☐ Original Article ☐

대 한 주 산 회 지 제26권 제3호, 2015
Korean J Perinatol Vol.26, No.3, Sep., 2015
http://dx.doi.org/10.14734/kjp.2015.26.3.208

Prediction of Neurodevelopmental Outcome in Hypoxic Ischemic Encephalopathy at 12 Months: Correlation of Brain MRI and EEG

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Purpose: The aims of this study were to estimate the neurodevelopmental outcome of hypoxic-ischemic encephalopathy (HIE) at 12 months, and determine the usefulness of brain magnetic resonance imaging (MRI) and electroencephalography (EEG) to predict neurodevelopmental outcome in term infants with HIE at 12 months.
Methods: This study was conducted retrospectively on term infants with HIE from January 2009 to June 2013. Based on neurodevelopmental outcome at 12 months, infants were categorized into 2 groups. Brain MRI and EEG findings were stratified into 4 categories as normal, mild, moderate and severe groups.
Results: Total 42 term infants were enrolled. Fifty seven point one percent (24/42) of total infants had favorable neurodevelopmental outcome at 12 months (favorable outcome, n=24). Thirty eight point one percent (16/42) of total infants had significant neurodevelopmental deficit at 12 months of age, and 4.8% (2/42) had mortality within 12 months (poor outcome, n=18). In brain MRI and EEG findings, there were significant correlations with neurodevelopmental outcome. Brain MRI showed sensitivity of 88.9%, specificity of 70.8%, positive predictive value of 69.6% and negative predictive value of 89.5%, while EEG showed sensitivity of 70.6%, specificity of 82.6%, positive predictive value of 75%, and negative predictive value of 79.2%. In the multivariate analysis, moderate-to-severe findings in brain MRI were the strongest risk factor (odds-ratio, 11.24; 95% confidence interval, 1.36-92.89; P=0.025).
Conclusion: Forty two point nine percent of total infants had poor neurodevelopmental outcome at 12 months. Brain MRI and EEG findings were correlated with neurodevelopmental outcome of term infants with HIE at 12 months.

Key Words: Asphyxia, Hypoxic ischemic encephalopathy, Developmental delay, Magnetic resonance imaging, Electroencephalography

Of the many etiologies including perinatal asphyxia, hemorrhage, infection, and metabolic disorder, perinatal asphyxia is the most common cause of perinatal brain injury.[1] Hypoxic-ischemic encephalopathy (HIE) is defined as brain damage caused by the combination of inadequate blood stream and lack of oxygen supplementation to the brain.[2] The incidence of HIE is approximately 2 to 5 of 1,000 live births in developed countries and 10-folds greater in developing countries.[3] Approximately 15% to 20% of infants who experienced HIE actually die during the neonatal period, and approximately 20% to 40% of infants who survive severe HIE developed permanent neurodevelopmental disabilities, such as cere-

Received: 13 July 2015
Revised: 6 September 2015
Accepted: 12 September 2015
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The Korean Journal of Perinatology · pISSN 1229-2605 eISSN 2289-0432 · e-kjp.org

bral palsy, mental retardation, learning disability, or epilepsy.[4] Therefore, proper assessment of severity of disease is important for prediction of neurodevelopmental outcome of HIE infants. Previous studies used various diagnostic tools to predict the neurodevelopmental outcome of HIE infants.[5–7] However, there were limitations of heterogenous, and small–sized population of study enrollment. The aims of this study were to estimate neurodevelopmental outcome, and determine the usefulness of brain magnetic resonance imaging (MRI) and electroencephalography (EEG) to predict neurodevelopmental outcome of term infants with HIE at 12 months.

Materiars Methods

1. Study population

This is a retrospective study through medical records conducted at Ajou University Hospital, Suwon, Korea between January 2009 and June 2013. The study population included term infants who were referred and admitted to the neonatal intensive care unit (NICU) with diagnosis of HIE.

The inclusion criteria were established as follows: (1) ≥37 weeks of gestational age, (2) clinical evidences of fetal distress (bradycardia, thick meconium staining), (3) Sarnat & Sarnat stage II–III, (4) need for positive pressure ventilation at least 10 minutes, (5) available for assessment of neurodevelopmental outcomes at 12 months.[8] All infants who were born with <37 weeks of gestational age or major congenital anomaly, chromosomal abnormality, and inborn error of metabolism were excluded from the study.

2. Brain magnetic resonance imaging

Brain MRI was performed between 3 and 14 days after birth with a 1.5 Tesla Signa Excite (General Electric Healthcare, USA). Brain MRI findings were categorized according to Barkovich et al.[5,9] (1) Normal: no observed pathologies related to HIE, (2) Mild: abnormal signal in basal ganglia or thalamus only, (3) Moderate: abnormal signal in cerebral cortex and basal nuclei (basal ganglia or thalamus), (4) Severe: abnormal signal in entire cerebral cortex, basal ganglia, thalamus and brainstem.

3. Electroencephalography

EEG findings were performed between 3 and 14 days after birth regardless of the presence of neonatal seizure. EEG was achieved on a portable device (Comet–Plus portable EEG, Grass technologies, USA) for a minimum duration of 30 min with electrodes using the 10–10 international system. EEG findings were graded by a pediatric neurologist and categorized as follows: (1) Normal: continuous activity with physiological EEG, appropriate synchrony for post–conceptional age, (2) Mild: isolated temporal spikes, preserved sleep state modulation with excessive sharp wave activity, (3) Moderate: predominant asymmetry and asynchrony for post–conceptional age, excessive discontinuity, (4) Severe: inactive or permanent discontinuous activity plus theta activity, burst–suppression pattern.[10–12]

4. Neurodevelopmental outcomes

The neurodevelopmental outcomes were assessed by using Denver Developmental Screening Test II (DDST–II) and Bayley Scales of Infant Development II (BSID–II).[13,14] DDST–II was done in all infants, but BSID–II was done in 30 infants (71.4%) whose parents agreed with the test. Based on the above tools, we evaluated neurodevelopmental outcome and classified the patients into 3 prognostic groups as normal, borderline, and severe (including death)

group. Detailed classification of neurodevelopmental outcome in HIE was presented in Table 1. Severe prognostic group was regarded as a "poor" outcome. Otherwise, normal-to-borderline prognostic group was regarded as a "favorable" outcome.[5,7]

5. Statistical analysis

IBM SPSS statistics version 22.0 (IBM Corporation, USA) was used for the statistical analysis. The student-*t* test was used to compare numerical scales. Chi-square test and Fisher's exact test were used to compare categorical scales. A multivariate logistic regression analysis was carried out to determinate association of factors related to neurodevelopmental outcome in HIE independently. *P*-value of <0.05 was considered statistically significant. The sensitivity, specificity, positive predictive values and negative predictive value of initially performed brain MRI and EEG were then calculated.

Table 1. Categorization of Neurodevelopmental Outcomes in Term Infants with Hypoxic-Ischemic Encephalopathy at 12 Months

Normal
- Scores within 20% of age-normative values in DDST-II
- BSID-II, MDI score more than 85
Borderline
- Scores between 20% and 30% of age-normative values in DDST-II
- BSID-II, MDI score between 70 and 85
Severe
- Scores higher than 30% of age-normative values in DDST-II
- BSID-II, MDI score less than 69
- Death during the follow up period

Abbreviations: DDST-II, Denver Developmental Screening Test II; BSID-II, Bayley Scales of Infant Development II; MDI, mental development index

Results

1. Subject characteristics

Total 42 infants diagnosed with HIE were enrolled in this study. Median gestational age was $38^{+3}\pm1^{+2}$ weeks (range, $37^{+0}\pm41^{+0}$ weeks). The mean birth weight was 3,165±472 g (range, 2,500-4,200 g), and male infants were 24 (57.1%). Twenty-eight (66.7%) were delivered via caesarean section. In obstetric histories, 13 infants (30.9%) had fetal distress and 6 infants (14.3%) had abnormal presentation in fetus. In evaluation of neurodevelopmental outcomes, 24 infants (57.1%) had a favorable neurodevelopmental outcome (favorable outcome group, n=24). Sixteen

Table 2. Comparison of Neurodevelopmental Outcomes according to Perinatal Characteristics

Characteristics	Favorable (n=24, 57.1%)	Poor (n=18, 42.9%)	*P*-value†
Gestational age (weeks)*	$39^{+2}\pm2^{+2}$	$39^{+3}\pm1^{+2}$	0.461
Birth weight (g)*	3192±483	3129±467	0.675
Male infants, n (%)	15 (62.5%)	9 (50%)	0.533
Cesarean section, n (%)	16 (66.7%)	12 (66.7%)	1.000
Apgar score at 1 minute*	6.1±2.2	4.5±2.4	0.029
Apgar score at 5 minutes*	7.8±1.5	6.2±2.2	0.010
Initial pH <7.0, n (%)	4 (16.7%)	4 (22.2%)	0.706
Initial base deficit ≥12 mmol/L, n (%)	5 (20.8%)	9 (50.0%)	0.096
Meconium stained, n (%)	2 (8.3%)	3 (7.1%)	0.636
Fetal distress, n (%)	8 (33.3%)	5 (27.8%)	0.748
Abnormal presentation, n (%)	5 (11.9%)	1 (2.4%)	0.214
Neonatal seizure, n (%)	21 (87.5%)	16 (43.2%)	1.000

*Data are given as mean±standard deviation.
†Student-t test and chi-square test.

infants (38.1%) had significant neurodevelopmental deficit at 12 months, and mortality occurred in 2 infants (4.8%) within 12 months (poor outcome group, n=18). Table 2 showed the comparisons between favorable outcome group and poor outcome group according to various perinatal risk factors and clinical manifestation. There were statistically significant differences in Apgar score at 1 and 5 minutes, and base deficit in initial blood gas analysis. The infants with a poor neurodevelopmental outcome had blood pH <7.0 and base deficit ≥12 mmol/L with higher proportion, as compared with favorable neurodevelopmental outcome, but these did not reach statistical significance.

2. Correlation between brain MRI and neurodevelopmental outcome

A correlation of brain MRI findings for prediction of neurodevelopmental outcome was presented in Table 3. Of the 24 infants with favorable outcome, brain MRI showed normal findings in 11 (45.8%), mild findings in 6 (25%), and moderate findings in 7 (29.2%), while none showed severe findings. In contrast, brain MRI of infants with poor outcome showed normal findings in 2 (11.1%), none with mild findings, moderate findings in 6 (33.3%), and severe findings in 10 (55.6%). When brain MRI findings were classified with normal–to–mild or moderate–to–severe, it was noted that the infants with normal–to–mild findings were 17 (70.8%) in the favorable outcome group, while the infants with moderate–to–severe findings were 16 (88.9%) in the poor outcome group. The brain MRI findings were significantly related with the neurodevelopmental outcomes (P<0.001). In predicting a poor neurodevelopmental outcome, brain MRI had a sensitivity of 88.9%, specificity of 70.8%, positive predictive value of 69.6%, negative predictive value of 89.5%, and accuracy of 78.6%.

3. Correlation between EEG and neurodevelopmental outcome

A correlation of EEG findings for prediction of neurodevelopmental outcomes was presented in Table 4. EEG findings of two infants could not be obtained due to expiration of medical records. Of the 23 infants with favorable outcome, EEG showed normal findings in 5 (21.7%), mild findings in 14 (60.9%), moderate findings in 3 (13.1%), and severe findings in 1 (4.3%). In contrast, EEG of infants with poor outcome showed normal findings in 3 (17.6%), mild findings in 2 (11.8%),

Table 3. Correlation of Brain Magnetic Resonance Imaging with Neurodevelopmental Outcome of Infants with Hypoxic-Ischemic Encephalopathy

	Favorable (n=24)	Poor (n=18)	*P*-value*
Normal-to-mild findings of MRI, n (%)	17 (70.8%)	2 (11.1%)	<0.001
Moderate-to-severe findings of MRI, n (%)	7 (29.2%)	16 (88.9%)	

Abbreviation: MRI, magnetic resonance imaging.
*Fisher's exact test.

Table 4. Correlation of Electroencephalography with Neurodevelopmental Outcome of Infants with Hypoxic-Ischemic Encephalopathy

	Favorable (n=23)	Poor (n=17)	*P*-value*
Normal-to-mild findings of EEG, n (%)	19 (82.6%)	5 (29.4%)	0.001
Moderate-to-severe findings of EEG, n (%)	4 (17.4%)	12 (70.6%)	

Abbreviation: EEG, electroencephalography.
*Fisher's exact test.

moderate findings in 4 (23.5%), and severe findings in 8 (47.1%). When EEG findings were classified with normal-to-mild or moderate-to-severe as in brain MRI, it was noted that the infants with normal-to-mild findings were 19 (82.6%) in favorable outcome group, while the infants with moderate-to-severe findings were 12 (70.6%) in poor outcome group. The EEG findings also showed significant relationship with the neurodevelopmental outcomes (P=0.001). In predicting a poor neurodevelopmental outcome, EEG had a sensitivity of 70.6%, specificity of 82.6%, positive predictive value of 75.0%, negative predictive value of 79.2%, and accuracy of 77.5%.

4. Analysis of risk factors of poor neurodevelopmental outcome

Independent risk factors of neurodevelopmental outcomes in HIE were analyzed using multivariate logistic regression with significant factors in univariate analysis. The result was shown in Table 5. As a result, brain MRI findings (adjusted odds-ratio, 11.24; 95% confidence interval, 1.36-92.89; P=0.025) were the strongest risk factors and reached statistical significance.

DISCUSSION

The study results indicated that 57.1% of total infants had a favorable neurodevelopmental outcome and 38.1% of total infants had a significant degree of developmental delay or neurodevelopmental deficit at 12 months. Mortality of 2 infants (4.8%) was observed within 12 months, in this study. Dixon et al[15] reported that 39% of infants had a poor outcome, such as developmental delay, cerebral palsy or death. Other studies also presented that the incidence of poor neurodevelopmental outcome in HIE was almost similar to our study.[5-7, 16, 17] However, several studies showed higher or lower degree of poor neurodevelopmental outcome in HIE. These results could be caused by the different criteria for enrollment and relatively heterogenous patient group in the other study.

Brain MRI is regarded as the best tool in establishing and predicting neurodevelopmental outcome of infants with HIE.[18] Various scoring systems have been used for pathologic brain MRI findings in HIE. Moreover, the optimal time of performing brain MRI has been reported as the first week before edema and atrophy becomes remarkable.[18] In this study, 11.1% had normal-to-mild findings and 88.9% had moderate-to-severe findings in the poor neurodevelopmental outcome group. Polat et al[5] reported that 50% of infants with poor neurodevelopmental outcome showed severe findings in brain MRI, such as basal ganglia involvement and diffuse cerebral cortex involvement, while only 1 neonate with diffuse involvement on brain MRI had normal development. Jose et al.[6] reported

Table 5. Significance of Risk Factors Related Prediction of Neurodevelopmental Outcomes in Hypoxic-Ischemic Encephalopathy by Multivariate Logistic Regression Analysis

	Adjusted odds ratio	*P*-value	95% confidence interval
1-min Apgar score	1.63	0.282	0.67-3.99
5-min Apgar score	0.44	0.171	0.14-1.43
Base deficit	0.98	0.831	0.85-1.14
Brain MRI findings	11.24	0.025	1.36-92.89
EEG findings	3.31	0.254	0.42-25.92

Abbreviations: MRI, magnetic resonance imaging; EEG, electroencephalography.

that 54.5% of infants with poor neurodevelopmental outcome showed abnormal signal in cortex and basal nucleus or thalamus. They reported that multifocal/diffuse cortical lesions and abnormal signal in basal ganglia or thalamus in Brain MRI were predictors of poor neurodevelopmental outcome in HIE.[5, 6]

Abnormal EEG background activity has been also regarded as a good predictor of poor neurodevelopmental outcome of infants with HIE.[10, 17, 18] Abnormal background activities related with poor neurodevelopmental outcome, have been described as a marked excessive discontinuity, burst–suppression pattern, low voltage pattern, and electrocerebral inactivity.[10] In this study, 29.4% had normal–to–mild findings and 70.6% had moderate–to–severe findings in the poor neurodevelopmental outcome group. Polat et al.[5] reported that 50% of infants with poor neurodevelopmental outcome had severe abnormal findings in EEG. Jose et al.[6] described that 86.7% of infants with poor neurodevelopmental outcome showed permanent discontinuous activity or burst suppression pattern. Ong et al.[7] described that 69.2% of infants with poor neurodevelopmental outcome showed intermediate to severe pattern of EEG findings. Although the proportion of moderate–to–severe findings with poor neurodevelopmental outcome were somewhat different for the respective studies, the results showed that severe patterns of EEG findings were associated with poor neurodevelopmental outcome in HIE at 12 months.

Biagioni et al.[18] reported that both brain MRI and EEG are predictive of neurodevelopmental outcome in HIE and affirmed their value in predicting the neurodevelopmental outcome. However, there were controversies of predictive value of brain MRI and EEG for demonstrating neurodevelopmental outcome in other studies. Polat et al.[5] reported that brain MRI had higher sensitivity (83.3%) and negative predictive value (91.6%), while EEG had higher sensitivity (100%) and negative predictive value (100%). El–Ayouty et al.[19] reported that brain MRI had higher sensitivity (100%) and negative predictive value (100 %), while EEG had similar sensitivity, specificity, positive predictive value and negative predictive value (100%). Jose et al.[6] reported that brain MRI had higher specificity (93.3%) and positive predictive value (90%), while EEG had higher sensitivity (100%) and negative predictive value (100%). Including the results of our study, brain MRI and EEG showed somewhat differences of predictive values, sensitivity and specificity. We suggested that these results were caused by the differences of patients' grouping and time of conducting each evaluations.

Polat et al.[5] analyzed whether the clinical factors, such as Apgar score, neurological examination, and modified Sarnat staging, would help to predict neurodevelopmental outcome of infants with HIE. They showed that various clinical factors had no significant relationship to predict the prognosis, but suggested a major role in establishing prognosis when accompanied by brain MRI and EEG.[5] In this study, the results of Apgar score and blood gas analysis were insufficient to determine the correlation with neurodevelopmental outcome. We reasoned that all infants were born in another institutes, and evaluated and underwent initial resuscitation and management before transfer. Therefore, brain MRI findings had the strongest correlation of neurodevelopmental outcome of infants with HIE at 12 months.

The limitations of this study were that we relied on medical records to determine neurodevelopmental outcome, and the follow–up duration for determining neurodevelopmental outcome was relatively short. Even if we reconsidered the results and a specialized

physician performed the analysis, the results of brain MRI and EEG were retrospectively analyzed in this study. Although this study was conducted on a relatively large and heterogenous patient group, as compared with other studies, further studies using larger numbers of patients and follow-up for longer duration are needed to confirm the findings of our study.

In conclusion, this study showed that 42.9% of term infants with HIE had poor neurodevelopmental outcome at 12 months. Moreover, brain MRI findings showed a significant correlation with neurodevelopmental outcome of infants with HIE at 12 months. With careful clinical evaluation, early brain MRI with EEG is necessary to predict neurodevelopmental outcome of infants with HIE at 12 months.

Acknowledgement

This study was presented at the 2015 Pediatric Academic Societies, held on April, 25-28, 2015 in San Diego, USA.

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