Semi-quantitative Assessment of Brain Maturation by Conventional Magnetic Resonance Imaging in Neonates with Clinically Mild Hypoxic-ischemic Encephalopathy

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Abstract

Background: Mild hypoxic-ischemic encephalopathy (HIE) injury is becoming the major type in neonatal brain diseases. The aim of this study was to assess brain maturation in mild HIE neonatal brains using total maturation score (TMS) based on conventional magnetic resonance imaging (MRI).

Methods: Totally, 45 neonates with clinically mild HIE and 45 matched control neonates were enrolled. Gestated age, birth weight, age after birth and postmenstrual age at magnetic resonance (MR) scan were homogenous in the two groups. According to MR findings, mild HIE neonates were divided into three subgroups: Pattern I, neonates with normal MR appearance; Pattern II, preterm neonates with abnormal MR appearance; Pattern III, full-term neonates with abnormal MR appearance. TMS and its parameters, progressive myelination (M), cortical infolding (C), involution of germinal matrix tissue (G), and glial cell migration bands (B), were employed to assess brain maturation and compare difference between HIE and control groups.

Results: The mean of TMS was significantly lower in mild HIE group than in the control group (mean ± standard deviation [SD] 11.62 ± 1.53 vs. 12.36 ± 1.26, \( P < 0.001 \)). In four parameters of TMS scores, the M and C scores were significantly lower in mild HIE group. Of the three patterns of mild HIE, Pattern I (10 cases) showed no significant difference of TMS compared with control neonates, while Pattern II (22 cases), III (13 cases) all had significantly decreased TMS than control neonates (mean ± SD 10.56 ± 0.93 vs. 11.48 ± 0.55, \( P < 0.05 \); 12.59 ± 1.28 vs. 13.25 ± 1.29, \( P < 0.05 \)). It was M, C, and GM scores that significantly decreased in Pattern II, while for Pattern III, only C score significantly decreased.

Conclusions: The TMS system, based on conventional MRI, is an effective method to detect delayed brain maturation in clinically mild HIE. The conventional MRI can reveal the different retardations in subtle structures and development processes among the different patterns of mild HIE.

Key words: Brain Maturation; Hypoxic-ischemic Encephalopathy; Magnetic Resonance Imaging; Neonates

Introduction

Neonatal hypoxic-ischemic encephalopathy (HIE) remains a major cause of neurodevelopmental impairment. Recent advances in neonatal care have markedly improved the survival rate and reduced the incidence of serious HIE, whereas mild HIE is becoming the dominant form in neonatal brain injuries. Mild HIE, mainly caused by partial and prolonged hypoxia, can lead to not only white matter (WM) injuries but also accompanied cortical gray matter (GM) degeneration,¹² which might bring a serious threat to brain development in this critical period. Assessing brain maturation of neonates suffered with mild HIE might be helpful in providing important prognostic information and facilitating the future study of human brain development in these neonates.

In the past few years, magnetic resonance imaging (MRI) has expanded its diagnostic capability in evaluating neonatal brain development, and conventional T1-and T2-weighted images (T1WIs and T2WIs), as the most widely used and easily implemented MRI approach, could reveal subtle morphological changes in brain maturation. So far, only limited studies focused on the quantitative evaluation of brain maturation using conventional MRI. The total maturation score (TMS) based on the graded assessment of the four parameters including cortical infolding (C), myelination (M), germinal matrix tissue (G), and glial cell migration bands (B), has been validated to be a simple...
and reproductive method for quantifying neonatal brain maturation on conventional MRI. However, TMS used in the assessment of brain maturation impacting by a variety of disorders, such as HIE, still remain to be proved. Therefore, the objective of this study was to contrastively evaluate brain maturation in mild HIE and normal neonates by using TMS to explore whether mild HIE is associated with a structural delay in brain development.

Methods

Subjects

This retrospective study was approved by the local Institutional Review Board and informed parental consent was obtained for each participating neonate. 402 neonates who underwent conventional MRI within 14 days after birth from December 2010 to December 2012 were consecutively recruited and studied. The neonates’ medical records, including pertinent demographic, clinical, laboratory were reviewed by an experienced neonatal neurologist. Inclusion criteria for neonates with mild HIE group were according to the National Institute of Child Health and Human Development Neonatal Research Network study, which has been demonstrated to be also applicable to preterm infants. The criteria consisted of: (1) A pH ≤7.0 or a base deficit ≥16 mmol/L on umbilical cord blood or any postnatal blood sample within 1 h of age; or history of an acute perinatal event and either no blood gas available, or a pH from 7.01 to 7.15 or a base deficit from 10 to 15.9 mmol/L, with a 10 min Apgar score ≤5, or assisted ventilation initiated at birth and continued for at least 10 min; (2) when above criteria fulfilled, mild (stage I) HIE was then determined by the modified Sarnat staging according to the level of consciousness, spontaneous activity, posture, tone, primitive reflexes, and autonomic nervous system signs within 6 h of age. The neonates who matched gestational age (GA), ages at magnetic resonance (MR) scan, postmenstrual age (PMA), sex and birth weight with each mild HIE neonate, without a history of perinatal asphyxia or other episodes that might lead to cerebral damage, and without symptoms of HIE were enrolled in control group. Neonates who were confirmed or suspected to have intraventricular infection or trauma, cardiac or central nervous system malformation, inborn metabolic error, chromosomal abnormality or hydrocephalus were excluded from this study. 45 mild HIE neonates and 45 matched control neonates were finally enrolled in this study. No MRI data were lost owing to technical problems, and the image quality was also well enough for further analysis.

Magnetic resonance imaging analysis

All neonatal MRI were independently reviewed by two pediatric radiologists who were blinded to the clinical data. Disagreements regarding image findings were resolved by means of discussion and mutual agreement. Injuries in WM, basal-ganglia and thalamus, posterior limb of the internal capsule (PLIC), cortex, brainstem, cerebellum, and hemorrhage were all evaluated and graded according to previous studies. According to MR findings and GA, mild HIE neonates enrolled in this study were grouped into three patterns: Pattern I, neonates with normal MR appearance; Pattern II, preterm neonates (GA <36 weeks) with abnormal MR appearance; Pattern III, full-term neonates (GA ≥36 weeks) with abnormal MR appearance. The flow chart for subjects’ selection and grouping was shown in Figure 1.

Neonatal brain maturation was semi-quantitatively assessed using the TMS based on conventional T1WIs and T2WIs. The TMS, a previously validated scoring system established by Childs et al., included two phenomena undergoing progressive maturation (M and C) and two structures...
undergoing progressive involution (G and B). A single score was determined for each of the four parameters (value ranges 1–7 for M, 1–6 for C, 1–4 for G, and 1–4 for B) and the TMS was then calculated as the sum of the four different scores [Table 1]. M and G scores were derived from assessment of the entire axial T1WIs and T2WIs while C and B scores were obtained from the evaluation of the T1WIs and T2WIs closest to the foramen of Monro. M was scored separately in T1WIs and T2WIs, and then an average value was recorded. The above-mentioned two pediatric radiologists, who were blind to the clinical history, calculated the TMS in each neonate independently, and the inter-observer agreement was assessed. The mean values of the two scores were calculated and used for further statistical analysis.

Statistical analysis
The statistical analyses were performed using SPSS for Windows version 17.0 (SPSS Inc., Chicago, IL, USA). P < 0.05 indicated statistical significance, and all analyses were two-tailed. The following analyses were performed: (1) Bland–Altman analysis was used to evaluate the agreement of TMS between the two observers; (2) linear correlation analysis was applied to show the distribution of the TMS score according to PMA in mild HIE and control group separately, and the power of the linear correlation coefficients (R) was classified as follows: R = 0.01–0.2: Negligible, R = 0.2–0.4: Weak, R = 0.4–0.7: Moderate, and R >0.7: Strong;[9] (3) paired-sample t-tests were used to determine the difference of TMS score between two groups, and Wilcoxon matched-pairs signed-ranks test were used to test the differences of four separate sub scores of TMS; for comparison of each pattern of mild HIE with control neonates, these tests were also performed separately.

Results
Study population
The detailed demographic data of enrolled subjects are shown in Table 2. The 45 mild HIE neonates included 28 boys and 17 girls, 24 preterm and 21 full term (median GA 36 + 1-week, range from 33 to 41 weeks; median PMA 37 + 1, range from 34 to 41 weeks). 10 (22%), 22 (49%) and 13 (29%) neonates of mild HIE group were grouped into Pattern I, II and III subgroups, respectively. The mild HIE and matched control groups were homogeneous in terms of GA, birth weight, ages at MR scan and PMA at MR scan (P > 0.05).

Figure 2 exhibits the representative T1WIs and T2WIs of three patterns of mild HIE group. For mild HIE neonates with overt brain injuries (Pattern II and III group), except WM injuries, no abnormities in basal-ganglia/thalamus, cortex, PLIC, and brainstem or hemorrhage was found. According to the WM grading,[7,8] there were 13 and 9 cases in Pattern II

### Table 1: Scoring system to assess four parameters of brain maturation in neonates[3]

| Parameter                  | Score | Definition                                                                 |
|----------------------------|-------|-----------------------------------------------------------------------------|
| Myelination (M)            | M1    | Myelination evident in brainstem, cerebellar peduncle, inferior colliculus, cerebellar vermis |
|                            | M2    | + Subthalamic nuclei, globus pallidus, ventrolateral thalamus               |
|                            | M3    | + Caudal portion of the PLIC                                               |
|                            | M4    | + Complete PLIC                                                            |
|                            | M5    | + Optic radiation                                                          |
|                            | M6    | + Corona radiata                                                          |
|                            | M7    | + Anterior limb of the internal capsule                                    |
| Cortical infolding (C)     | C1    | Frontal and occipital cortex completely smooth, insula wide open; thin bright cortical rim on T1WIs, generally low-intensity WM on T1WIs |
|                            | C2    | Frontal cortex still very smooth, some sulci evident in the occipital cortex; insula still wide with almost smooth internal surface; WM low intensity on T1WIs |
|                            | C3    | Frontal and occipital cortex similar number of convolutions; frontal sulci still quite shallow; internal surface of insula more convoluted; WM still somewhat low intensity on T1WIs |
|                            | C4    | Frontal and occipital cortex folded and rich in sulci; frontal sulci obvious along the interhemispheric fissure; occipital WM separated into strands by deeper sulci; insula more convoluted and infolded; WM still slightly low intensity on T1WIs |
|                            | C5    | Frontal and occipital WM separated into strands by deeper sulci; insula completely infolded; WM still distinguishable from gray matter on T1WIs |
| Germinal matrix (G)        | G1    | Matrix seen in the posterior horn, at CTN and anterior horns of lateral ventricles |
|                            | G2    | Matrix evident at CTN and anterior horns only                               |
|                            | G3    | Matrix at anterior horns alone                                              |
|                            | G4    | No matrix evident                                                          |
| Bands of migrating glial cells (B) | B1 | Broadband with additional narrower bands                                   |
|                            | B2    | Broadband alone                                                            |
|                            | B3    | Narrow band alone                                                          |
|                            | B4    | No bands seen                                                              |

PLIC: Posterior limb of the internal capsule; WM: White matter; CTN: Caudothalamic notch; T1WIs: T1-weighted images.
group, 11 and 2 cases in Pattern III group presented moderate and severe WM injuries, respectively. For control group, no MRI abnormalities were found in any neonates.

Inter-observer agreement of total maturation score
The Bland–Altman plot derived from TMS of all 90 neonates showed excellent agreement between the two independent observers (Figure 3): The mean difference in score was −0.31 (standard deviation [SD] = 0.82), and 95% limits of agreement were from −1.91 to 1.30.

Correlation between total maturation score and postmenstrual age
Linear positive correlation was demonstrated between TMS and PMA in both control group ($r = 0.83$, $P < 0.001$) [Figure 4a] and mild HIE group ($r = 0.81$, $P < 0.001$) [Figure 4b]. These strong correlations between TMS and PMA in control and mild HIE neonates confirmed the reproducibility of TMS in assessing brain maturation.

Comparison of total maturation score in mild hypoxic-ischemic encephalopathy and control group
Table 3 summarizes the detailed data of comparison of TMS between mild HIE and control neonates. The mean of TMS was significantly lower in mild HIE group than in the control group (mean ± SD, 11.62 ± 1.53 vs. 12.36 ± 1.26, $P < 0.001$). In four parameters of TMS, the M and C scores in mild HIE group were significantly lower than them in control group (M score: Median/range 3.0/2.0–3.5 vs. 3.0/2.0–3.5, $P < 0.001$; C score: Median/range 4.0/2.5–5.0 vs. 4.0/2.5–5.0, $P < 0.001$). No statistically significant differences were observed in G and B between the two groups.

With regard to three subgroups of mild HIE, the mean of TMS showed significant decrease in Pattern II (mean ± SD
However, \(\frac{3.0/1.5-3.5}{3.0/2.5-3.5} \times \frac{3.0/1.5-4.0}{3.0/2.5-4.0} \times \frac{3.0/2.0-4.0}{3.0/3.0-4.0}\) Total mild HIE/control (4.5/3.5-5.0)/(5.0/3.5-5.0)

[14-16]

\(\frac{2.5/2.0-3.0}{3.0/2.0-3.0} \times \frac{3.25/3.0-3.5}{3.25/3.0-3.5} \times \frac{4.0/2.0-5.0}{4.0/2.5-5.0}\) 10.56 ± 0.93/11.48 ± 0.55

[23]

12.70 ± 1.36/13.12 ± 1.06

[24-26]

\(\frac{3.5/2.5-3.5}{3.5/3.5-4.0} \times \frac{4.0/3.5-5.0}{5.0/4.0-5.0}\) Our results show the brain maturation in studies, cortical GM volume was reduced in babies with HIE compared to control. According to Inder and Marin–Padilla's evolution process, seems also to be delayed due to mild CORTICAL INFOLDING, another parameter standing for cerebral WM injury. As the major locations of HIE injuries, nevertheless, the migrating of oligodendrocyte precursor cells is affected, which might lead to the delayed myelination in distant WM. Cortical infolding, another parameter standing for cerebral evolution process, seems also to be delayed due to mild HIE in our study. According to Inder and Marin–Padilla's studies, cortical GM volume was reduced in babies with periventricular WM injury, and the morphology and organization of neurons in the cerebral cortex overlying areas of periventricular leukomalacia were also altered.[12,17] They considered that the hypoxic-ischemic injury impaired neuronal differentiation and migration. Another possible explanation is the “tension-based theory” proposed by Van Essen.[19] In this theory, the process of cortical infolding needs the tension along axons in the WM. So WM injury might impair the tension-based morphogenesis and decrease
cortical infolding.

A further analysis in three MR patterns of mild HIE in this study indicates different effects in neonatal brain development. Mild HIE without any abnormalities on MRI is quite common phenomenon in clinic, and this pattern accounts for nearly a quarter in this study. It is widely accepted that Pattern I is a sign of favorable prognosis.[19-22] Our results show the brain maturation in this population seems to be the same as control neonates, which confirms this point from the view of morphology. While for both preterm (Pattern II) and full term (Pattern III) mild HIE neonates with obvious brain injuries on MRI, the decreased TMS all suggests a negative effect in their brain maturation. However, full-term neonates suffered mild HIE only show decreased C score than control neonates, which suggests only a disturbance in cortical development, while for preterm neonates, besides C score, M and G score are also decreased, which means more severe impediment. These different changes might be related with different vascular supply to the brains with brain maturation. In the immature brain, ventriculopetal penetrating arteries extend inward from the surface of the brain to supply the periventricular regions; hence, periventricular border zone, where also the germinal matrix locates, is more vulnerable in hypoperfusion injury.[23] The germinal matrix is the origin sites of migrating cortical neurons and glial cells, and they should gradually involute and become less obvious on conventional MRI after 30 weeks.[24-26] However, when the immature oligodendroglia cell injured due to hypoxic-ischemic injuries, germinal matrix might maintain their function of proliferation and vanish later than normal involution. Thus, the C, M and G process all might be delayed in preterm neonates with mild HIE. With maturation of the brain, vessels extend into the brain from the lateral ventricles, and the intervascular border zone

**Table 3: TMS and four parameters in control and mild HIE groups**

| Items                  | Total mild HIE/control (n = 45) | Pattern I/control (n = 10) | Pattern II/control (n = 22) | Pattern III/control (n = 13) |
|------------------------|--------------------------------|---------------------------|---------------------------|-----------------------------|
| TMS (mean ± SD)        | 11.62 ± 1.53/12.36 ± 1.26*     | 12.70 ± 1.36/13.12 ± 1.06  | 10.56 ± 0.93/11.48 ± 0.55* | 12.59 ± 1.28/13.25 ± 1.29*  |
| Myelination (M)        | (3.0/2.0-3.5)/(3.0/2.0-3.5)*   | (3.5/2.5-3.5)/(3.5/3.0-3.5) | (2.5/2.0-3.0)/(3.0/2.0-3.0)* | (3.25/3.0-3.5)/(3.25/3.0-3.5) |
| Cortical infolding (C) | (4.0/2.0-5.0)/(4.0/2.5-5.0)*   | (4.5/3.5-5.0)/(5.0/3.5-5.0) | (3.0/2.0-4.0)/(3.0/2.5-4.0)* | (4.0/3.5-5.0)/(5.0/4.0-5.0)* |
| Germinial matrix (G)   | (3.0/1.5-4.0)/(3.0/2.5-4.0)    | (3.0/2.0-4.0)/(3.0/2.5-4.0) | (3.0/1.5-3.5)/(3.0/2.5-3.5)* | (3.0/2.5-4.0)/(3.0/3.0-4.0) |
| Bands of migrating glial cells (B) | (2.0/1.0-4.0)/(2.0/1.5-4.0) | (2.0/1.5-2.5)/(2.0/1.5-2.5) | (2.0/1.5-3.0)/(2.0/1.5-2.5) | (2.0/1.0-4.0)/(2.0/2.0-4.0) |

*P<0.05; †P<0.001. HIE: Hypoxic-ischemic encephalopathy; SD: Standard deviation; TMS: Total maturation score.

**Figure 4:** Scatter graphs showing the distribution of total maturation score according to postmenstrual age in the control group: (a) and mild hypoxic-ischemic encephalopathy group; (b) The linear correlation coefficients (r).

10.56 ± 0.93 vs. 11.48 ± 0.55, \(P < 0.05\) and Pattern III (12.59 ± 1.28 vs. 13.25 ± 1.29, \(P < 0.05\) but no significant increase or decrease in Pattern I (12.70 ± 1.36 vs. 13.12 ± 1.06, \(P > 0.05\)). Further analysis of the four parameters revealed that M, C, and GM score was significantly lower in Pattern II, while only C score was significantly lower in Pattern III.

**DISCUSSION**

In this study, the significantly decreased TMS in mild HIE group demonstrates the retarded brain maturation as a result of hypoxia-ischemia. Of the four parameters of TMS, myelination and cortical infolding show more obvious retardation. Myelination, as an important evolution process, can be identified by conventional MRI from 26 weeks of GA and the peaks of gliocyte proliferation and myelin sheath forming have been proved during the perinatal period.[10-13] Since the preoligodendrocytes are vulnerable to oxidative and excitotoxic injuries as a result of the hypoxia,[14-16] the process of myelination in mild HIE group is likely to be disturbed in this critical period. Although the regions of myelination assessed in TMS are not exactly the same as the major locations of HIE injuries, nevertheless, the migrating of oligodendrocyte precursor cells is affected, which might lead to the delayed myelination in distant WM. Cortical infolding, another parameter standing for cerebral evolution process, seems also to be delayed due to mild HIE in our study. According to Inder and Marin–Padilla’s studies, cortical GM volume was reduced in babies with periventricular WM injury, and the morphology and organization of neurons in the cerebral cortex overlying areas of periventricular leukomalacia were also altered.[12,17]
moves peripherally to subcortical WM and parasagittal cortical regions,[21] which might explain the only cortical infolding delay in full term neonates with HIE.

The TMS used in this study is demonstrated to be a validated and reproducible approach in quantitatively and noninvasively assessing brain development and maturation in neonates with mild HIE. As far as we known, the TMS is also available in evaluating brain maturation of neonates with a variety of diseases or under pathological states, such as congenital heart defects, severe congenital diaphragmatic hernia, extremely low birth weight, and intrauterine growth restriction,[27-30] which suggested that the TMS system was an effective method to evaluate brain development in neonatal period under both physiological and pathological conditions. Recently, based on TMS, Vossough et al. even preliminarily set up a fetal TMS on conventional MRI for clinical fetal MRI assessment and interpretation.[31] Therefore, there is only a vacancy of a standardized scale for the development stage beyond neonatal period, which should be established to make up for the noninvasive imaging methods to comprehensively depict human brain development in vivo.

This study has several limitations. First, there were no follow-up data for all enrolled neonates. Further studies are needed in these HIE neonates in order to assess whether the delay in morphological changes on MR will be associated with long-term abnormalities. Second, the problem of an ideal and physiological control group population is still far to be solved since the state for each neonate is complex and difficult to match. Third, although previous study preliminarily proved that the criterion of mild HIE for full-term neonates was also applicable in preterm neonates, the accuracy for diagnosis and grading of HIE in this population has not be validated by more specific further researches. Therefore, the misdiagnoses and missed diagnoses for mild HIE in preterm neonates also cannot be ruled out completely in this study.

**Conclusion**

This study demonstrated delayed brain maturation in neonates who suffered from mild HIE using TMS. The myelination and cortical infolding are more obvious retardation. The conclusion is that the TMS system was an effective method to evaluate brain development in neonatal period.

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