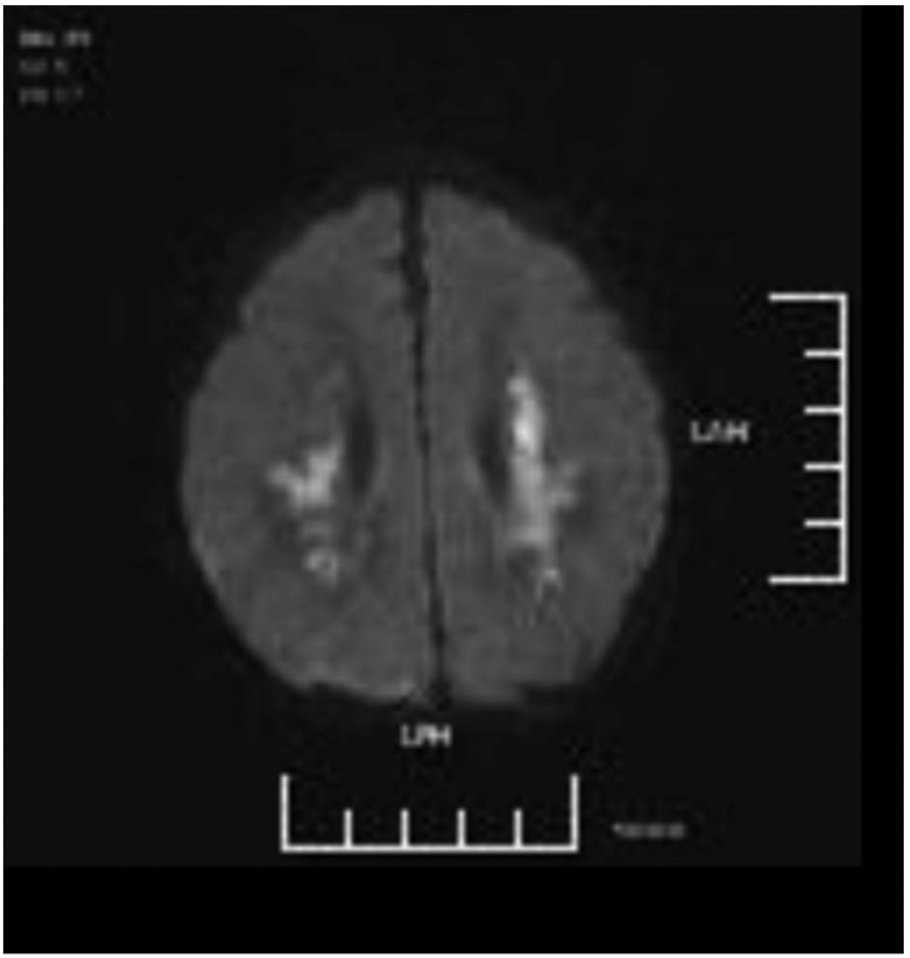
4. Discussion

In our study, we observed that more extension of injury in the basal ganglia and thalamus and a trend towards more abnormal scans in brain MRI were significantly associated with abnormal neurodevelopment (ND) at 18 to 24 months of age, which was in line with our initial hypothesis. Among the infants with abnormal MRI findings, 35 (30%) had injuries that involved deep brain structures such as the basal ganglia and thalamus, which was similar to the reported incidence of 44 (40%) BG injuries.[14] The location of injury according to MRI NICHD Score systems allowed a better characterization of brain injury patterns and



Abbreviations: HIE: hypoxic–ischemic encephalopathy

Figure 1. HIE in both lateral thalami and corpus callosum. HIE = hypoxic–ischemic encephalopathy.



Abbreviations: HIE: hypoxic–ischemic encephalopathy

Figure 2. Multifocal HIE in corpus callosum and posterior limbic of anterior and posterior area. HIE = hypoxic–ischemic encephalopathy.

improved prediction of the ND outcome at 18 to 24 months of age in infants with HIE.

MRI is a noninvasive method that can be a good tool to assess perinatally acquired cerebral lesions associated with HIE. The correlation between the injury location and development of infantile spasms[4] was also studied, which emphasized the importance of the injury location. Severe acute hypoxic-ischemic insults and lesions in the basal ganglia and thalamus are often associated with abnormalities days.[15]

TH is reported to have a protective effect on brain lesions in the BG and thalamus that may further reduce sequelae of brain injury. Because our TH-treated infants were not compared with noncooled infants with HIE, the effect of TH solely on the MRI findings was not clear. However, we expected that 72 hours of TH may have caused an improvement in neurological assessments and structural injuries by minimizing secondary inflammation. Azzopardi et al[16] reported that TH treatment increased the likelihood of survival with normal IQ and improved survival without neurological abnormalities at follow-up at 6 to 7 years of life. Our infants with hypoxic encephalopathy who were promptly treated with TH may have potential additional benefits, such as increased survival rates and better prognosis. Despite the MRI injury findings on the thalamus and BG of our patients, follow-up MRIs showed a resolved injury pattern (94.7%) approximately 1 month following the first MRIs. The clinical significance of white matter injury usually receives less attention than BG and thalamus injury due to the possibility of a watershed or temporary injury in the HIE cooled group.[17–21] Other trials of whole-body or head-only cooling for neonatal encephalopathy showed beneficial outcomes of hypothermia at 18 to 24 months of age when compared with those not receiving TH.[10,22,23] A previous study that evaluated whole body cooled and noncooled infants showed that there was a correlation between the location of injury and the development of infantile spasms later in life.[24]

Currently, there are no defined MR biomarkers for developmental delay or intellectual impairment in later childhood for TH-treated survivors of HIE.[25] Our study determined that early anatomical injury patterns on MRI are associated with significant clinical factors and suggests that MRI is a feasible and reliable surrogate measure to predict long-term outcomes. In our study, the abnormal MRI group of infants with HIE with perinatal asphyxia had more clinical seizures with greater usage of additional AED. Numerous studies have shown that seizures occur frequently with HIE at presentation, during cooling, and with rewarming. During or immediately following hypothermia, electrographic and clinical seizures were noted in 30% to 90% of infants.[26–28] Therefore, continuous recording of aEEG has been shown to be useful beyond the first 6 hours of life. The

development of the sleep wake cycle (SWC) within 36 hours of birth in infants with HIE was reported to be associated with good neurodevelopmental outcomes.[29] Overall, the risk of poor outcome on long-term follow-up is reported to increase threefold with a history of seizures.[30] Perinatally, the incidence of fetal heart-rate deceleration was significantly more prevalent in the severe MRI group (97% vs 73%, $P = .003$). One clinical trial reported that TH-treated infants (n = 97) had a 71% incidence of fetal heart-rate deceleration[31]; our severe MRI group had a 97% incidence of fetal heart-rate deceleration.

In conclusion, at 18 to 24 months, more lesions in the basal ganglia and thalamus, posterior limb of internal capsule or severe white matter lesions were associated with abnormal ND outcomes at 18 to 24 months of age. This study has a few limitations. Several factors may have contributed to a potential selection bias in our review: first, this was a retrospective study design, which might be unable to fully confirm the examined relationships; second, we only had a relatively small sample size of the study group; third, many clinical conditions of the neonates may have comingled; and fourth, hidden disabilities may subsequently have become apparent, and many infants might have important developmental lags that were not classified as impairments. Despite these limitations, detecting abnormalities in the basal ganglia and thalamus and the posterior limb of the internal capsule in addition to clinical seizures and more use of AED can assist clinicians in predicting disabilities in infants in the future.

Further studies on the long-term outcome of infants with HIE are warranted to assess unreported milder disabilities in infants with perinatal asphyxia.

5. Conclusions

In our study, clinical seizures and increased use of AEDs were closely associated with abnormal brain MRI and poor long-term outcomes. As a pattern of injury, more lesions in the basal ganglia and thalamus, posterior limb of internal capsule, or severe white matter lesions were associated with abnormal neurodevelopmental outcomes at 18 to 24 months of age, which suggests that MRI can be a feasible and reliable surrogate measure predictive of long-term outcomes.

Author contributions

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Supervision: YoungAh Youn.
Writing – original draft: Yu-Mi Seo, YoungAh Youn.
Writing – review & editing: YoungAh Youn.

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