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Original Article

Value of amplitude-integrated electroencephalograph in early diagnosis and prognosis prediction of neonatal hypoxic-ischemic encephalopathy

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Abstract: To investigate value of amplitude-integrated electroencephalograph (aEEG) in early diagnosis and prediction of long-term prognosis of neonatal hypoxic-ischemic encephalopathy (HIE), 120 HIE Children were randomly assigned into aEEG group and control group (n = 60 per group). Children in each group were sub-divided into mild, moderate and severe HIE groups (n = 20 per group). 1, 3, 14 and 28 days after birth, aEEG was performed in aEEG group; 3, 14 and 28 days after birth, neonatal behavioral neurological assessment (NBNA) was done in both groups. Children who discharged were followed up at adjusted gestational age of 12 months with Denver Developmental Screening Test (DDST) and prognosis evaluation. Results: aEEG manifestation was positively related to clinical severity of HIE (r = 0.843, $P < 0.01$). On day 3 and 14, NBNA score was comparable between two groups ($P > 0.05$), but significant difference in NBNA score was noted on day 28 ($P < 0.05$). On day 3, 14 and 28, aEEG manifestation was positively associated with prognosis at adjusted gestational age of 12 months (r = 0.832, 0.857, 0.778, 0.743, $P < 0.01$). In aEEG group, disability rate was 13.8%, which was significantly lower than that in control group (23.2%); cure rate in aEEG group (60%) was significantly higher than that in control group (40%). Moreover, long-term prognosis was also dramatically different between aEEG group and control group ($\chi^2 = 4.107$, $P < 0.05$). Conclusion: aEEG manifestation is significantly associated with clinical severity of HIE and may be helpful for early diagnosis of HIE. aEEG may be used to predict long term prognosis of HIE children.

Keywords: Amplitude-integrated electroencephalograph, neonatal hypoxic-ischemic encephalopathy, early diagnosis, prognosis

Introduction

Hypoxic-ischemic encephalopathy (HIE) refers to the hypoxia and ischemia induced brain injury secondary to perinatal hypoxia and asphyxia. The incidence of HIE is 1‰-6‰ in other countries and 3‰-6‰ in China [1]. In China, the incidence of poor prognosis is 43% in HIE children, and as high as 73.16% in children with severe HIE. Among these children, 15-20% of neonates will die, and 25-30% of survived HIE children may develop permanent brain dysfunction (sequelae of nervous system) such as epilepsy, mental retardation and cerebral palsy [2]. Currently, the diagnosis of HIE is dependent on medical history and clinical manifestations, and only interventions performed within 6 h after hypoxia/ischemia can attenuate cell apoptosis or delayed neuronal death, exerting neuroprotection [3].

Amplitude integrated electroencephalography (aEEG) is easy to perform and less interfered by the external environments, its data are easy to expatiate and this detection can be used for continuous bedside monitoring of EEG in the neonatal intensive care unit (NICU). aEEG is a trend derived from raw EEG after extensive data processing, reduction, and compression, and has been widely applied in NICU. Studies have shown that aEEG has significantly enhanced the sensitivity and specificity in the detection of seizure activity [4]. El-Dib et al proposed that aEEG monitors can be useful to screen or monitor infants 1) when no cEEG is available, 2) with clinical encephalopathy or

Table 1. Correlation analysis of aEEG and severity of HIE (n = 60)

Severity of HIE	aEEG on the 1st day (n)		
	Normal	Mild abnormality	Severe abnormality
Mild	6	14	0
Moderate	0	10	10
Severe	0	5	15
r/P	r = 0.843, $P < 0.01$		

suspicion for acute brain injury (e.g., intraventricular hemorrhage), 3) with clinical suspicion for seizures but when prolonged cEEG monitoring is unavailable, and 4) with those considered at high risk for acute brain injury (e.g., extracorporeal membrane oxygenation, ventricular access devices), as well as to longitudinally assess for maturational changes in premature infants [5].

In the present study, HIE children were monitored using aEEG and their neurological behaviors were evaluated at different time points. Moreover, the correlation of aEEG with the severity of HIE and prognosis was evaluated. Our study aimed to evaluate the value of aEEG in the early diagnosis and prediction of long term prognosis of HIE children.

Materials and methods

Design

This was a randomized, controlled, prospective study. Study design, recording of clinical data, detection of aEEG and analysis of aEEG were performed independently. Investigators received training of aEEG theory and operation. This study was approved by the Ethics Committee of Beijing Military General Hospital. The relatives of patients were informed of the objective and methods, and informed consent was obtained before study. A total of 120 HIE children were recruited from the NICU of our hospital from August 2010 to February 2013. The gestational age was 34 weeks to 42^{+2} weeks. These patients were randomly assigned into aEEG group and control group (n = 60 per group). Moreover, children in each group were subdivided into mild, moderate and severe HIE group according to the severity of HIE (n = 20 per group). 1, 3, 14, and 28 days after birth, aEEG was measured in aEEG group. 3, 14 and 28 days after birth, the neurological behaviors were evaluated with NBNA score. After discharging, children were followed up at the adjusted gestational age of 12 months and the Denver Developmental Screening Scale scoring and prognosis evaluation were performed.

Detection of aEEG

After routine skin preparation, the electrodes coated with conductive paste were placed and fixed on the parietal and frontal bones (P3 and P4 of the international 10-20 system). The name and ID of children were input, followed by recording. The EEG signals were output in the forms of semi-logarithm on paper (0-100 μV). The paper speed was 6 cm/h. The paper speed was slow, and the adjacent waves overlapped and integrated manifesting the alterative wide and narrow waves. The second track recorded the impedance of electrodes, and the impedance was < 20 Ω. The waves of EEG could also be observed via the screen [6].

Assessment of neurological behaviors

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 [7]. Denver Developmental Screening Test (DDST) was used to evaluate the adaptability, fine motor, language and major movements at the left part of age lines of 3 months, 6 months and 12 months [8]. Determination: abnormal: 2 or more retardations in 2 or more domains; 2 or more retardations in one domain in combination with 1 retardation in 1 or more domains and items of the same line were not passed. Suspiciousness: 2 or more retardation in 1 domain; 1 retardation in 1 or more domains and items of the same line were not passed. Normal: absence of above manifestations.

Determination of prognosis

Normality: DDST showed normal and no sequela of nervous system; Mild abnormality: DDST showed suspiciousness, and re-examination also revealed suspiciousness, or child had mild motor development delay and mild muscle tone abnormality; Severe abnormality: one of following findings was present: 1) DDST showed abnormal; 2) the central coordination function was abnormal; 3) there was epilepsy.

Table 2. NBNA score of different aEEG subgroups at different time points (n = 20, $\bar{x} \pm s$)

Severity of HIE	NBNA score of aEEG group at different time points			F	*P*
	3 days	14 days	28 days		
Mild	34.85 ± 1.95	36.85 ± 1.46	38.1 ± 1.55	19.281	0.000
Moderate	31.7 ± 2.75	33.25 ± 2.45	34.9 ± 2.17	8.395	0.001
Severe	13.3 ± 4.26	16 ± 6.3	18.65 ± 9.4	2.938	0.061
F	275.33	155.89	68.35		
P	0.000	0.000	0.000		

Table 3. NBNA score of control subgroups at different time points (n = 20, $\bar{x} \pm s$)

Severity of HIE	NBNA score of control group at different time points			F	*P*
	3 days	14 days	28 days		
Mild	33.5 ± 2.93	34.55 ± 2.84	35.55 ± 2.61	2.693	0.076
Moderate	29.05 ± 3.76	30.3 ± 3.79	31.55 ± 3.56	2.278	0.112
Severe	11.5 ± 5.34	11.35 ± 6.75	11.55 ± 7.69	0.005	0.995
F	158.53	134.65	126.09		
P	0.000	0.000	0.000		

Statistical analysis

Statistical analysis was done with SPSS version 17.0 and data were expressed as mean ± standard deviation ($\bar{x} \pm SD$). After normality test and homogeneity of variance test, F test was employed. Qualitative data and frequencies were compared with chi square test. Paired data were compared with t test. Correlation was evaluated with Spearman rank correlation analysis. A value of $P < 0.05$ was considered statistically significant.

Results

Clinical information

For 120 children, the ventilation was maintained, and oxygen therapy was used if necessary. Artificial ventilation was performed if necessary. The blood perfusion of different organs was assured, and the heart rate and blood pressure were maintained in normal range. The blood glucose was normal. Phenobarbital was used to treat convulsion; Furosemide and mannitol were used to reduce the intracranial pressure; when disease deteriorated, naloxone treatment or mechanical ventilation was used. For HIE children with mild or severe aEEG abnormality, Phenobarbital in combination with other drugs were used to treat convulsion; when there were epileptiform waves in aEEG, antiepileptic therapy was performed. For HIE children with severe aEEG abnormality, intracranial pressure lowering treatment was performed on the basis of extent of low-amplitude in aEEG.

Correlation between aEEG and severity of HIE

The correlation analysis of aEEG and severity of HIE is shown in **Table 1**. Results showed the aEEG was significantly related to the severity of HIE ($r = 0.843$, $P < 0.01$).

NBNA scores in different groups at different time points

Significant difference was noted in the NBNA score among three subgroups of aEEG group and control group at different time points ($P < 0.001$) (**Tables 2**, **3**). However, there was no significant difference in the NBNA score between aEEG group and control group at 3 days ($t = 1.034$ $P = 0.303$) and 14 days ($t = 1.704$ $P = 0.091$). Significant difference was observed between two groups at 28 days ($P < 0.05$) (**Tables 4**-**6**).

Correlation of aEEG with long term prognosis of HIE children

The aEEG manifestation on day 1, 3, 14 and 28 was significantly related to the prognosis of HIE children at the adjusted gestational age of 12 months ($r = 0.832$, 0.857, 0.778, 0.743, $P < 0.01$). On day 1, severe abnormality of aEEG

Table 4. NBNA score of different subgroups at 3 days (n = 20, $\bar{x}$ ± s)

Group	Severity of HIE		
	Mild	Moderate	Severe
aEEG	34.85 ± 1.95	31.7 ± 2.75	13.3 ± 4.26
Control	33.5 ± 2.93	29.05 ± 3.76	11.5 ± 5.34
t	1.715	2.541	1.179
P	0.095	0.016	0.246

Table 5. NBNA score of different subgroups at 14 days (n = 20, $\bar{x}$ ± s)

Group	Severity of HIE		
	Mild	Moderate	Severe
aEEG	36.85 ± 1.46	33.25 ± 2.45	16 ± 6.3
control	34.55 ± 2.84	30.3 ± 3.79	11.35 ± 6.75
t	3.223	2.927	2.252
P	0.003	0.006	0.030

Table 6. NBNA score of different subgroups at 28 days (n = 20, $\bar{x}$ ± s)

Group	Severity of HIE		
	Mild	Moderate	Severe
aEEG	38.1 ± 1.55	34.9 ± 2.17	18.65 ± 9.4
control	35.55 ± 2.61	31.55 ± 3.56	11.55 ± 7.69
t	3.760	3.591	2.614
P	0.001	0.001	0.013

predicted a poor prognosis of HIE children with the sensitivity of 95.8%, specificity of 94.4%, positive predictive value of 92% and negative predictive value of 97.1%. The prognosis of HIE children in aEEG group and control group is shown in **Table 7**. Results showed the disability rate in aEEG group was markedly lower than that in control group, but the cure rate in aEEG group dramatically increased when compared with control group. Significant difference was noted in the long-term prognosis between aEEG group and control group ($\chi^2 = 4.107$, $P < 0.05$).

Discussion

With the development of neonatal intensive care, the focus in NICU has changed from reduction in mortality to decrease in mortality and disability. The key mechanism underlying the HIE is hypoxia which may occurs at any stage of perinatal period [2]. Thus, early diagnosis, effective control of disease condition and prevention and treatment of sequelae have been a hot topic in studies of neonatal medicine [1, 2].

In recent years, with rapid development of imaging techniques, some imaging examinations have been used to help the diagnosis of HIE in neonates. Routine MRI can identify the myelination growth in the brain, differentiate gray matter, white matter and deep nuclei and localize the site, size and type of intracranial lesions. Moreover, MRI is non-invasive and non-radiant and has the advantages of multi-plane and multi-parameter imaging. Thus, MRI has been an optimal imaging examination of HIE [9]. Although experience has been accumulated in the evaluation of HIE with MRI, it has limitations in the ultra-early diagnosis of HIE and localization of size of intracranial lesions [10]. In addition, bedside MRI is infeasible because the instruments are immovable. Thus, MRI cannot be widely applied in the Department of NICU. aEEG is easy to perform, less influenced by external environment, convenient for determination and feasible for bedside detection. It can reflect not only the background activity of EEG, but also the epilepsy-like activity and thus has great application value in the monitoring of brain function of HIE children [11, 12]. In the present study, results showed the aEEG 1 day after birth was significantly correlated to the severity of HIE. In addition, of 6 HIE children died early, the aEEG showed severe abnormality. This suggests that the severe abnormality of aEEG predicts a high risk for mortality, and the abnormal aEEG can be used for early determination of the severity of HIE. This was consistent with previous studies [13]. Above findings indicate that aEEG is helpful for the early diagnosis of HIE.

Historically, neonatal intensive care focused on reducing infant mortality and morbidity by closely monitoring cardiorespiratory integrity through continuous monitoring of vital signs, pulse oximetry, and even continuous blood gas monitoring. These are indirect parameters associated with brain health, however, and do

Table 7. Long term prognosis of HIE children in two groups

Group	Long term prognosis		
	Cure	Improvement	Disability
aEEG	36 (60%)	14 (23.3%)	8 (13.8%)
control	24 (40%)	19 (31.7%)	13 (23.2%)
χ^2/P	$\chi^2 = 0.04$, $P = 0.041$		

not directly measure cerebral cortical function. Moreover, improved survival is sometimes associated with increased neurodevelopmental disabilities [14]. This situation raises the question of whether monitoring could evolve to more directly reflect brain status, and whether this knowledge can lead to management strategies to improve long-term neurodevelopmental outcome.

In neonates, aEEG has been used to determine the prognosis and treatment for those affected by hypoxic-ischemic encephalopathy, seizures, meningitis and even congenital heart disease. Its application as inclusion criteria for therapeutic hypothermia remains controversial. In preterm infants, normative values and patterns corresponding to gestational age are being established. As these standards emerge, the predictive value of aEEG increases, especially in the setting of preterm brain injury and intraventricular hemorrhage. The sensitivity and specificity of aEEG are enhanced by the display of a simultaneous raw EEG, which aids interpretation [15].

In the present study, aEEG was performed 1, 3, 14 and 28 days after birth, and corresponding therapies were performed on the basis of aEEG (epilepsy, convulsion and low amplitude), and NBNA score was obtained 3, 14 and 28 days. Results showed the NBNA score was comparable between aEEG group and control group 3 days and 14 days, but significant difference was noted 28 days after birth. The prognosis of HIE children was evaluated at the adjusted gestational age of 12 months, and results showed significant difference between aEEG group and control group. The disability rate in aEEG group was significantly lower than that in control group, and the cure rate in aEEG group was markedly higher than that in control group. These findings suggest that monitoring of aEEG is helpful for the administration of treatments on the basis of severity of aEEG abnormality, which may reduce the disability rate and improve the prognosis. Our results also revealed that the aEEG 1, 3, 14 and 28 days after birth was closely related to the long-term prognosis at the adjusted gestational age of 12 months. This suggests that early monitoring of aEEG in HIE children is helpful for the prediction of long-term prognosis.

aEEG used for monitoring of brain function has been an important method in the monitoring of brain function of HIE children [16]. In China, aEEG has been used to monitor the EEG and for the early diagnosis of diseases (such as asphyxia, intracranial hemorrhage) of pre-term and term infants several hospitals [17, 18]. Our findings provide theoretical evidence for the early diagnosis of HIE, timely and effective treatment of HIE, reduction of sequelae of HIE and improvement of long term prognosis of HIE.

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Disclosure of conflict of interest

None.

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References

[1] Gadzinowski J, Gulczynska E, Michniewicz B, Opala T, Buks J. [The use of therapeutic whole body cooling in treating hypoxic-ischemic encephalopathy in the newborn--the first case in Poland]. Ginekol Pol 2012; 83: 630-632.

[2] Shao XM, Ye HM, Qiu XS. Practical Neonatology. Beijing: People's Health Publishing House, 2011.

[3] Azzopardi DV, Strohm B, Edwards AD, Dyet L, Halliday HL, Juszczak E, Kapellou O, Levene M, Marlow N, Porter E, Thoresen M, Whitelaw A, Brocklehurst P. Moderate hypothermia to treat perinatal asphyxial encephalopathy. N Engl J Med 2009; 361: 1349-1358.

[4] Shah DK, Mackay MT, Lavery S, Watson S, Harvey AS, Zempel J, Mathur A, Inder TE. Accuracy of bedside electroencephalographic monitoring in comparison with simultaneous continu-

ous conventional electroencephalography for seizure detection in term infants. Pediatrics 2008; 121: 1146-1154.
[5] El-Dib M, Chang T, Tsuchida TN, Clancy RR. Amplitude-integrated electroencephalography in neonates. Pediatr Neurol 2009; 41: 315-326.
[6] van Rooij LG, Toet MC, van Huffelen AC, Groenendaal F, Laan W, Zecic A, de Haan T, van Straaten IL, Vrancken S, van Wezel G, van der Sluijs J, Ter Horst H, Gavilanes D, Laroche S, Naulaers G, de Vries LS. Effect of treatment of subclinical neonatal seizures detected with aEEG: randomized, controlled trial. Pediatrics 2010; 125: e358-366.
[7] Bao XL, Yu RJ, Li ZS. 20-item neonatal behavioral neurological assessment used in predicting prognosis of asphyxiated newborn. Chin Med J (Engl) 1993; 106: 211-215.
[8] Bolat F, Oflaz MB, Guven AS, Ozdemir G, Alaygut D, Dogan MT, Icagasoglu FD, Cevit O, Gultekin A. What is the safe approach for neonatal hypernatremic dehydration? A retrospective study from a neonatal intensive care unit. Pediatr Emerg Care 2013; 29: 808-813.
[9] Utsunomiya H. Diffusion MRI abnormalities in pediatric neurological disorders. Brain Dev 2011; 33: 235-242.
[10] Barkovich AJ, Miller SP, Bartha A, Newton N, Hamrick SE, Mukherjee P, Glenn OA, Xu D, Partridge JC, Ferriero DM, Vigneron DB. MR imaging, MR spectroscopy, and diffusion tensor imaging of sequential studies in neonates with encephalopathy. AJNR Am J Neuroradiol 2006; 27: 533-547.
[11] Foreman SW, Thorngate L, Burr RL, Thomas KA. Electrode challenges in amplitude-integrated electroencephalography (aEEG): research application of a novel noninvasive measure of brain function in preterm infants. Biol Res Nurs 2011; 13: 251-259.
[12] Lawrence R, Mathur A, Nguyen The Tich S, Zempel J, Inder T. A pilot study of continuous limited-channel aEEG in term infants with encephalopathy. J Pediatr 2009; 154: 835-841 e831.
[13] Spitzmiller RE, Phillips T, Meinzen-Derr J, Hoath SB. Amplitude-integrated EEG is useful in predicting neurodevelopmental outcome in full-term infants with hypoxic-ischemic encephalopathy: a meta-analysis. J Child Neurol 2007; 22: 1069-1078.
[14] Wilson-Costello D, Friedman H, Minich N, Fanaroff AA, Hack M. Improved survival rates with increased neurodevelopmental disability for extremely low birth weight infants in the 1990s. Pediatrics 2005; 115: 997-1003.
[15] Tao JD, Mathur AM. Using amplitude-integrated EEG in neonatal intensive care. J Perinatol 2010; 30 Suppl: S73-81.
[16] Kato T, Okumura A, Hayakawa F, Tsuji T, Natsume J, Hayakawa M. Amplitude-integrated electroencephalography in preterm infants with cystic periventricular leukomalacia. Early Hum Dev 2011; 87: 217-221.
[17] Shi YY, Cheng GQ, Shao XM, Zhuang DY, Liu DL, Liu XZ, Wang JM, Yao MZ, Wang ZZ and Zhou WH. Amplitude integrated EEG characteristics of normal full-term newborns: a multicenter clinical study. Chin J Evid Based Pediatr 2009; 6: 11.
[18] Huang XH, Yang M, Chen X, Sun MS, Wu ZH, Luo SW, Liu T. Characteristics of early amplitude integrated electroencephalograph of 85 neonates with suffocation. Shandong Med J 2012; 52: 44-47.