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Original Article

Significance of amplitude integrated electroencephalography in early stage of neonatal hypoxic-ischemic encephalopathy and cerebral function monitoring in Neonatal Intensive Care Units

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Abstract: Objective: To investigate the role of amplitude integrated electroencephalography (aEEG) diagnosis in early stage of neonatal hypoxic-ischemic encephalopathy (HIE), and to evaluate the feasibility of aEEG in cerebral function monitoring in Neonatal Intensive Care Units (NICU). Methods: 60 cases of term infants with neonatal HIE were included in the observation group, and 50 healthy term infants were enrolled as the control group. Both groups received aEEG monitoring within 6 hours after birth, and the results were analyzed. Results: The correlation coefficient between the degree of asphyxia, SWC, SA and aEEG background activity was r = 0.571 (P<0.001); r = 0.512 (P<0.001) and r = 0.293 (P<0.001), respectively. The correlation coefficient between HIE degree and aEEG background activity, SWC was r = 0.742 (P<0.001) and r = 0.763 (P<0.001), respectively. The Gessell scores of the control group at 1, 3, 6, 9, and 12 months after birth were higher than those of the mild asphyxia group and the severe asphyxia group, and the mild asphyxia group showed higher Gessell scores than the severe asphyxia group (P<0.001). The predicted ROC curve of aEEG monitoring on the occurrence of neonatal HIE showed the area under the curve (AUC) = 0.6354, Std. Error = 0.05668 (95% CI: 0.5243-0.7465, P = 0.0209). Conclusion: aEEG had obvious diagnostic value in brain injury in the early stage of full-term neonates with asphyxia, and could be used to monitor the cerebral function of NICU, which is helpful for early clinical detection of brain injury of full-term neonates with asphyxia, so as to improve early diagnosis and treatment.

Keywords: Full term, asphyxia, brain injury, neonate, amplitude-integrated EEG, cerebral function, monitoring

Introduction

Statistics show that around one million newborns die of asphyxia worldwide each year. The proportion of asphyxia and hypoxia among live born neonates in China exceeds 10% each year [1]. Birth asphyxia is the main cause of intellectual disability in neonates. In addition, neonatal asphyxia can cause cerebral hemodynamic disturbances, hypoxia, ischemia-reperfusion, leading to the release of large amounts of inflammatory mediators, free radicals and lipid metabolites, systemic inflammatory response syndrome and causes damage to many organs of newborns [2, 3].

Cerebral nerve cells are very sensitive to hypoxia. There is a high risk of brain injury following neonatal asphyxia. Newborns will experience intracranial hemorrhage and hypoxic-ischemic encephalopathy, which increases the risk of intellectual developmental disorders, cerebral palsy, and death [4]. Early diagnosis of neonatal asphyxia is an important prerequisite for delaying the occurrence of brain injury. Early diagnosis and timely treatment can effectively prevent brain necrosis, reduce brain injury, and control the occurrence of neurological sequelae [5]. However, there are no effective diagnostic tools and methods for newborns. Studies have shown that electroencephalography (EEG) could reflect the cerebral function more sensitive than some diagnostic indicators in infants. EEG examination can help determine the development of the brain, the degree of brain injury, and the prognosis [6, 7]. However, some studies have shown

that the deficiency of EEG is manifested in the obvious influence of artifacts, difficulty of detoxification, and high technical skill requirements for physicians. In its simplest form, amplitude integrated electroencephalography (aEEG) is a processed single-channel electroencephalogram that is filtered and time compressed. The amplitude change is accurately reflected, and the trace represents the voltage change of EEG background activity [8].

aEEG is widely used in neonatal monitoring. However, no studies have focused on its application in term infants with neonatal hypoxic-ischemic encephalopathy (HIE). This study included 60 cases of term infants with neonatal HIE and 50 healthy term infants to investigate the diagnosis value of aEEG in neonatal HIE, and to evaluate the value of aEEG for cerebral function monitoring in Neonatal Intensive Care Unit (NICU).

Materials and methods

Data

60 cases of term infants with neonatal asphyxia admitted to the NICU of our hospital from July 2019 to July 2020 were enrolled as the observation group, and 50 healthy term infants were included as the control group. Inclusion criteria: infants with over gestational age of 37 weeks; within 6 h after birth; the control group consisted of 50 healthy newborns, and 60 infants in the observation group met the diagnostic criteria for neonatal asphyxia [9], including 42 neonates of mild asphyxia (1-minute Apgar score of 4-7 points), 18 neonates of severe asphyxia (1-minute Apgar score of 0-3 points). Their parents signed a written informed consent. This study had obtained ethical approval of the hospital. Exclusion criteria: neonates with hypoglycemia; intrauterine infection; genetic metabolic diseases; congenital diseases; electrolyte disorders.

Methods

Neurofax EEG system (EEG-1200c, Japan Optoelectronics) was configured with software that could convert the VEEG to aEEG. Other required equipment included scrub, razor, conductive paste for brain monitor, and multi-parameter monitor. Before monitoring was turned on, a disinfected cotton ball moistened with 70% alcohol was used for disinfection of local scalp. The razor was used to shave off the hair with scrub applied locally. The space between the electrode disc and the skin was filled with conductive paste, which also helped them to bond to the scalp. The power was turned on to check the information of the child. The amplifier, headbox and connecting wire were placed in the incubator and connected with the electrode. Under the supine position, disc electrodes were fixed with tape, and the electrode was placed on both sides of the prefrontal (Fpl, Fp2), central (C3, C4), parietal lobe (P3, P4) of the brain. The distance between symmetric electrodes was controlled at 7.5 cm, the ground electrode was placed at G, and the reference electrode was placed at the midpoint of CZ and PZ. The resistance between the disc electrode and the scalp should not exceed 20 kQ, and the filter frequency was controlled between 2-15 Hz.

Within 6 hours after birth, a semilogarithmic graph of EEG signal was saved in the form of aEEG. The raw EEG was saved as well for more than 4 hours. aEEG was interpreted separately by a professional electroencephalologist and a neonatal physician (more than 3 years of interpretation experience). Before analyzing aEEG, it was necessary to interpret the entire video EEG, mark interference factors and attacks during recording to reduce errors.

Observation indicators

aEEG waveform analysis: (1) Background activity [10]: Continuous Normal Voltage (CNV); Discontinuous Normal Voltage (DNV); Burst Suppression (BS); Continuous low voltage (CLV); Flat Trace (FT), or can be divided into normal amplitude; mild amplitude abnormality; severe amplitude abnormality. (2) Sleep-Wake Cycling (SWC) [11]: No SWC; immature SWC; mature SWC. (3) Seizure Activity (SA) [12]: Single seizure; recurrent seizures; continuous seizures.

HIE: It was divided into mild, moderate and severe based on the diagnosis criteria of HIE for neonates [13] and clinical staging [14] established by the Chinese Medical Association.

Intracranial hemorrhage was evaluated in terms of medical history, symptoms and signs using skull B-ultrasound, MRI and CT.

Table 1. Comparison of baseline data ($\bar{x}$±s)/[n (%)]

Data		Observation group (n = 60)	Control group (n = 50)	t/X^2	*P*
Gender	Male	34 (56.67)	30 (60.00)	0.125	0.724
	Female	26 (43.33)	20 (40.00)		
Gestational age (weeks)		39.52 ± 1.43	39.31 ± 1.28	0.804	0.423
Birth weight (kg)		3.26 ± 0.41	3.19 ± 0.38	0.922	0.359
1-minute Apgar score		4.08 ± 1.06	9.02 ± 0.34	31.606	0.000
Delivery method	Vaginal delivery	38 (63.33)	31 (62.00)	0.021	0.885
	Cesarean section	22 (36.67)	19 (38.00)		
Meconium aspiration syndrome		10 (16.67)	0 (0.00)	9.167	0.002
Mechanical ventilation		6 (10.00)	0 (0.00)	5.289	0.021

Gesell Developmental Schedules: Follow-up was carried out at 1, 3, 6, 9, and 12 months after the birth of newborns. Gesell Developmental Schedules [15] was used to assess the developmental status of infants in five areas of behavior: adaptive behavior, gross motor movement, fine motor movement, language, and personal-social behavior. The development quotient (DQ) of each field can be obtained by calculation, DQ = DA/CA * 100, among which CA refers to the actual age while DA indicates developmental age, 76≤DQ≤85 indicates marginal status, 55≤DQ≤75 indicates mild developmental delay, 40≤DQ≤54 indicates moderate developmental delay, 25≤ DQ≤39 indicates severe developmental delay, and DQ<25 indicates that there is extremely severe developmental delay.

Statistical analysis

Statistical analysis was performed with SPSS 23.0. Measurement data ($\bar{x}$±s) were compared by independent sample *t* test; Count data [n (%)] were compared by X^2 test; The multipoint comparison was analyzed by ANVOA with post hoc F test, and the correlation was by Spearman correlation analysis. Figures were plotted with Graphpad Prism 8. *P*<0.05 was considered statistically significant.

Results

Baseline data

There was no statistical difference in terms of sex ratio, the proportion of vaginal and cesarean sections, gestational age at birth, and birth weight between the two groups (*P*>0.05). The observation group showed lower Apgar scores at 1 min after birth and higher incidence of meconium aspiration syndrome and mechanical ventilation treatment rate than the control group (*P*<0.05) (**Table 1**; **Figure 1**).

aEEG monitoring results

Background activity: 49 cases of CNV and 1 case of DNV in 50 cases of the control group. There were 42 cases of mild asphyxia neonates and 18 cases of severe asphyxia neonates in the observation group. Severe asphyxia group included 5 cases of CNV, 6 cases of DNV, 1 case of BS, and 6 cases of CLV. Mild asphyxia group included 1 case of CLV, 20 cases of DNV, and 21 cases of CNV. aEEG showed that 49 of 50 cases in the control group had normal background activity, and 1 case was mildly abnormal background activity. In the observation group, there were 18 cases of severe asphyxia neonates with normal background activity, 7 cases with mild abnormalities, and 6 cases with severe abnormalities. In 42 cases of mild asphyxia neonates, there were 21 cases of normal background activity, 20 cases of mild abnormalities, and 1 case of severe abnormalities.

SWC: 1 case of immature SWC and 49 cases of mature SWC in the control group. Of the 42 neonates with mild asphyxia, there were 1 case without SWC, 13 cases with immature SWC, and 28 cases with mature SWC. Of 18 neonates with severe asphyxia, there were 5 cases without SWC, 5 cases with immature SWC, and 6 cases with mature SWC.

None of the 50 neonates in the control group had SA. In the observation group, 2 of 42 neonates with mild asphyxia had SA, and 4 of 18 neonates with severe asphyxia had SA.

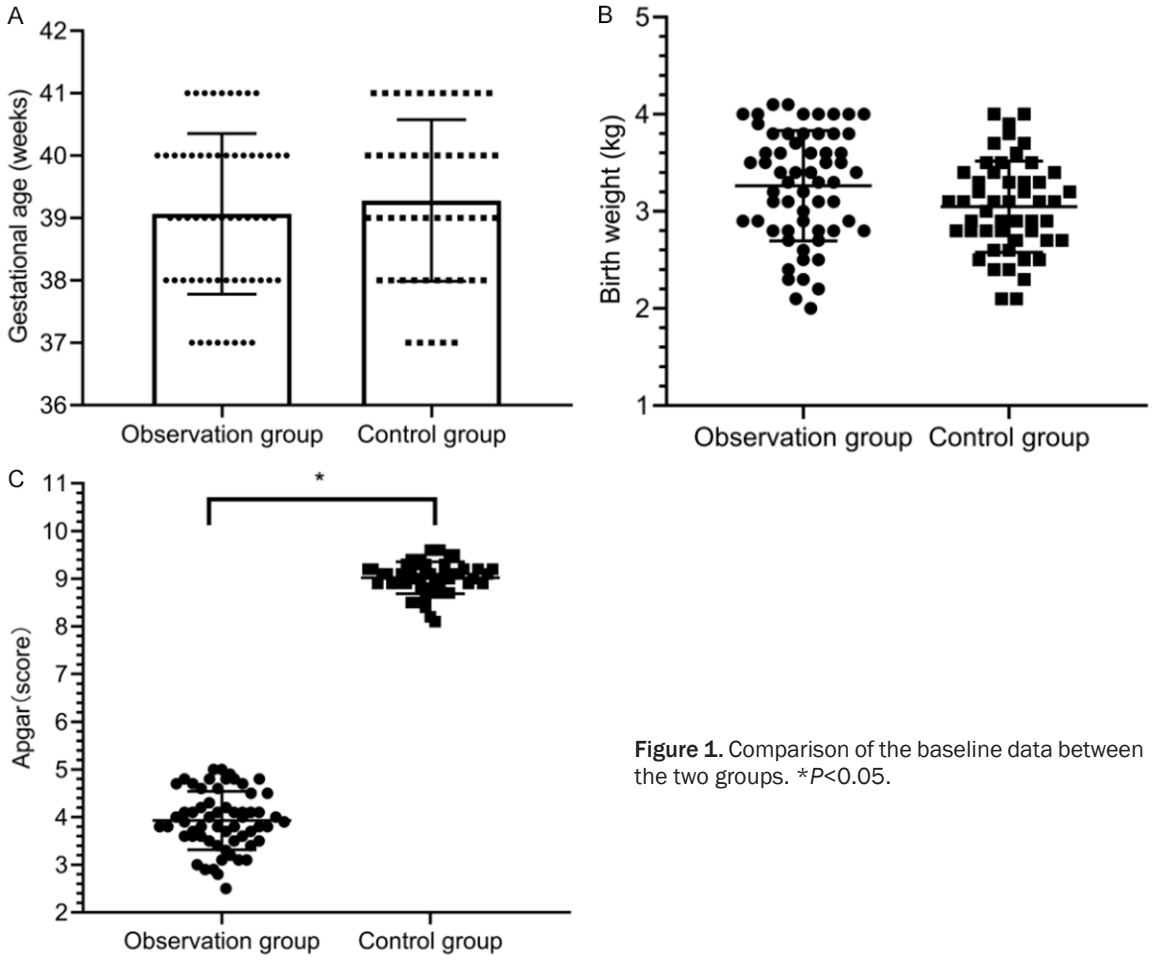

Figure 1. Comparison of the baseline data between the two groups. *P<0.05.

Table 2. Spearman correlation analysis of aEEG monitoring results and degree of asphyxia

Factor	r	P
Asphyxia and aEEG	0.571	<0.001
Asphyxia and SWC	0.512	<0.001
Asphyxia and SA	0.293	<0.001

Correlation between aEEG and the degree of asphyxia

It was found that the correlation coefficient of asphyxia and aEEG background activity, SWC and SA was r = 0.571, 0.512 and 0.293 (All P<0.001) (**Table 2**).

Occurrence of brain injury

CT and MRI confirmed 23 cases of brain injury (including 20 cases of HIE and 3 cases of intracranial hemorrhage). Of 42 cases with mild asphyxia, there were 13 cases of HIE. Of the 18 cases with severe asphyxia, 10 developed HIE. There were 50 cases without brain injury in the control group.

The predictive value of aEEG for brain injury and the correlation between aEEG monitoring and the degree of brain injury

According to aEEG monitoring results, the predictive value of neonatal brain injury in the observation group was determined, and ROC curve was drawn, which showed that AUC = 0.6354, Std. Error = 0.05668, 95% CI: 0.5243-0.7465, P = 0.0209 (**Figure 2**).

Background activity: 2 cases of aEEG with normal background activity had mild HIE, 1 case had moderate HIE, and 0 case had severe HIE; 8 cases with mild abnormal aEEG background activity had mild HIE and 3 cases had moderate HIE. In infants with severe abnormal activity of aEEG, there was 1 case of moderate HIE, and 5 cases of severe HIE. Spearman correlation

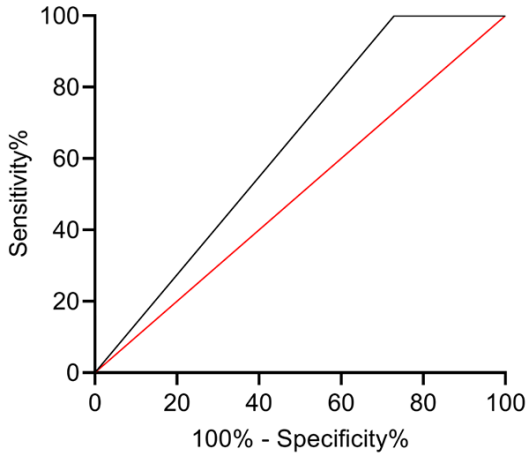

Figure 2. The predictive value of aEEG monitoring on the occurrence of brain injury in asphyxia neonates. The ROC curve showed the area under the curve (AUC) = 0.6354, Std. Error = 0.05668, 95% CI 0.5243-0.7465, *P* = 0.0209.

Table 3. aEEG background activities and HIE

aEEG background activities	Mild HIE	Moderate HIE	Severe HIE
Normal	2	1	0
Mild abnormality	8	3	0
Severe abnormality	0	1	5

analysis between aEEG background activity and HIE showed that the correlation coefficient of HIE and aEEG background activity was r = 0.742 (*P*<0.001) (**Table 3**).

SWC: There were 5 cases of mild HIE, 1 case of moderate HIE, and 0 case of severe HIE in mature SWC; 6 cases of mild HIE, 3 cases of moderate HIE, and 0 case of severe HIE in immature SWC; 0 case of mild HIE, 1 case of moderate HIE, and 5 cases of severe HIE in infants without SWC. The correlation coefficient of HIE and SWC was r = 0.763, *P*<0.001 (**Table 4**).

Results of Gesell Developmental Schedules (GDS)

The GDS scores of the control group at 1, 3, 6, 9, and 12 months after birth were higher than those of the mild asphyxia group and the severe asphyxia group in the observation group, and the mild asphyxia group had higher GDS scores than the severe asphyxia group (*P*<0.001) (**Figure 3**).

Table 4. SWC and HIE

SWC	Mild HIE	Moderate HIE	Severe HIE
Mature	4	1	0
Immature	6	3	0
None	0	1	5

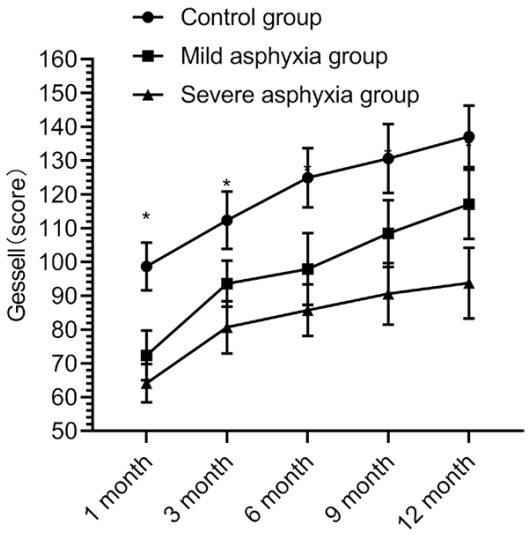

Figure 3. Comparison of the Gessell score among the three groups. The Gessel scores of mild asphyxia group and severe asphyxia group at 1, 3, 6, 9, and 12 months after birth were lower than those of control group (*P*<0.05). The Gessel scores of severe asphyxia group at 1, 3, 6, 9, and 12 months after birth were lower than those of mild asphyxia group (*P*<0.05). * indicated that *P*<0.05 for comparison between groups.

Discussion

More and more pregnant people go to the hospital every month for prenatal checkups. With the gradual advancement of childbirth techniques and life support technology in NICU, the incidence of neonatal asphyxia reduces gradually, and the corresponding neonatal mortality rate is also decreased. However, many neonates still develope neurological complications [16]. Statistics show that about 5 out of 1000 full-term neonates suffer from brain injury, and about one-fifth of neonates with brain injury will die, and another one-quarter will develop movement disorders and cognitive impairment [17].

The physical abilities of newborns have not yet been fully developed, thus the brain CT, MRI or Apgar scores cannot guarantee sufficient sensitivity for the diagnosis of brain injury in new-

borns. In contrast, aEEG has a higher sensitivity, which is more suitable for cerebral function monitoring in asphyxia neonates with brain injury [18, 19]. Studies have confirmed that aEEG has good consistency with conventional EEG. Compared with conventional EEG, aEEG is simpler to operate, less difficult to analyze, and the obtained graphics are more intuitive. Inexperienced physicians could correctly perform aEEG after a short time of training [20, 21]. aEEG can be monitored continuously for a long time, and is more suitable for bedside monitoring of high-risk newborns [22]. This study analyzed aEEG of asphyxiated neonates at 3 to 6 hours after birth and followed up them to 24 months after birth. The results showed that early detection of aEEG abnormalities can be used as a predictor of HIE in neonates with asphyxia [23]. We have shown that early neurological examination combined with aEEG monitoring could improve the accuracy of predicting the severity of HIE in term neonates with asphyxia [24].

In this study, the Spearman correlation analysis between aEEG background activity and asphyxia showed that more severe birth asphyxia leads to less mature SWC and higher incidence of SA. Further analysis of the correlation between aEEG monitoring results and the degree of brain injury showed that the severity of HIE in neonates with asphyxia could be predicted according to the background activity of a EEG. The SWC result had a negative correlation with the severity of HIE. The higher level of HIE indicated the less mature SWC [25]. It can be seen from the above results that the change in background activity of aEEG is related to the severity of neonatal asphyxia, HIE, and SWC. The incidence of SWC was significantly different among normal neonates, neonates with mild asphyxia, and neonates with severe asphyxia. Severe neonatal asphyxia could lead to less mature SWC or no SWC. The incidence of SA in severe asphyxia neonates was significantly higher than that in mild asphyxia neonates or healthy neonates. Therefore, it was believed in this study that the aEEG analysis on neonatal brain injury caused by asphyxia should start with aEEG background activity, SWC, and SA. This study analyzed the cerebral function with HIE, and assumed that HIE accounted for a large proportion of children with brain injury.

This study showed that the predicted ROC curve of aEEG for the occurrence of brain injury in asphyxia neonates was 0.6354, $P = 0.0209$, indicating that aEEG had a high value in predicting the occurrence of brain injury in asphyxia neonates, and could more accurately reflect brain injury in asphyxia neonates. The study also showed that the GDS scores of the control group were higher than those of the mild and severe asphyxia groups, indicating that the neonatal asphyxia could affect the growth and development status, and more serious asphyxia indicated more serious impact on growth and development, suggesting that it was very important to do early accurate diagnosis of brain injury to achieve the greatest improvement in prognosis.

In summary, aEEG could be used in the diagnosis of brain injury in full-term neonates with asphyxia by monitoring cerebral function in NICU. However, this study also has certain shortcomings. It focused only on one type of brain injury, i.e. HIE. Therefore, the results are not sufficiently representative. In addition, a small number of subjects were included in this study, and the follow-up period was short. These shortcomings need to be improved in future studies.

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Disclosure of conflict of interest

None.

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