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Amplitude-Integrated Electroencephalography for Early Diagnosis and Prognostic Prediction of Hypoxic Encephalopathy in Preterm Infants

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Background: The aim of this study was to analyze amplitude-integrated electroencephalography (aEEG) in early diagnosis and prognosis of hypoxic encephalopathy (HE) in premature infants.

Material/Methods: Thirty-six premature infants with HE who were treated in Linyi Central Hospital were enrolled into the study group, while 40 premature infants without HE were assigned into the control group. aEEG was conducted within 6 h after delivery to compare aEEG continuity, mature sleep-wake cycle, and maximum and minimum voltage in the 2 groups. Correlations between aEEG abnormalities and clinical grading, neurological prognosis, Apgar score, and blood gas were also analyzed among the premature infants with HE.

Results: Compared with the control group, there were reductions in the continuous rate of aEEG, mature sleep-wake cycle, and the minimum voltage, and an increase in the maximum voltage in the study group (all $P<0.05$). The study group had a higher abnormal rate of aEEG and a lower normal rate of aEEG than in the control group (both $P<0.05$). Spearman's rank correlation coefficients for abnormal aEEG and clinical grade and poor neurological prognosis were 0.758 and 0.799, respectively. The sensitivity of abnormal aEEG in predicting severity of clinical grading was 100% with a specificity of 82.5%. The sensitivity of abnormal aEEG in predicting neurological prognosis was 100% with a specificity of 90.3%. The Apgar scores and blood glass pH of the infants with various abnormal rates of aEEG were significantly different at 1 min, 5 min, and 10 min after delivery (all $P<0.05$).

Conclusions: HE in premature infants has specific aEEG characteristics, which can be used to predict the severity and prognosis of HE.

MeSH Keywords: Diagnosis • Electroencephalography • Hypoxia-Ischemia, Brain • Infant, Premature • Prognosis

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Background

Hypoxic encephalopathy (HE) in preterm infants is a cerebral injury caused by perinatal asphyxia, with a high rate of poor prognosis. It has been deemed as a major cause of cerebral palsy, epilepsy, and even death in infants. Currently, the latest treatment methods for HE in preterm infants, such as mild hypothermia therapy, are recommended to be conducted as early as possible because early diagnosis and prognostic prediction can provide evidence for its early treatment. In the past, however, the early diagnosis of HE in preterm infants mainly depended on previous onset, clinical manifestations, and MRI images, which lagged in time and delayed the diagnosis, resulting in missing the best time for treatment [1]. Multiple studies globally have concluded that it is difficult to assess prognosis and take measures for neurological protection based on previous onset, clinical manifestations, and MRI imaging and other early diagnostic techniques, as well as the severity of the disease, because the best therapeutic range of HE in preterm infants is approximately 6 h [2,3]. In this regard, it is essential to find more convenient, effective, and sensitive outcome measures to improve the early diagnosis of HE in preterm infants.

Amplitude-integrated electroencephalography (aEEG) is an electroencephalogram (EEG) monitoring technique which determines the severity of injury in the nervous system and reflects the electroencephalogram (EEG) background activity, with simple operation and highly stable results. It is optimal for point-of-care intensive care of preterm infants with HE [4]. In addition, the abnormal EEG background activities of preterm infants with HE tend to present earlier than the clinical symptoms, signs, and related manifestations of imaging [5]. In the present study, we made a deeper analysis of the association of aEEG with severity of HE and predictors of its prognosis, to evaluate the performance of aEEG in early diagnosis of HE in preterm infants and its prognostic significance value.

Material and Methods

Study participants

Thirty-six preterm infants with HE who were treated in Linyi Central Hospital between December 2015 and December 2016 were enrolled into the study group (20 males and 16 females, gestational age 35.2±1.3 weeks (31–36 weeks), birthweight 3089±682 g). Among them, 26 infants were born by vaginal delivery and 10 infants were born by cesarean delivery. Meanwhile, another 40 preterm infants without HE during the same period of time were assigned into the control group (22 males and 18 females, gestational age 35.9±2.1 weeks (32–36 weeks), birthweight 3126±714 g). Among them, 28 infants were born by vaginal delivery and 12 infants were born by cesarean delivery. No intergroup differences were found in sex ratio, gestational age, birthweight, or delivery mode (all P>0.05) (Table 1).

The infants were included if they met the diagnostic criteria and clinical grading for HE enacted by the Group of Neonatology, Pediatric Society, Chinese Medical Association, and had not received sedatives, neuroprotection, or other treatment before enrollment [4]. Exclusion criteria were congenital malformations, chromosomal disorder, family history of genetic disease; complication with cerebral injury from other causes; and failure in completion of monitoring and follow-ups for subsequent aEEG. Meanwhile, 40 premature infants without HE during the same period of time were chosen as controls. Infants in this group had experienced no fetal distress or other abnormalities in perinatal period.

This study was approved by the Ethics Committee of Linyi Central Hospital and all the parents were informed of the contents and provided written informed consent.

Study methods

AEEG monitoring

Within 6 h after delivery, the continuous aEEG monitoring was performed using an Olympic CFM brain function monitor

Table 1. Comparison of general data in the two groups.

Group	Sex ratio (Male: Female)	Gestational age (week)	Birth weight (g)	Birth head circumference (cm)	Delivery mode (n, %)	
					Cesarean section	Vaginal delivery
Control	22: 18	35.9±2.1	3,126±714	31.2±0.9	12 (30.00)	28 (70.00)
Study	20: 16	35.2±1.3	3,089±682	30.3±1.1	10 (27.78)	26 (72.22)
t/χ^2	6.735	1.678	2.220	0.793	0.282	0.243
P	0.060	0.201	0.062	0.482	0.646	0.586

aEEG – amplitude integrated electroencephalography.

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(Olympic Medical Corp.) for more than 6 h. During the aEEG tracing process, the electrode location was identified, with bilateral parietal bone at 50 mm posterior to the central vertex of the head as the electrode points (one point was 75 mm far away from the other); a reference electrode was placed on the middle line of the forehead 25 mm anterior to the central vertex of the head. The signals monitored by aEEG were quantized in a semi-logarithmic form on thermal paper and exhibited as an amplitude-like spectral band. The tracing started within 12 h of birth and each tracing lasted for over 2 h.

Outcome measures

aEEG outcome measures: The monitoring outcomes included continuity, mature sleep-wake cycle, and maximum and minimum voltage. The continuity of EEG monitoring was assessed based on the advantageous aEEG background activities. The EEG monitoring was continuous if there was a minimum voltage of 5–10 μV, a maximum voltage of 10–50 μV, absence of equipotential phase, and a decreased variability. Otherwise, the EEG monitoring was discontinuous. If the EEG amplitude presented regular sine wave changes and the cycle was over 20 min, broad and narrow bands were combined as a mature sleep-wake cycle. Otherwise, it was an immature sleep-wake cycle. The minimum level of EEG activity or the lower trajectory of voltage was determined as the minimum voltage, whereas the maximum level of EEG activity or the upper trajectory of voltage was the maximum voltage.

Clinical grading and prognosis: Clinical grades were measured based on the infants' consciousness, muscle tension, primitive reflex, convulsions, central respiratory failure, pupil changes, and anterior fontanel tension [6]. The clinical prognosis was classified into 3 levels – normality, mental retardation, and death – based on the physical growth, behavioral ability, and neuromotor and intelligence development within the first 12 months after birth.

Apgar score and blood gas: At 1, 5, and 10 min after delivery, Apgar scoring was performed by the obstetricians who delivered the neonates and who were not involved in this study. The blood gas values of the micro-capillaries at the soles of infants' feet, including pH and base excess (BE), were also measured.

aEEG criteria

Background amplitude was classified into 3 grades – normal, moderately abnormal, and severely abnormal – in terms of aEEG background activities of the premature infants with HE. The maximum and minimum voltage for these 3 amplitudes were >10 μV and >5 μV (normal), >10 μV and ≤5 μV (moderately abnormal), and <10 μV and <5 μV (severely abnormal).

Criteria for abnormal aEEG: aEEG recordings were classified into normal, moderately abnormal, and severely abnormal aEEG on the basis of normality or abnormality of amplitude with regard to aEEG background activities in the premature infants with HE and whether they were accompanied by epileptic-like activities. A normal aEEG result showed normal amplitudes without epileptic-like activities; a moderately abnormal aEEG showed moderately abnormal amplitudes without epileptic-like activities or normal amplitudes with epileptic-like activities; and a severely abnormal aEEG showed moderately abnormal amplitudes with epileptic-like activities or severely abnormal amplitudes without epileptic-like activities [7].

Data analysis

The data were analyzed using SPSS software, version 17.0. The measurement data with distribution and in line with homogeneity test of variance are expressed as mean ± standard deviation and the F test was performed, and the paired data were analyzed using the *t* test. The count data analysis was conducted using of the chi-square test. Spearman rank correlation analysis was utilized for analyzing the correlation of aEEG monitoring with clinical grade and neurological prognosis. The sensitivity and specificity were used to evaluate the predictive value of abnormal aEEG results in predicting clinical grades and neurological prognosis in premature infants with HE. A value of $P<0.05$ was considered as statistically significant.

Results

General data in the study group and the control group

No significant differences were found in sex ratio, gestational age, birth head circumference, birth weight, or delivery mode between the premature infants with HE in the study group and the premature infants without HE in the control group (Table 1).

Comparison of aEEG background activity between the 2 groups

The proportions of continuous aEEG, mature sleep-wake cycle rate, and maximum and minimum voltage were compared between the 2 groups and the differences were statistically significant (all $P<0.05$, Table 2, Figures 1, 2).

Comparison of abnormal and normal rates of aEEG monitoring results between the study group and the control group

As compared with the control group, the abnormal rate of aEEG monitoring results was higher and the normal rate was lower in the study group ($P<0.05$, Table 3).

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Table 2. Comparison of aEEG background activity between the two groups.

Group	Control	Study	t or χ^2	P
Case	36	36		
Continuous rate (%)	100.0 (36/36)	33.33 (12/36)	36.00	<0.001
Mature sleep-wake cycle rate (%)	100.0 (36/36)	19.44 (7/36)	48.56	<0.001
Maximum voltage (μV)	37.69±2.56	55.32±18.52	6.452	0.015
Minimum voltage (μV)	7.81±0.75	4.33±1.42	4.125	0.024

aEEG – amplitude integrated electroencephalography.

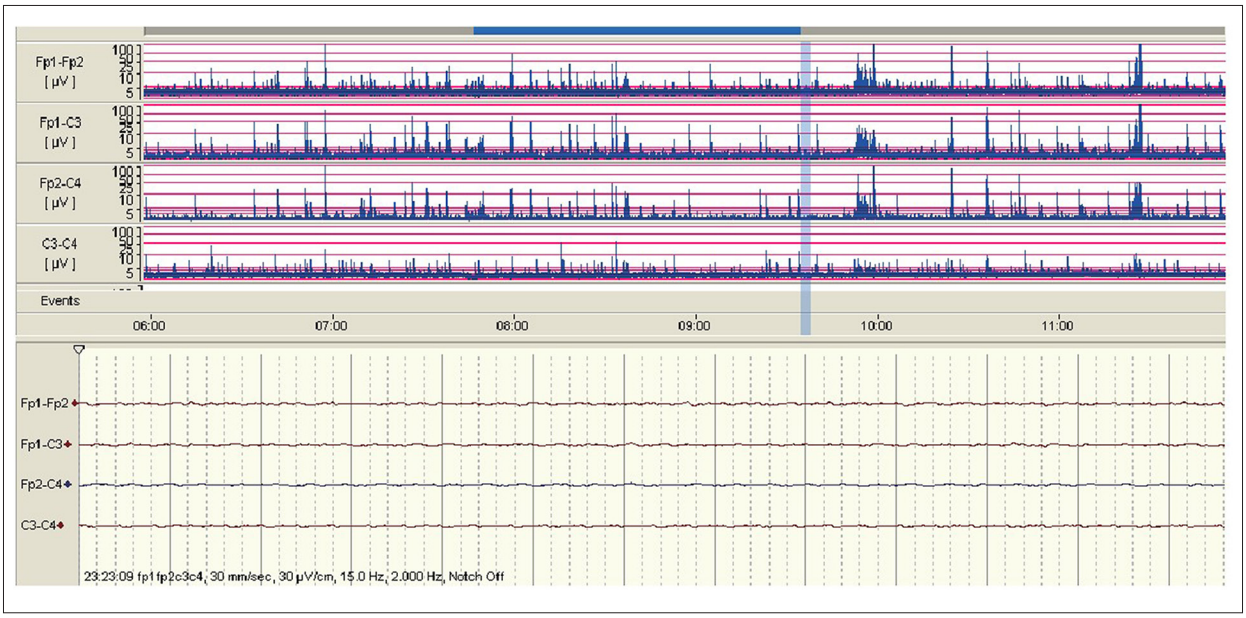

Figure 1. aEEG image of premature infants with HE: Severe abnormality can be found in amplitude with regard to background activities. The image shows a flat tracing background pattern.

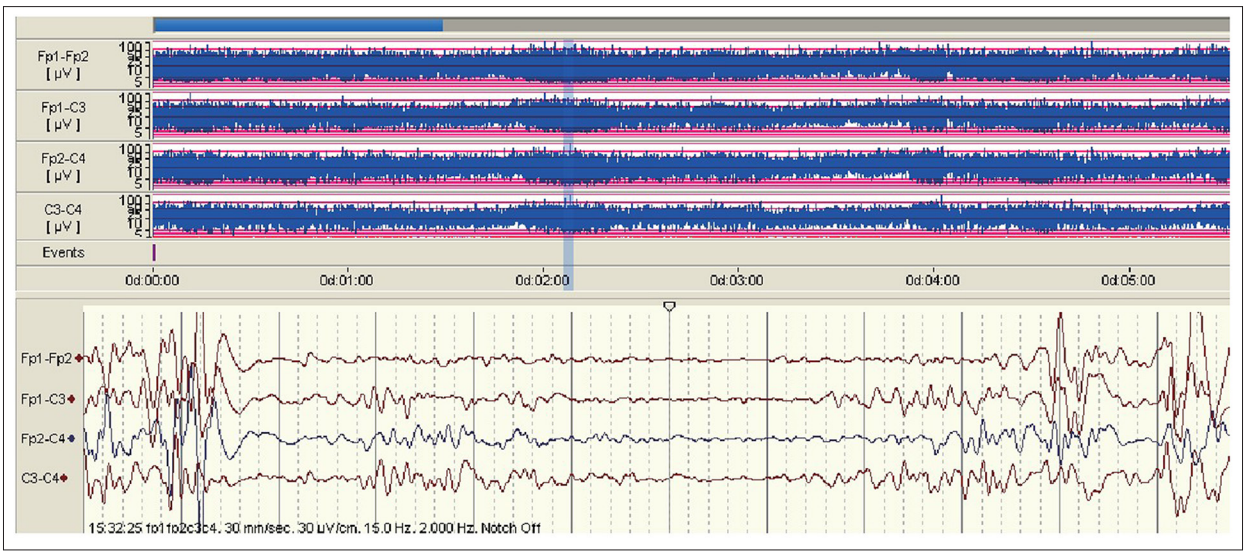

Figure 2. aEEG image of premature infants without HE: A continuous normal voltage background pattern is displayed and patients had good prognoses.

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Table 3. Comparison of abnormal and normal rates of aEEG monitoring between the two groups.

Group	Case	Abnormal rate of aEEG monitoring (%)
Control	36	0 (0/36)
Study	36	55.56 (20/36)
χ^2		27.692
P		<0.001

aEEG – amplitude integrated electroencephalography.

Table 4. Correlation analysis among aEEG monitoring results, clinical grades and neurological prognosis (n).

aEEG monitoring	Clinical grades			Neurological prognosis		
	Mild	Moderate	Severe	Normal	Mental deficiency	Death
Normal	15	1	0	21	0	0
Moderately abnormal	5	7	0	6	1	0
Severely abnormal	0	3	5	0	1	7

aEEG – amplitude integrated electroencephalography.

Table 5. Association among aEEG abnormalities, Apgar scores and blood gas analysis.

aEEG monitoring	Apgar scores			Blood gas	
	1 min	5 min	10 min	Blood gas pH	Blood gas BE (mmol/L)
Normal	6.05±2.39	9.08±1.28	9.58±0.57	7.18±0.12	11.5±3.71
Moderately abnormal	5.58±2.41	8.63±1.54	9.02±1.21	7.15±0.16	13.3±4.52
Severely abnormal	4.59±2.12	6.47±1.69	8.02±1.87	6.99±0.18	15.4±7.58
F	5.026	14.584	9.629	8.014	2.236
P	0.048	0.012	0.032	0.035	0.092

aEEG – amplitude integrated electroencephalography.

Correlations between aEEG monitoring and clinical grades and neurological prognosis

The Spearman rank correlation coefficients for the correlations between abnormal aEEG monitoring and clinical grades, as well as poor neurological prognosis, in premature infants with HE were 0.758 and 0.799, respectively. The sensitivity of abnormal aEEG monitoring to predict the clinical grade was 100% and the specificity was 82.5%; the sensitivity predicting neurological prognosis was 100% and the specificity was 90.3% (Table 4).

Correlations of different abnormal aEEG values with Apgar score and blood gas analysis

There were intergroup differences in the Apgar scores and blood gas pH among premature infants with various aEEG abnormalities at 1 min, 5 min, and 10 min after delivery. However, no intergroup differences were found in blood gas BE (base excess) (Table 5) [8].

Discussion

EEG, an important technique used to evaluate cerebral injury in premature infants with HE and to reflect the status of brain function according to electrical activity, is more sensitive,

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convenient, and easier to follow up than MRI, CT, and other imaging techniques [9]. As compared with the conventional EEG, aEEG has fewer electrodes, smaller effect of environmental factors on aEEG results, and more intuitive graphics, and is especially appropriate for continuous ICU monitoring of premature infants with HE. Multiple studies have indicated that aEEG background activity is clinically more significant than paroxysmal abnormality in diagnosis and prognostic prediction of HE in premature infants. In the present study, continuity of aEEG background activity was mainly subdivided into 2 patterns: continuous and discontinuous EEG. The continuous EEG activity accounted for 33.33% in the study group, which was significantly lower than that in the control group (100%).

Cyclical changes in aEEG activity presented as mature sleep-wake cycling demonstrated more mature EEG activity and better prognosis. Some researchers argued that aEEG activity which did not have a mature sleep-wake cycle suggested immature EEG activity, as EEG amplitude did not show regular sine wave changes and the cycle did not last more than 20 min in quiet or active sleep [10,11]. In the present study, the sleep-wake cycle was classified into mature and immature patterns to facilitate cerebral function monitoring. The rate of mature sleep-wake cycle was 19.44% in the study group, which was significantly lower than that in the control group (100%), indicating that immature sleep-awake cycle can be a crucial indicator for poor neurological prognosis in premature infants with HE.

In a previous study, Wei et al. found that both the aEEG activity or upper and lower limit of tracings was correlated with the severity and prognosis of HE in premature infants with HE [12]. In this study, the maximum and minimum voltage in the study group significantly differed from those in the control group. Since the maximum and minimum voltages in aEEG were found to vary greatly in premature infants with HE, measurement of these indices may help with the early diagnosis and prognostic prediction.

According to the relevant literature, aEEG activity is clinically important in the early diagnosis and prognostic prediction of HE in premature infants, as brain electrical activity and physiological changes in the cerebral cortex can be recorded by aEEG. In addition, the monitoring electrodes were placed on both sides of the parietal bone, which is the border zone of the cerebral perfusion area. This is a major reason why aEEG is highly sensitive to ischemia and hypoxia. Merchant et al. held that if HE occurred in premature infants within or even less than 6 h after delivery, aEEG could be applied to monitor their brain electrical activity and physiological changes [13]. The results could provide evidence for an early diagnosis and severity assessment of HE in premature infants, so as to catch the optimal time for treatment. Finn et al. found that the changes in aEEG activity were more obvious in the HE model [14]. In case of a lar ge decrease in aEEG activity, the level of EEG activity was still lower than the normal level, even if the level of cerebral reperfusion was significantly increased after drug intervention, suggesting that abnormal aEEG monitoring is a sensitive predictor of cerebral injury in premature infants with HE. Ochoa et al. considered abnormal aEEG monitoring as one of the indications of mild hypothermia in treatment of neonates, effectively improving the nerve behavior of the neonates [15]. Liu et al. conducted aEEG monitoring of 63 premature infants with HE within 6 h after delivery [16]. They also found that abnormal aEEG monitoring was a sensitive predictor for HE in premature infants. In the present study, we found that aEEG monitoring results in premature infants with HE were significantly correlated with clinical grades ($P<0.05$). Lower clinical grades were found in HE premature infants with normal or moderately abnormal aEEG monitoring results, but higher clinical grades were found in the infants with severely abnormal aEEG monitoring results. Spearman's rank correlation coefficient was 0.758 and the correlation was high, which was consistent with the results of the previous studies. The sensitivity of abnormal aEEG monitoring of clinical grades was 100% and the specificity was 82.5%. aEEG has high clinical value in the early diagnosis and prognostic prediction of HE in premature infants and can be used as a predictor of the severity and prognosis of HE.

In treatment of HE in premature infants, aEEG monitoring combined with early neurological examination was shown to further improve the accuracy of prognostic prediction. Zhou et al., during aEEG monitoring of premature infants with HE, found that the infants with normal aEEG amplitude had high survival rate and normal intelligence, whereas those with abnormal aEEG amplitude were susceptible to mental retardation and even death [17]. According to Utsunomiya, neurological prognosis was closely correlated with aEEG background activity and with epileptic-like activity in premature infants with HE [18]. In the present study, on the basis of normality/abnormality of aEEG amplitude and whether it was accompanied by epilepsy-like activity, we made a comprehensive evaluation of the aEEG monitoring results, and classified abnormal aEEG monitoring results into mild and severe patterns, which had a favorable effect on assessing the severity and prognosis of HE in the premature infants. Ci et al. analyzed neurological prognosis in 55 premature infants with HE [19]. They found better neurological prognosis in the infants with normal aEEG monitoring results as compared to those with severely abnormal aEEG monitoring results. Furthermore, with a gradual improvement in aEEG amplitude, the neurological prognosis of the infants was improved faster if they were not accompanied by epileptic-like activity. In the present study, the premature infants with HE underwent aEEG monitoring within 6 h after delivery. We found that the infants with normal or moderately abnormal aEEG monitoring results had better neurological prognosis and most of them

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had normal intelligence, with few having mental retardation. On the contrary, the infants with severely abnormal aEEG monitoring results had poorer neurological prognosis and higher rate of death. The aEEG monitoring outcomes were markedly correlated with neurological prognosis in the premature infants with HE ($P<0.05$). The Spearman's rank correlation coefficient was 0.799 with a sensitivity of 100% and a specificity of 90.3%, suggesting that aEEG can play a positive role in assessing the prognosis of HE in premature infants.

The Apgar score is a recognized predictor of severity and prognosis of HE in premature infants, but its performance is quite limited when it comes to the prediction cerebral damage and especially early prediction of prognosis of HE in premature infants [19]. However, in the present study, the Apgar scores of infants with HE were closely associated with the abnormal aEEG monitoring results. Given the specific aHEEG background activity in premature infants with HE, aEEG was used as a marker to determine the sensitivity of HE in premature infants. Apgar scores and blood gas pH values were significantly different among HE premature infants with various abnormalities of aEEG activity at 1, 5, and 10 min after delivery (all $P<0.05$), but the differences in blood gas BE were insignificant ($P>0.05$). This suggests that it was necessary for the infants with lower Apgar scores at 5 and 10 min after delivery to undergo aEEG monitoring, evaluating the probability of HE in the premature infants. In addition, blood gas analysis can reflect the severity of hypoxia in neonates, especially for the premature infants with HE who had lower blood gas pH and BE values, indicating more severe hypoxia. Nevertheless, blood gas analysis shows low sensitivity for prediction and prognostic assessment of HE in premature infants. In the present study, blood gas pH values were different among the infants with various abnormal aEEG values ($P<0.05$), whereas no significant difference was observed in terms of blood gas BE values. This may be because most HE infants were referrals, so it was difficult to take blood for blood gas analysis within 2 h after delivery. Consequently, it was hard to obtain accurate data. Premature infants with particularly abnormal blood gas pH should receive timely aEEG monitoring. aEEG monitoring results are important because they can improve the diagnosis of HE in premature infants.

There were some limitations to our study. For example, the sample size was relatively small; the long-term monitoring and follow-ups were not conducted; and there was a lack of imaging data with regard to early diagnosis of HE in premature infants and prognostic assessment. Moreover, gestational age, birth weight, and brain development might also affect the aEEG background activities in neonates, and it was difficult to determine whether the condition was hypoxic cerebral injury or immature cerebral development based on the aEEG results, which reduced the predictive accuracy of aEEG monitoring. Therefore, further research is needed to expand and verify the present results.

Conclusions

HE in premature infants has specific aEEG characteristics that can be used to predict the severity and prognosis of HE.

Conflicts of interest

None.

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