Neonatal hypoxic encephalopathy: Correlation between post-cooling brain MRI findings and 2 years neurodevelopmental outcome

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Abstract

Objective: This study aims to evaluate the magnetic resonance imaging (MRI) brain patterns among hypoxic-ischemic encephalopathy (HIE) babies who underwent post-cooling MRI brain as well as to correlate the post-cooling brain scoring with patient's neurodevelopmental outcome at 2 years. **Subjects and Methods:** It was a retrospective cross sectional study carried out at a tertiary university hospital. Record of patients diagnosed with neonatal HIE from 2007 until 2016 who completed 72 h of cooling therapy and had MRI brain within 2 weeks of life were included in this study. A new scoring system by Trivedi *et al.* that emphasizes on subcortical deep gray matter and posterior limb internal capsule injury were utilized upon MRI assessment, using TW, T2W, and diffusion-weighted imaging (DWI) sequences. Cumulative MRI brain score was obtained and graded as none, mild, moderate, and severe brain injury. The MRI brain scoring was then correlated with patient's 2 years neurodevelopmental outcome using Fisher's Exact Test. **Results:** A total of 23 patients were eligible of which 19 term neonates were included. 13% of these neonates (n = 3) had mild MRI brain injury grading with 52.2% (n = 12) moderate and 34.8% (n = 8) severe. There was no significant correlation seen between MRI brain grading and developmental outcome at 2 years old (P > 0.05). **Conclusion:** There was no significant correlation between neonatal MRI brain injury grading and 2 years neurodevelopmental outcome. Nevertheless, the new MRI brain scoring by Trivedi *et al.* is reproducible and comprehensive as it involves various important brain structures, assessed from different MRI sequences.

Key words: MRI brain scoring; neonatal hypoxic ischemic encephalopathy; post-cooling therapy

Introduction

Hypoxic-ischemic encephalopathy (HIE) is one of the leading causes of birth complications and acquired brain

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injury affecting full-term infant,[1] leading to long-term neurological sequela or death.[2] Magnetic Resonance Imaging (MRI) has become the preferred neuroimaging modality following HIE because of its sensitivity[3] that can be graded and related to neurodevelopmental outcome.[4]

The purpose of this study is to evaluate the correlation between the severity of MRI brain findings and the neurodevelopmental outcome among HIE babies in our institution. A new scoring system by Trivedi *et al.* was used for MRI brain evaluation and scoring.[5]

Subjects and Methods

Study population

This was a retrospective study conducted in a Radiology Department of a tertiary university hospital. Institutional review board approval was obtained for this cross-sectional retrospective study. Institution ethics committee approval was received on the 13th May 2016.

The patients' data were collected from the Neonatal Intensive Care Unit (NICU) records from 2007 to 2016. These neonates underwent cooling therapy with the core body temperature maintained at 33.5ºC and monitored by a rectal thermometer probe for 72 h after birth, when the diagnosis of HIE was made clinically. This is then followed by a re-warming phase for at least 4 h. After discharge, they were then followed up at 18–24 months to determine their developmental outcome; either (a) normal, or (b) adverse (died/cerebral palsy).

The inclusion criteria were (a) term and preterm babies which include babies more than 36 weeks, (b) MRI brain performed within 2 weeks after birth, (c) hypothermic therapy completed for 72 h, and (d) developmental outcome was assessed at 18 to 24 months. Cases with the incomplete sequence of the MRI images were excluded from the study.

MRI brain

The MRI was performed in our Radiology Department using 1.5 T (Avanto, Siemens, Erlangen Germany) MR scanners with 12-channel phased-array head coil. Patients had the MRI either with general anesthesia, sedation, or using feed and sleep technique. Images were obtained following HIE protocols, which include: T1, T2, and DWI sequences. T1-weighted spin-echo sequences (TR/TE, 205–730/4–16 ms), T2-weighted spin-echo sequences (TR/TE, 1553–5897/80–200 ms), and DWI sequences by using single-shot spin-echo echo-planar sequences (TR/TE, 5132–5000/74–68 ms with a b-value of 800–1000 s/min) were routinely obtained in the axial plane. Section thickness ranged from 4–7 mm with an intersection gap of 0.4–0.7 mm.

MRI brain scoring

One pediatric radiologist (Reader 1) and one radiology resident (Reader 2) scored the MRI studies independently. Both observers were blinded to all clinical data. The images were reviewed using the institution picture archiving system (PACS). Five regions of each cerebral hemisphere were evaluated and scored 0–3 according to Trivedi *et al.* for each of the sequences; T1W, T2W, and DWI. These regions were: (I) subcortical region, (a) globus pallidus, (b) caudate nucleus, (c) thalamus, and (d) posterior limb internal capsule; (II) white matter; (III) cortex; (IV) brainstem; and (V) cerebellum. The sum of the score was then determined the severity of the brain injury. Score of 0 was taken as normal while sum of 1–11 was graded as mild, 12–32 as moderate, and 33–138 as severe. This scoring system emphasizes on subcortical injury in the deep nuclear gray matter and posterior limb of the internal capsule.[5]

Patients' developmental outcomes at 2 years old were obtained from the medical record. The outcome was divided into normal developmental outcome versus adverse outcome; the latter includes cerebral palsy (CP) and death, which were stated by the clinicians in the medical record.

Statistical analysis

Statistical analysis was performed with the SPSS software package IBM version 23. Statistics were estimated for demographic data as means and standard deviations [SD]. An inter-reader correlation is considered significant when the *P* value is less than 0.050. Reader 1 MRI scoring and patient's outcome was then correlated using the Fisher's Exact test. A significant correlation was defined *as P-* value less than 0.05.

Results

Between 2007–2016, a total of 102 patients were diagnosed with HIE in our center. Unfortunately, therapeutic hypothermic cooling was only started in mid-2010. Therefore only 23 of 49 patients who underwent cooling therapy were eligible for this study, since 26 patients had to be excluded as MRI was performed after 2 weeks of postnatal period (n = 5) and there was no subsequent follow-up at 2 years of age (n = 21). Nineteen of them were term and four were preterm. The rest of the demographic data is presented in Table 1.

Reader I scored 3 mild, 12 moderate, and 8 severe HIE patients while reader 2 scored 3, 14, and 6 patients as mild, moderate, and severe HIE respectively. We also reviewed other associated findings in our neonatal cohort, which includes cephalohematoma or intracranial bleed. The summaries of the MRI findings are tabulated in Table 2.

All 3 patients with mild MRI brain grading had a normal developmental outcome. 12 patients had moderate MRI brain grading of which 8 were normal in terms of developmental outcome at 2 years of age and the rest (n = 4) had adverse outcome (death = 1, cerebral palsy = 3). 8 patients had

severe MRI brain grading whereby 50% (n = 4) suffered adverse outcome (death = 3, cerebral palsy = 1) and another 50% (n = 4) had normal developmental outcome at 2 years old [Table 3].

We present examples of severe HIE in term neonates with adverse and normal outcome respectively [Figures 1 and 2]. An additional image of an uncommon presentation of intraventricular hemorrhage in a term neonate is also included [Figure 3].

Table 1: Demographics of study population

	n (%)
Maturity	
Term	19 (82.6)
Preterm	4 (17.4)
Birth location	
Inborn	22 (95.7)
Outborn	1 (4.3)
Year of birth	
2010	1 (4.3)
2012	5 (21.7)
2013	5 (21.7)
2014	8 (34.8)
2015	2 (8.7)
2016	2 (8.7)
Delivery	
Vaginal	11 (47.8)
Cesarean section	12 (52.2)
Gender	
Male	11 (47.8)
Female	11 (47.8)
Ambiguous	1 (4.3)
Ethnic	
Malay	19 (82.6)
Chinese	3 (13.0)
Others	1 (4.3)
SARNAT score	
Mild	3 (13.0)
Moderate	16 (69.6)
Severe	4 (17.4)
Outcome	
Normal	15 (65.2)
CP	4 (17.4)
Died	4 (17.4)
Birth weight (g)	
Mean (SD)	2941.83 (493.43)
Cord blood pH	
Median (IQR)	6.99 (0.32)
APGAR score (1 min) Median (IQR)	2.0 (4.0)
APGAR score (5 mins) Median (IQR)	4.0 (4.0)

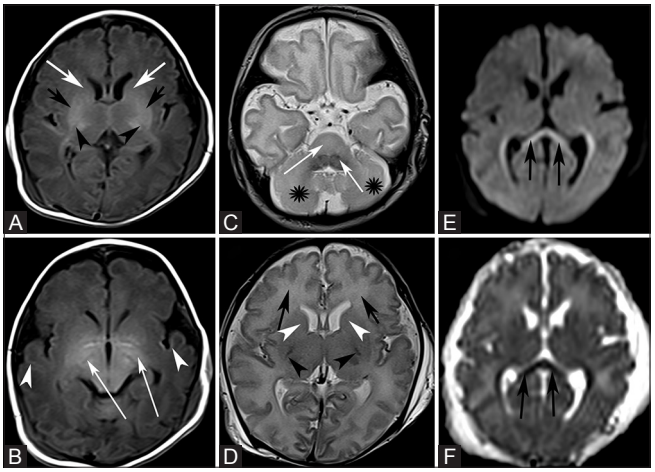

Figure 1 (A-F): This is a MRI brain of a term neonate who has been classified as moderate Sarnat clinically. T1W (A and B), T2W (C and D), DWI (E), ADC (F). (A and B) Absent myelination [black arrowheads] of the posterior limb of both internal capsules (PLIC), which is better depicted on T1WI (3 + 3). Abnormal signal demonstrated in the caudate nucleus (1 + 1) [white arrows], globus pallidus/putamen (3 + 3) [black arrows], thalamus (2 + 2) [white thin arrows] and cortex (1 + 1) [white arrowheads] on T1WI. Abnormal signal in brainstem (1 + 1) and white matter (1 + 1) (not shown). (C and D) On T2WI, there is presence of PLIC myelination (0 + 0) [black arrowheads]. Normal signal of caudate nucleus (0 + 0) [white arrowheads]. Also noted abnormal signal of globus pallidus/putamen (2 + 2) and thalamus (1 + 1) (not shown). Abnormal signal of brainstem (1 + 1) [white arrows], cerebellum (1 + 1) [white stars] and white matter (2 + 2) [black arrows] on T2WI. (E and F) Restricted diffusion noted at the corpus callosum on DWI and ADC (1 + 1) [black arrows]. Therefore, the total score is 40which is classified as severe HIE. The child has cerebral palsy at 2 years old

Table 2: MRI findings

MRI score	Mean score		Median score		No. of patients (%)	
	Reader 1	Reader 2	Reader 1	Reader 2	Reader 1	Reader 2
Total	33.91	28.17	26.00	20.00	23 (100)	23 (100)
Mild (1-11)	7.00	9.33	6.00	10.00	3 (13.0)	3 (13.0)
Moderate (12-32)	22.08	18.71	22.00	20.00	12 (52.2)	14 (60.9)
Severe (33-138)	61.75	59.67	49.00	50.00	8 (24.8)	6 (26.1)
Cephalohaematoma			No. (%)			
No			17 (73.9)			
Yes			6 (26.1)			
Intracranial Bleed						
No			16 (69.6)			
Subdural hemorrhage			3 (13.0)			
Intraventricular hemorhage			1 (4.3)			
Left parietal extradural, left parietal cortical hemorrhage			1 (4.3)			
Subarachnoid hemorrhage			1 (4.3)			
Severe petechial hemorrhage			1 (4.3)			

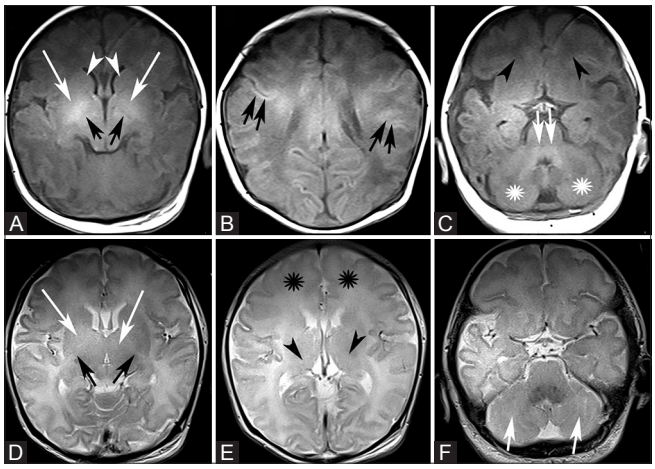

Figure 2 (A-F): This is an MRI brain of a term neonate who had been classified as moderate Sarnat clinically. T1W (A-C), T2W (D-F). (A-C) Absent myelination [black arrows] of PLIC, on T1WI (3 + 3). Normal caudate nucleus (0 + 0) [white arrowheads]. Abnormal signal in globus pallidus/putamen (3 + 3) [white arrows], thalamus (1 + 1) (not shown) and cortex (1 + 1) [double black arrows] on T1WI. Abnormal signal in brainstem (1 + 1) [double white arrow], cerebellum (1 + 1) [white stars] and white matter (1 + 1) [black arrowheads] on T1W1. (D-F) On T2WI there is also absence of PLIC myelination (3 + 3) [black arrows]. Normal signal of caudate nucleus (0 + 0). However abnormal signal of globus pallidus/putamen (3 + 3) [white arrows] and thalamus (2 + 2) [black arrowheads] on T2WI. Abnormal signal in cerebellum (1 + 1) [white arrows] and white matter (2 + 2) [black stars] on T2WI. No areas of restricted diffusion on DWI and ADC images (not shown). Therefore, the total score is 44 which is classified as severe HIE. The child, however, had normal developmental outcome at 2 years of age

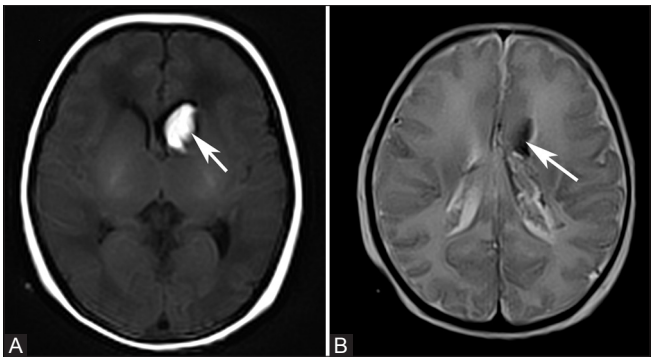

Figure 3 (A and B): MRI brain of a term neonate; day 5 of life, term baby at 38-week gestations was born via emergency low cesarean section for fetal distress and thick meconium-stained liquor had poor Apgar score at birth. There is focal T1 hyperintensity and T2 hypointensity within left lateral ventricle on T1WI (A) and T2WI (B) represents intraventricular hemorrhage [white arrow]. Child was investigated for venous sinus thrombosis and coagulopathy which were turned out to be negative

Table 3: Association between MRI reader 1 and outcome

	Outcome		Total ($n=23$)	P^a
	Adverse ($n=8$)	Normal ($n=15$)		
MRI score severity				
Mild HIE	0 (0.0)	3 (20.0)	3 (13.0)	0.350
Moderate HIE	4 (50.0)	8 (53.3)	12 (52.2)	
Severe HIE	4 (50.0)	4 (26.7)	8 (34.8)	

[a]Fisher's Exact Test

Interclass correlation coefficient

The two-way mixed intraclass correlation coefficient was used to determine the interclass correlation between readers 1 and 2 for MRI scoring. There were strong inter-reader correlations for single measures (ICC = 0.793, 95% CI = 0.577–0.906, $P < 0.001$) and average measures (ICC = 0.885, 95% CI = 0.732–0.951, $P < 0.001$) between both readers.

MRI brain grading and 2 years developmental outcome

The MRI brain scoring from Reader 1 was correlated with the 2 years outcome of these patients with a significant value taken as P value less than 0.05. According to Fisher's Exact Test, there was no significant association between reader 1's MRI score and outcome ($P = 0.350$) [Table 3].

Discussion

We validated the MRI brain assessment using the new scoring system by Trivedi *et al.*[5] emphasizing on subcortical injury in the deep nuclear gray matter and posterior limb of the internal capsule,.[6,7] All of the neonates with moderate and severe brain injury had predominant subcortical injury when assessed with Trivedi *et al.* scoring system. The deep nuclear gray matter and posterior limb of the internal capsule were strongly associated with poor developmental outcome as per well-documented by previous studies.[2,4,8] A most recent study published in 2018 concluded that the deep gray matter injury among infants treated with hypothermia is associated with adverse outcome in general and motor impairment. The authors also used modified scoring system utilizing T1, T2, and DWI sequences and concluded that the gray matter subscore can be used independently to predict the neurodevelopmental outcome at 2 years old.[9]

Miller *et al.* demonstrated that the clinical presentations and neurodevelopmental outcome of children with HIE correlates with the pattern of brain injury. The intensity of resuscitation at birth, the severity of encephalopathy, and the severity of seizures were associated more strongly with the basal ganglia/thalamus predominant pattern (all $P < 0.0001$), compared with watershed pattern.[4] Liauw *et al.* also reported that the presence of abnormal signal intensity in the basal ganglia and/or thalamus, or abnormal signal intensity on T1-weighted images in the posterior limb of the internal capsule are predictive of poor outcome.[8] Children with predominant basal ganglia/thalamus predominant pattern were associated with severely impaired motor and cognitive outcomes at 30 months of age, so do children with watershed predominant pattern of brain injury which initially does not show any cognitive impairment at 12 months but at later at 30 months of age.[2] In our study, there was no significant correlation between MRI grading and patient's 2 years developmental outcome (P value = 0.350). One of the reasons why we had such result could be due to the small sample

size, which primarily contributed by our strict inclusion criteria to obtain a homogenous sample population.

Van Handel *et al*. described that none of the children with mild HIE developed cerebral palsy, which was also seen in our study. The authors also showed that 23% to 82% of moderate HIE developed CP indicating a wide range of presentations.[10] In our study, 4 out of 12 patients with moderate MRI brain grading had an adverse outcome (CP/died) of which 3 had CP and 1 died [Figure 1]. A local study in 2010 reviewed the outcome of 72 h post-hypothermic cooling of which two out of 17 patients with severe HIE succumbed with their MRI/CT showed global ischemic changes.[11] Despite that, 4 patients with severe MRI brain grading in our study had a normal developmental outcome at 18–24 months. When we re-reviewed this subset group of patient we noticed that most of the abnormality was predominantly depicted by T2-weighted images whereas the DWI and T1 hyperintensity abnormalities are scanty. White matter injury, which is primarily detected by T2-weighted images are not associated with increased severity of the outcome. The previous study discussed that most of the cases with white matter injury alone would present with mild-to-moderate lesion that did not have significant cognitive impairment later in life.[9] An example of this scenario is described in Figure 2.

This study shows that there was a strong inter-reader correlation for single and average measures between the 2 readers with *P* value <0.001. This means that the objective assessment from the MRI scoring system proposed by Trivedi *et al.* is reproducible and reliable between readers of different levels of exposure and experience to pediatric neuroimaging review of HIE. This scoring system is easy to use, well-structured, and comprehensive as it covers all the different structures that need to be assessed in neonatal HIE MRI assessment. Furthermore, the fact that different sequence namely T1, T2, and DWI were taken into consideration for summation of the MRI score. Thus, this made the scoring system highly recommended for objective assessment, especially for research purpose based on our experience using this scoring system.

Although the exact pathophysiology of HIE is poorly understood, it is well-documented that a cascade of deleterious events leads to vascular autoregulation failure, reperfusion injury, eventual neuronal cell death, and diffuse brain injury in HIE.[12,13] In HIE, the nature of the injury is very much dependent on the degree of brain maturation and the severity of the hypotension. The blood supply to the brain differs with brain maturation. In the preterm brain, the arteries extend in a ventriculopetal configuration while in term infants, the blood supply is in a ventriculofugal pattern.[13] The most important areas of the deep gray matter of the brain are the thalami and the brainstem that are most metabolically active in the preterm brain. On the other hand, injury involving the lateral thalami, globus pallidus, posterior putamina, hippocampi, brainstem, and sensorimotor cortex is seen more in term infants.[13]

Therapeutic hypothermia is shown to improve survival with normal neurological function as well as reducing the rates of severe disability following HIE which include cerebral palsy, mental, and psychomotor developmental.[14] TOBY study was carried out from 2002–2006 to study the outcome of moderate whole-body hypothermia therapy which showed reduction in basal ganglia, thalami, white matter, and posterior limb of internal capsule lesions. Cooled infants are more likely to have normal brain MRI findings and fewer scans predictive of later neuromotor abnormalities[15] Another study showed that at 18 months of age, therapeutic hypothermia for HIE has shown to reduce death rates or severe disability.[2] However, death and disability continue to occur in 30%–70% of infants with moderate-to-severe encephalopathy despite treatment with cooling.[4]

It is well known that intraventricular hemorrhage (IVH) is commonly seen in premature neonates due to its premature brain autoregulation.[16] However, in our study, there was one (4.3%) term neonate with IVH. IVH itself is rare in term neonate and its correlation with HIE and hypothermic cooling therapy is not well documented. A study by Al Yazzidi *et al.* described that IVH in term neonates is usually associated with severe hypoxia that underwent therapeutic cooling therapy caused by fluctuating cerebral blood flow.[17] Our patient had moderate MRI brain grading and eventually demonstrated normal 2 years developmental outcome. Another study by Gorelik *et al.* showed that 7% of term infants developed IVH and it was more prevalent in those treated with hypothermic cooling therapy.[16]

Limitations

Our study is restricted to a few limitations due to the retrospective nature of the study. Firstly, it is subjected to potential bias. Secondly, the cooling therapy in our center was only started in mid- 2010. Therefore many patients had to be omitted from this study. Some patients had incomplete cooling due to hemodynamic instability and no MRI was performed since children were not stable to be sent to MRI suite. These patients were also excluded. The majority of patients with neonatal HIE defaulted or lost in follow-up in our institution. Therefore, no developmental assessment was carried out at 18–24 months even though they had completed cooling therapy and MRI brain within the desired time frame. Lastly, the neurodevelopmental assessment is not adequate since we only include general clinical assessment of either normal development, cerebral palsy, or death.

The best developmental assessment is using Bayleys Scales of Infant and Toddler developmental III (Bayley-III) score

to assess the cognitive, motor, and language domains in children with HIE at 18 to 24 months of age since the component of the development is broad and involves different type of assessment. The score of <85 were associated with adverse outcome while score of >85 was associated with good outcome in all 3 individual domains. The score was then correlated with the MRI brain grading.[5] This was a better neurodevelopmental assessment tool than what we used in this study. Unfortunately not all of our patients had this Bayley neurodevelopmental assessment and thus could not be used in this research. Patients that came for follow up were mainly assessed on their motor skills to determine whether they were normal or CP. Developmental and speech delay was not fully emphasized during this assessment. Hence this study showed that even though the MRI brain grading was high, some patients do have normal neurodevelopmental outcome.

Conclusion

In conclusion, we revealed that there is no correlation between the MRI grading and the patient's 2 years neurodevelopmental outcome due to several limitations as mentioned above. Further studies with larger number of patients should be carried out to further determine this correlation and better assessment. The MRI scoring tool established by Trivedi *et al.* is an objective measurement for assessment of MRI in neonatal HIE and shows strong interobserver correlation.

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Conflicts of interest

There are no conflicts of interest.

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