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Original Article

Predictors of neurodevelopmental outcomes at 12 months in term newborns with hypoxic ischemic encephalopathy

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Abstract: The aim of this study was to evaluate the validity of different predictors and establish an effective prediction of the prognosis of hypoxic ischemic encephalopathy (HIE). The general information, cerebral computed tomography (CT) imaging, Apgar scores, and NBNA score were collected from 42 term newborn infants with HIE and 80 normal infants. The Bayley Scale of Infant Development was used to evaluate the levels of mental, motor and behavior of infants. The mental developmental index (MDI) and behavioral rating of normal infants were significantly higher than those of HIE group ($P<0.05$), while such differences were not noted in psychomotor developmental index (PDI). Significant correlations were found between MDI and PDI scores and some items of the behavioral rating. The HIE infants with severe CT degree were associated with markedly lower PDIs when compared with the normal infants and the infants with mild CT degree ($P<0.05$). For the NBNA scores, significant differences of MDI were noted both in the case and control groups ($P<0.01$). HIE significantly influenced the progression of mental, psychomotor and behavioral in infants. Cranial CT could be considered as a reliable index for helping to establish the prognosis of HIE.

Keywords: Hypoxic-ischemic encephalopathy, cognitive-behavioral development, Bayley scales, prognosis prediction, computed tomography

Introduction

Hypoxic-ischemic encephalopathy (HIE) is a severe complication of perinatal asphyxia with serious illness condition and high mortality, which may result in long-term neurological deficits and remains a leading cause of brain injuries of term infants [8]. It is reported that hypoxic-ischemic occurs in 2-6 per 1000 full-term infants [4]. Of all hospitalized neonates in China, HIE infants accounted for 18.4% [26]. Severe injured infants will have lifetime disabilities and neurodevelopmental delays, which will undoubtedly give families a huge mental stress and financial burden, for further cause a negative influence on improving population quality of the whole society.

Infancy is a period of the booming development of brain, with the fastest neurodevelopmental speed, the most powerful compensation and plasticity [12]. The crucial period of brain development equals to the crucial period of intellectual development; moreover, it is the most sensitive period of getting injured, especially brain injuries [18]. Thus, the intellectual development level of infancy is of critical importance to the intellectual level and social competence of childhood, adolescence, or even the whole adulthood. The follow-up to children with moderate or serve HIE demonstrated that the sequelae of HIE, which universally appeared in the neonatal period, were almost invariably been detected by some parents until the 4 to 6 months of age, or even one year [10]. Therefore, it is of essential significance to detect HIE in early stage and accurately establish the prognosis.

To date, a number of clinical neurologic examinations and tests had been used to establish the prognosis of HIE, such as Apgar Index, NABA

Index, cranial computed tomography (CT), electroencephalography (EEG) and magnetic resonance imaging (MRI) [1, 15, 29]. However, the validity of these methods and tests varies, and some of them still remain to be evaluated. It has been reported that EEG and MRI are limited tools particularly in cases of moderate severity [20]. Also, Apgar scores at 1 and 5 min is of limited use in terms of establishing neurologic injury [2]. In addition, the efficacy of these predictive factors varies substantially among different ethnicities [23]. Most previous researches were specific to Europeans and Americans, but the studies in Asian especially in China still remains limited. Consequently, it is of great importance to establish effective markers that can provide guidance in predicting prognosis of HIE in order to improve the living quality of HIE infants.

In the present study, we evaluated the validity of different predictors and established an effective prediction of the prognosis by comparing the effects of these different clinical neurologic examinations or tests on the prognosis of HIE.

Materials and methods

Subjects

Single birth term infants who were diagnosed with HIE, with gestational ages between 37 and 40 weeks and weight between 2500 g and 4000 g, delivered at the Department of Pediatrics, the First Affiliated Hospital of Xi'an Jiaotong University was recruited as case group. The diagnosis and severity of HIE were assessed clinically according to the standard set by American College of Obstetricians and Gynecologists and American Academy of Pediatrics [14, 27]. The severity of infants with HIE was classified as 1) mild degree: the clinical symptom disappeared in 72 hours and had good prognosis; 2) moderate degree: The clinical symptom disappeared in 14 days while the sequelae might exist; 3) severe degree: The symptom might last for weeks, with the high mortality and severe sequelae of most survivors.

The exclusion criteria included: (1) infants were also with other coexisting significant comorbidity (congenital disease, genetic syndrome, metabolic and/or endocrinologic disease) during the period from birth to 1 year old, or with poor physique growth and malnutrition; (2) infants had a history of familial or hereditary disease; (3) the pregnant age of mothers were not in the range of 24 to 35; (4) mothers were not healthy in gestation period, or existed pregnancy complication; and (5) parents or one of them had a history of nervous system disease (e.g., hypophrenia and convulsions), psychiatric disease and unstable endocrine disease.

The healthy newborns at birth in the Obstetrical Department of the hospital meantime were enrolled in our study as the control group. The inclusion and exclusion criteria of this group were all the same as the case group, except without HIE.

All parents of the infants provided written informed consent prior to participation in the study, and the study protocol was approved by the medical ethics committee of Xi'an Jiaotong University.

Study design and outcome predication

After enrollment, a detailed anthropometric examination was conducted on all infants, including height, birth weight, head circumference, arm circumference, number of teeth. In the meantime, the demographics and socioeconomic data of parents of infants were recorded, including age of parents, maternal education level, occupation, number of family members, lifestyle, income and marital status. Cerebral CT imaging within the first week of birth, 1 min and 5 min Apgar scores, and NBNA score at the 14^{th} day after birth were recorded. Besides, the levels of mental, motor and behavioral rating of infants were also evaluated. All of the infants were evaluated at 12 months old as follow-up visits.

The levels of mental, motor and behavior of infants were evaluated using the Bayley Scale of Infant Development (BSID) [5]. The BSID is presently the gold standard test for assessing neurodevelopmental delay in high-risk infants up to the age of 42 months [17]. It includes a Mental Developmental Index (MDI) that assesses the child's level of cognitive, language and personal-social skills, a psychomotor developmental index (PDI) that evaluates fine and gross motor development, a behavioral rating score that evaluates the behavioral level of infants.

Table 1. Demographic characteristics in infants with HIE and controls

Variable	Study group		*P* value*
	Controls (n=80)	HIE infants (n=42)	
Sex, n (% female)	32.0 (40.0)	16.0 (38.1)	0.69
Gestational age (weeks), mean ± SD	39.3±1.4	38.9±1.7	0.72
Birth weight (Kg), mean ± SD	3.4±0.5	3.2±1.3	0.58
Mother's education level, n (%)			
High school or below	38.0 (47.5)	20.0 (47.6)	0.99
Above high school	42.0 (52.5)	22.0 (52.4)	
Father's education level, n (%)			
High school or below	19.0 (23.8)	13.0 (31.0)	0.39
Above high school	61.0 (76.2)	29.0 (69.0)	
Average monthly income (yuan), n (%)			
>5000	18.0 (22.5)	8.0 (19.1)	0.86
1000-5000	35.0 (43.8)	18.0 (42.9)	
<1000	27.0 (33.7)	16.0 (38.0)	
Antenatal education, n (% yes)	39.0 (48.8)	17.0 (40.5)	0.38

Abbreviations: HIE, Hypoxic-ischemic encephalopathy; MDI, mental developmental index; PDI, psychomotor developmental index; SD, standard deviation. **P* values for the difference in HIE and control group derived from T test for continuous variables or the chi-square test for categorical variables.

During the assessment, children were in good mental status, completely conscious and kept quiet in the whole process. Assessments were performed in the order of intelligence scale, psychomotor scale, and then behavioral rating scale. The assessment universally took about 45 to 90 minutes. All tests were performed by the same designated board-certified neonatologist. Diagnosis of excellent development was defined as a mental developmental index (MDI) or psychomotor developmental index (PDI) score of ≥120, moderate development was defined as MDI or PDI score of 80 to 119, and low development as <79. Items of Behavioral rating scale were used to record the personality characteristics of infants. Scores were assigned from 1 to 5 for each item.

The NBNA were measured at the 14th day after birth of infants. The NBNA contains 20 items, and the total score is 40. The score of ≥35 is defined as normal, the score of <35 is defined as abnormal [29].

The cranial CT finding of the infants with HIE was classified as 3 degrees according to the distribution range of the white matter low density: 1) mild degree: sporadic low-density areas distributed in 2 lobes; 2) moderate degree: The low-density areas could be found in more than 2 lobes, and the gray matter (GM)/white matter (WM) differentiation was not evident; 3) severe degree: Diffuse low-density areas were found with the disappeared boundaries of the GM and WM, while basal ganglia and epencephalon showed in a normal density. The moderate degree and severe degree were generally complicated with subarachnoid hemorrhage, intraventricular hemorrhage and intracerebral hemorrhage.

Statistical analysis

Continuous variables were expressed as mean and standard deviation. Test of normality was explored by Shapiro-Wilk test. T tests was used to compare the difference on the general information, the demographics (sex, gestational age, birth weight) and socioeconomic data (mother's education level, father's education level, average monthly income, antenatal education), the levels of mental, motor and behavior of infants. Categorical variables, such as clinical grading and CT degree, were reported as percentages and compared by the chi-square test. Pearson correlation or Spearman correlation analysis was performed to assess relationships between MDI, PDI and behavioral rating. In addition, the statistical significances in MDI and PDI between different groups were evaluated by analysis variance (ANOVA); and least significant difference (LSD) adjustment was applied within analyses to account for multiple comparisons. All statistical analyses were conducted using SPSS version 13.0., and a *P* value of less than 0.05 was regarded as statistically significant.

Results

Participant characteristics

42 infants with HIE and 80 normal infants were enrolled in this study. The demographic and clinical characteristics of them were shown in **Table 1**. Of the HIE group, 22 infants (52.38%)

Table 2. Comparison of MDI, PDI and the behavioral rating in infants with HIE and controls after 12 months follow-up

Variable	Study group		*P* value*
	Controls (n=80)	HIE infants (n=42)	
MDI, mean ± SD	109.8±12.5	101.1±19.7	0.01
≥120, n (%)	34.0 (42.5)	9.0 (21.4)	0.01
80-120, n (%)	46.0 (57.5)	30.0 (71.4)	
≤79, n (%)	0.0 (0.0)	3.0 (7.1)	
PDI, mean ± SD	104.4±15.9	102.8±17.8	0.45
≥120, n (%)	12.0 (15.0)	5.0 (11.9)	0.85
80-120, n (%)	62.0 (77.5)	33.0 (78.6)	
≤79, n (%)	6.0 (7.5)	4.0 (9.5)	
The behavioral rating, mean ± SD			
Social orientation	11.4±1.2	10.9±1.3	0.67
Reactivity	4.7±1.0	4.2±1.4	0.03
Cooperation	3.8±1.0	3.3±1.6	0.42
Nervous/Fear	4.8±1.9	4.8±2.3	0.88
The tendency of search	4.7±1.3	4.5±1.7	0.79
Interest to the outside world	32.6±4.4	30.1±5.2	0.04
Goal orientation	4.7±1.0	4.3±1.3	0.02
Attention	4.5±1.1	3.9±2.4	0.01
Persistence	4.6±1.4	4.1±2.5	0.14
Activity	4.9±1.8	4.7±2.2	0.76

Abbreviations: HIE, Hypoxic-ischemic encephalopathy; MDI, mental developmental index; PDI, psychomotor developmental index; SD, standard deviation. *T test for continuous variables or the chi-square test for categorical variables was conducted to calculate *P* values for between-group difference.

Table 3. The correlation analysis of MDI and PDI with behavioral rating

The behavioral rating	MDI		PDI	
	Controls (n=80)	HIE infants (n=42)	Controls (n=80)	HIE infants (n=42)
Social orientation	0.20	0.19	0.15	0.11
Reactivity	0.23*	0.34*	0.19	0.17
Cooperation	0.29*	0.17	0.17	0.30*
Nervous/Fear	-0.11	-0.12	-0.12	-0.09
The tendency of search	0.13	0.14	0.13	0.14
Interest to the outside world	0.25*	0.28*	0.28*	0.16
Goal orientation	0.26*	0.30*	0.26*	0.29*
Attention	0.28*	0.17	0.16	0.18
Persistence	0.29*	0.16	0.25*	0.15
Activity	0.12	0.15	0.29*	0.30*

Abbreviations: HIE, Hypoxic-ischemic encephalopathy; MDI, mental developmental index; PDI, psychomotor developmental index; SD, standard deviation. Pearson correlation analysis was performed to assess relationships between MDI, PDI and behavioral rating. *Statistical significance, *P*<0.05.

were diagnosed as mild HIE, while 13 (30.95%) and 7 (16.7%) were moderate HIE and severe HIE. There were no significant differences of gestational age, weight, height, head circumference at birth between two groups (*P*>0.05).

The level of mental, psychomotor and behavior during the follow-up

After 12-month follow-up, the MDI standard score of the HIE group was 101.06±19.68, while the control group was 109.83±12.52 (**Table 2**). There were statistically significant differences between these two groups (*P*<0.05). All control subjects had a MDI score of greater than 79, with 34 of them showing excellent mental development. The proportion of the HIE group with excellent mental development was noted significantly lower than that of the control group (42.5% vs. 21.4%, *P*<0.05).

Moreover, 3 (7.1%) infants in the HIE group had MDI scores of less than 80.

Although both the PDI scores and proportions of infants who showed excellent development in the control group was slightly higher than those in the HIE group (15.0% vs. 11.9%, *P*<0.05), such differences of PDI between two groups did not reach statistical significance (*P*>0.05).

The behavioral rating of the control group was generally higher than that of the HIE group. Furthermore, remarkable differences were observed in reactivity, area sensorial in interest, target orientation, and attention span between the two groups (all *P*<0.05).

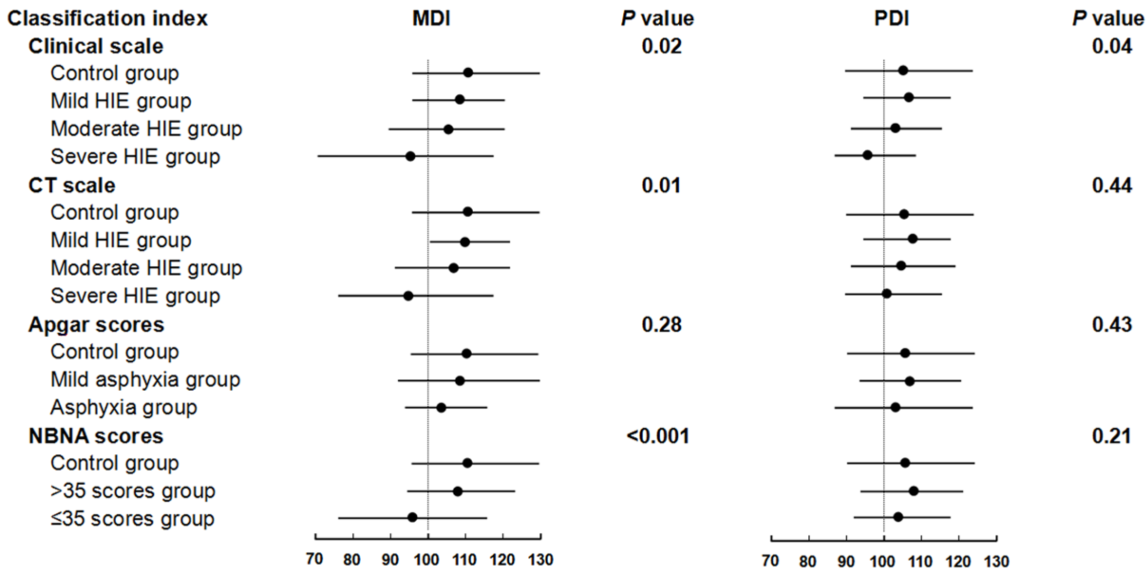

Figure 1. The comparison of MDI and PDI with different classification indexes. *P* values for the difference in different groups derived from analysis of variance. CT, computed tomography; HIE, Hypoxic-ischemic encephalopathy; MDI, mental developmental index; PDI, psychomotor developmental index.

Correlation of MDI, PDI with behavioral rating

MDI scores of the HIE group were significantly related to the reactivity, area sensorial in interest, and target orientation (**Table 3**). Similar trend of the correlation could be found in the control group; in addition, MDI scores in the control group were significantly associated with the attention span and the durability.

Likewise, PDI scores in the HIE group were positively correlated with target orientation, cooperative, and activity (**Table 3**). In the control group, significant correlations were found between PDI scores and some items of the behavioral rating, including the target orientation, area sensorial in interest, attention span, durability, and activity.

Predictors for 12-month MDI, PDI and behavioral rating

According to different clinical severities, the MDI scores of infants significantly varied in different groups (**Figure 1**). The result of LSD showed that infants with severe HIE had remarkable lower MDI scores than those with mild HIE (t=2.07, P=0.04) and the normal infants (t=2.67, P=0.01). Parallel to the results of MDI, the PDI of the severe HIE group was also slightly lower than those of the mild HIE group and the control group.

Compared with the normal infants and the infants with mild CT degree, those with severe CT degree were associated with significant lower PDIs (t_{normal}=2.18, P=0.04; $t_{mild\ HIE}$=2.08, P=0.04). However, there were no significant differences for the PDI scores among the four groups (P>0.05).

For MDI scores, HIE infants with a NBNA score of less than or equal to 35 presented a lower MDI than those with a NBNA score of greater than 35 (t=2.08, P=0.04), as well as the normal infants (t=2.62, P=0.01). As for the PDI scores, no significant differences were observed among the three groups (P>0.05).

The result of ANOVA indicated that the Apgar scores have no significant effect on both MDI and PDI scores (P>0.05).

Discussion

In this study, we established the predictors for evaluating the prognosis of HIE for early clinical intervention, via investigating the differences of mental, motor and behavioral development between infants with HIE and normal infants at the age of 1. Our results showed that the mental, psychomotor and behavioral rating of HIE infants were significantly lower than normal infants. MDI, PDI scores were significantly correlated with the behavior rating scores.

Moreover, compared with other predictors, cranial CT could be considered as a reliable index for helping to establish the prognosis of HIE.

It have be demonstrated that HIE can result in the injury of the cerebral cortex and the hippocampus, for further lead to decline of space memory and study ability [3]. Besides, a delay of psychomotor development is a general sequelae of HIE. Perinatal period asphyxia was related to the damaging of long-term cognitive behavior, which might cause schizophrenia in serious situation [7]. Freier et al found that of the infants with sequelae of neuro development after the surgery, MDI scores could reduce significantly, especially at the 18th month and the 28th month [11]. Previous studies also reported that the premature delivery, one of the cause of HIE, could also lead to a delay of mental, psychomotor and behavior development [21, 25]. Sajaniemi et al reported that preterm infants who had lower MDI, PDI scores than the term infants also showed a low level in several items of behavioral rating scale, including rhythmicity, social tendency, cooperative, and attention span [24]. According with the results of these previous studies, our study found that compared with the infants with HIE, normal infants had better development rating of mental, psychomotor and behavior. Thus a low BSID score was related to some aspects of temperament evaluation. Moreover, the study of Wijnroks et al found that the posture and psychomotor level of preterm infants at 6 months age could predict the attention development of the healthy infants among them at 6 to 18 months [28]. The results were also supported by our finding that both MDI and PDI were significantly associated with the behavioral rating for infants with HIE, suggesting that the mental and psychomotor scale are highly valuable for the prognosis evaluation and following clinical intervention.

The death of neuron after hypoxic ischemic injury was in two stages, necrosis and apoptosis, respectively. The apoptosis, which started from several hours after hypoxic ischemic injury, was a slowly progressive reversible neurodegenerative process [19]. Due to the persistence of apoptosis, the rehabilitation of neuron could start from the neonatal period and might last until several weeks or months after neonatal period, even longer. Koldewijn et al reported that the preterm infants in the early intervention group had higher 6-month MDI and PDI scores compared with the preterm infants without treatment [16]. Therefore, it was critically important to discover the potential factors which lead to abnormality of mental and psychomotor at early stage. Due to the ante- and intra-partum primary injury in HIE, the severity of injury and prognosis is difficult to be established; thus, a precise prediction of the prognosis in neonates with HIE is of essential importance in terms of neuroprotective therapy. Apgar scores have been considered to be likely to related with the prognosis of HIE. However, Polat et al found that the Apgar scores were not significantly related with developmental tests; meanwhile, Apgar scores had a low sensitivity of 16% [22]. In consistence with results of the study by Polat et al., our results showed that for the Apgar scores, no significant differences of MDI, PDI were noted between the case and control groups. This could be partly attributed that many other factors, such as prematurity, anesthetic used during delivery, drugs used by mother and congenital abnormalities, might lead to a declined Apgar scores; in the meantime, the impacts of five components of Apgar scoring on the central nervous system were actually different, which might have led to underestimation or overestimation of the association. This method could only reflect a neonate's condition at particular moment but be invalid to provide enough information regarding long-term and permanent implications of intrapartum asphyxia, thus was poorly related with prognosis [6, 13].

The results of present study found that the changes of MDI were paralleled to the changes of cranial CT. Additionally, infants with HIE who had severe cranial CT degree were more likely to have a poor prognosis, which suggested that this measure could differentiate on varied severity of HIE. Therefore, performing cranial CT can be used as an essential indicator for evaluating the prognosis of HIE. Cranial CT could not only provide important information regarding intracranial hemorrhage, infarction, and cerebral edema to evaluate the severity of brain injury accurately, but also detect the dynamic change to establish proper strategies of therapeutic interventions. In addition, compared with other neurodiagnostic methods like MRI, CT is easier to perform even during the acute stage; while MRI needs deep sedation, which is risky in asphyxiated infants [15]. Eghbalian et al. found that the sensitivity of the CT scan to differentiate on the severity of the brain lesions caused by HIE was significantly higher than that of neonatal brain ultrasounds [9]. Although the cranial CT was supposed to be performed at the 3 to 4 weeks of life, our results showed that it could already classify the severity of disease of most cases at the 7th day of birth, which suggested that it could be an essential effective method to lead the pediatricians to perform the therapeutic intervention in the early stage. In our study, it is observed that HIE infants NBNA scores at the 14th day after birth were commonly with a significantly lower MDI at 12-month old. However, since many infants with HIE also got normal NBNA scores and NBNA scoring was assessed at the 14th day, it could be inferred that the NBNA scores might have less effect to predict the neurological outcome and prognosis of HIE.

In conclusion, the findings of this present study suggested that HIE significantly influenced the progression of mental, psychomotor and behavioral in infants. Compared with other evaluation methods, CT could be a better predictor helping to establish prognosis. Consequently, a careful clinical evaluation combined with some specific examinations including CT could be very effective in predicting the prognosis of HIE. However, considering the relatively small sample size, further large researches are still required to confirm our findings.

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Disclosure of conflict of interest

None.

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