Clinical Manifestations and Amplitude-integrated Encephalogram in Neonates with Early-onset Epileptic Encephalopathy

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Abstract

Background: The patients with early-onset epileptic encephalopathy (EOEE) suffer from neurodevelopmental delay. The aim of this study was to analyze the clinical manifestations and amplitude-integrated encephalogram (aEEG) characteristics of infants with EOEE with onset within the neonatal period, to make early diagnosis to improve the prognosis.

Methods: One-hundred and twenty-eight patients with neonatal seizure were enrolled and followed up till 1 year old. Sixty-six neonates evolved into EOEE were as the EOEE group, the other 62 were as the non-EOEE (nEOEE) group. Then we compared the clinical and aEEG characteristics between the two groups to analyze the manifestations in neonates with EOEE.

Results: Compared to the nEOEE group, the incidence of daily seizure attacks, more than two types of convulsions, more than two antiepileptic drugs (AEDs) application, severely abnormal aEEG background, absence of cyclicity, and more than two seizures detection were significantly higher in the EOEE group ($P < 0.05$) (97% vs. 54.8%; 30.3% vs. 14.5%; 97.0% vs. 25.4%; 39.4% vs. 3.2%; 57.6% vs. 9.7%; and 56% vs. 3.2%, respectively). Severely abnormal background pattern (odds ratio [OR] = 0.081, 95% confidence interval [CI]: 0.009–0.729, $P = 0.025$) and more than two seizures detection by aEEG ($OR = 0.158$, 95% CI: 0.043–0.576, $P = 0.005$) were the independent risk factors for the evolvement into EOEE. The upper and lower margins of active sleep (AS) and quiet sleep (QS) were significantly higher in EOEE group than those of the control group ($P < 0.05$) (34.3 ± 13.6 vs. 21.3 ± 6.4; 9.9 ± 3.7 vs. 6.7 ± 2.2; 41.2 ± 15.1 vs. 30.4 ± 11.4; and 11.9 ± 4.4 vs. 9.4 ± 4.0; unit: μV, respectively). AS upper margin was demonstrated a higher diagnostic specificity and sensitivity for EOEE than another three parameters according to the receiver operating characteristic curves; the area under the curve was 0.827.

Conclusions: The clinical characteristics of the neonatal seizure which will evolve into EOEE were more than two AEDs application, high seizure frequency (daily attack), and more than two types of the seizure. Significant high voltage, severely abnormal background, absence of cyclicity, and more than two seizures detected on aEEG were the meaningful indicators to the prediction of EOEE.

Key words: Amplitude-integrated Electroencepholography; Early-onset Epileptic Encephalopathy; Neonatal-onset; Newborn

Introduction

Early-onset epileptic encephalopathy (EOEE) is characterized by refractory seizures occurred within the first 6 months of life, severely abnormal electroencephalogram, and neurodevelopmental delay.[1,2] Seizures occur more frequently in the neonatal period. Population-based studies suggest that the incidence of seizures in term neonates is 1–3 per 1000 live births.[3] Some of the seizures are intractable and will terminally evolve into EOEE. Amplitude-integrated encephalogram (aEEG) is a simplified method newly applied in bedside real-time cerebral function monitoring for neonates. Our study focused on the clinical manifestations and aEEG characteristics of infants with EOEE with onset within the

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neonatal period, to make a contribution to early diagnosis and prognosis prediction for these patients.

METHODS

Ethical approval

The study design was approved by the Peking University First Hospital Ethics Committee. Informed consent was obtained from all the infants' parents.

Patients

The newborns with seizure admitted to the neonatal ward of the Peking University First Hospital from January 1, 2007 to December 31, 2015, were retrospectively enrolled in this study and assigned into two groups: research group and control group.

Research group (neonatal seizures evolved into EOEEs, EOEE group). The inclusion criteria were as follows: (1) the patients with refractory seizures of neonatal onset were treated with at least two antiepileptic drugs (AEDs) to control the seizure;[4] (2) severely abnormal background and at least one electrographic seizure detected by multichannel video-EEG (vEEG); (3) the patients were followed till at least 1 year old and survived with developmental delay.

Control group (neonatal seizures did not evolve into EOEEs, non-EOEE [nEOEE] group). Other newborns with seizure were also followed till at least 1 year old. All the patients in this group were not diagnosed with EOEE since they were easily controlled with single AED or the follow-up outcome was normal.

The causes of seizures in preterm infants are complicated, so only full-term infants were enrolled in our study.

Clinical and EEG data of the patients were collected, including gestational age (GA), birth weight (BW), onset, type, and frequency of seizure, whether the neonates with status convulsion (SC), administration of AEDs, etiology, and results of aEEG and vEEG. Trained nurses in the neonatal ward were responsible for aEEG recording within 24 h of the newborns' admission and observing clinical seizures. vEEG was obtained within 3 days of admission in the EEG department and interpreted by a pediatric electroencephalographers.

Patients enrolled in this study were followed up to at least 1 year old.

Amplitude-integrated encephalogram

In our study, seizure monitoring with single-channel aEEG was initiated within 24 h of admission. A total of three Ag-AgCl-disk electrodes were attached to the scalp for monitoring according to the International 10–20 System, including two detecting electrodes fixed in P3 and P4 and a ground electrode placed in Fz. Every aEEG examination continued for at least 2 h and included a complete sleep-wake cycling (SWC). If the SWC was not clearly distinguishable, the recording time would continue for at least 1 h. The aEEG tracings and the lower and upper margins of AS and QS period were calculated according to the algorithm previously described by Zhang et al.[5]

Background of amplitude-integrated encephalogram

The background of aEEG was classified into five types according to the method previously described by Hellström-Westas et al.:[6] (1) continuous normal voltage (CNV): continuous tracing with a voltage of upper margin between 10 and 50 μV and a voltage of lower margin between 5 and 10 μV; (2) discontinuous normal voltage (DNV): discontinuous tracing with voltage predominantly >5 μV; (3) burst suppression (BS): the background pattern with periods of very low voltage (lower margin was between 0 and 2 μV) without variability (<5 μV) intermixed with bursts of higher amplitude (>25 μV); (4) continuous low voltage (CLV): continuous background and maximum voltage around or below 5 μV; (5) flat trace (FT): with inactive background and very low voltage below 5 μV. Infants who exhibit CNV or DNV recordings are likely to survive without sequelae, while infants who have BS, CLV, or FT tracings have a high risk for death or handicap.[6]

Sleep-wake cycling

The SWC pattern is recognized as periodic changes in the bandwidth of the aEEG tracing, with narrower and lower periods for AS and broader and higher periods for QS. Moreover, the SWC was divided into three patterns: (1) mature SWC: clearly identifiable variations by >2 μV and with a cyclic duration of ≥20 min; (2) immature SWC: imminent cyclicity displayed less clear variations between sleep stages as compared with the fully developed mature tracing; and (3) none SWC: absence of cyclicity.[5,7]

Voltage of amplitude-integrated encephalogram amplitude

The voltage of aEEG amplitude is usually measured semisubjectively with the naked eye from the voltage scale on the screen of the aEEG monitoring equipment which was available in the market. In our study, instead of interpretation by visual inspection, the aEEG margin was properly defined and automatically calculated according to the algorithm previously described by Zhang et al.,[5] to analyze the brain function quantitatively and accurately. Two 10-min segments were selected from each aEEG tracing, one from the middle section of AS and the other from the middle of QS. Then, the upper and lower margins of the two segments were calculated and recorded. If the SWC of the patient was difficult to distinguish, a 10-min segment from interictal pattern was chosen and calculated.

Seizure

The seizure activity was verified by both aEEG tracing and simultaneously presented raw EEG. Seizures in aEEG were defined as a characteristic pattern with sudden increases of both the lower and upper margins.[8] Seizures in EEG were defined as a sudden, repetitive, evolving, and stereotyped ictal pattern with a clear beginning, peak and ending, an amplitude of ≥2 μV, and a minimum duration of 10 s.[6]

Each aEEG was interpreted by two neonatologists who had at least 5-year experience to analyze the aEEG data. Every neonatologist was blinded to the patient identity and clinical data for the objectivity of the results.

Statistical analysis

Statistical analyses were performed using Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, version 22.0, New York, USA) to compare the characteristics of clinical manifestations and aEEG between the research group and control group. Statistical significance was assumed for $P < 0.05$ (two-sided).

Univariate analysis

Categorical variables were expressed as n (%) and compared using Chi-square test or Fisher's exact test, including onset, type, frequency, and administration of AEDs of seizure, background, SWC, and frequency detection of the aEEG. Continuous data were presented as a mean ± standard deviation (SD) and compared by independent sample's t-test between two groups, including the voltage of upper and lower margins in the AS and QS.

Multivariate analysis

Characteristics of the aEEG index, including background, SWC, and frequency detection of seizures detected by aEEG, were analyzed by logistic multivariate regression analysis to find the independent risk factors for the newborns with seizure to evolving into EOEE.

Receiver operating characteristic curve

If there is significant difference of the voltage of upper and lower margins in the AS and QS between the research and control groups, the receiver operating characteristic (ROC) curves were drawn to analyze the sensitivity and specificity among the four parameters and to calculate the best diagnostic cutoff value for predicting whether the neonatal seizure evolve into EOEE.

RESULTS

Clinical characteristics

A total of 128 full-term neonates with seizures were enrolled in the study, GA from 37 weeks to 41 weeks, BW from 2410 to 4200 g, 66 of them evolved into EOEE and were assigned to the EOEE group. Among these 66 infants, only six of them were diagnosed with EOEE within the neonatal period. Fifty-seven of them manifested neonatal refractory seizures, while the developmental retardation emerged later during follow-up and terminally diagnosed with EOEE after neonatal period. The other two patients with neonatal seizures were initially controlled by phenobarbital satisfactorily, but manifested refractory seizure till 3 months old with severely abnormal vEEG and developmental delay, were finally diagnosed with EOEE.

The onset within 7 days after birth between the EOEE and nEOEE groups had no statistically difference (52 cases vs. 44 cases, $P < 0.05$). As for the seizure frequency, 64 infants (97%) in EOEE group had daily seizure attacks,

obviously higher than 34 infants (55%) in the nEOEE group ($P < 0.05$). High seizure frequency was one of the manifestations in the newborns evolved into EOEEs. Cases of SC were five in the EOEE group and two in the nEOEE group. The incidence of SC was relatively low in our study. In respect to types of seizures, partial seizure was the main type in the two groups. In the early stage, 20 infants in EOEE group manifested as more than two types of epilepsy, while only nine in the nEOEE group ($P < 0.05$). Thus, more frequent attacks (daily seizure) and manifold seizure types can be seen as the characteristics of EOEE occurred within the neonatal period [Table 1].

The primary etiology of the enrolled cases was listed below. As for the infants in the EOEE group, 10 of them had perinatal cerebral injury, including severe hypoxic ischemic encephalopathy (HIE), hypoglycemic brain damage with occipital lobe encephalomalacia, bacterial meningitis complicated with hydrocephalus, intraventricular hemorrhage (IVH) of degree IV, bilirubin encephalopathy, cerebral infarction. Seven of them had congenital encephalodysplasia, including macrogyria, focal cortical dysplasia, and agenesis of corpus callosum. Five of them were diagnosed with congenital metabolic diseases, which were glucose transporter type 1 deficiency syndrome, maple syrup urine disease, methylmalonic aciduria, and mitochondrial disease. There were one case of tuberous sclerosis and another case of incontinentia pigmenti in our study. The etiology of other 42 cases (63.6%) in the EOEE group remained unclear in spite of various laboratory and imaging examinations had been performed. Preliminary studies indicate that agnogenic EOEE might be related to gene mutation,[9] and the results of genetic tests of part of our enrolled cases showed gene mutation in gene STXBP1, SCN1A, and KCNQ2 in our patient, which also have been reported in the previous studies.[10,11] 33 (53.2%) infants in the nEOEE group had certain etiology, and most of them were mild to moderate HIE, IVH of degree II, benign familial neonatal convulsion, transient hypoglycemia, hypocalcemia, and hypomagnesemia.

In terms of therapeutic effect, only two infants in EOEE group got well controlled by single AED during the neonatal period; however, the number of that was 46 cases (74.2%)

Table 1: Comparison of the characteristics of seizure between the EOEE and nEOEE groups

Characteristics	EOEE (n,%)	nEOEE (n,%)	χ^2	P
N	66	62		
Onset (days)			1.043	0.307
≤7	52 (78.8%)	44 (71.0%)		
~28	14 (21.2%)	18 (29.0%)		
Frequency			31.623	<0.01
intermittent	2 (3.0%)	28 (45.2%)		
daily	64 (97.0%)	34 (54.8)		
Types			4.047	0.033
≥2	20 (30.3%)	9 (14.5%)		
1	46 (69.7%)	53 (85.5%)		

in the nEOEE group, and the difference between the two groups was statistically significant (χ^2 = 71.664, $P < 0.01$). Although treated by multiple AEDs, there were still three infants in the EOEE group died of refractory seizures, the others all suffered from neurodevelopmental delay, and four of them were diagnosed with cerebral palsy. EOEEs include some syndromes such as Ohtahara syndrome (OS), West syndrome (WS), early myoclonic encephalopathy (EME), malignant migrating focal seizures of infancy, and Dravet syndrome.[2] In our study, there were 12 cases of WS, 16 of OS, and 1 of EME in the research group.

Amplitude-integrated encephalogram

VEEG is considered as the "golden standard" for the diagnosis of seizures. All the infants in our study were confirmed with seizures by vEEG and the vEEG background patterns were severely abnormal.

The number of normal aEEG background pattern CNV and DNV in the research group was 34 and 4, respectively, while 26 of them presented severely abnormal background pattern known as BS in the neonatal period. In the control group, the number of cases of CNV, DNV, and BS was 54, 6, and 2, respectively. As for the SWC, 38 infants in the research group demonstrated absence of cyclicity, while only six cases in the control group were in lack of SWC. The differences of both background pattern and

cyclicity were statistically significant between the two groups ($P < 0.05$). Therefore, severely abnormal aEEG background pattern and absence of SWC can be identified as the characteristics of aEEG of EOEE occurred within the neonatal period [Figure 1 and Table 2].

Moreover, the aEEG tracings in the study were calculated according to the algorithm described by Zhang *et al.*[5] Four parameters gained from the algorithm including the upper and lower margins of AS and QS were compared between the two groups. All of the four parameters of the research group were significantly higher than those of the control group [Table 3]. ROC curves were performed to evaluate the value of these four parameters in diagnosing EOEE [Figure 2]. According to the ROC curves, the area under the curve of AS upper margin (0.827) was larger than other three parameters, which demonstrated a higher diagnostic specificity and sensitivity for EOEE [Figure 3]. Meanwhile, a cutoff value of 23.6 μV (chosen by Youden's index) of AS upper margin provided a sensitivity of 81.5% and a specificity of 71.7%.

Forty-one cases in the EOEE group got detected of seizure attacks by aEEG monitoring, the diagnostic sensitivity was 62.1%, while the results in nEOEE group were 21 cases and 33.9%, the difference was statistically significant [$P < 0.05$, Table 2]. If recording by aEEG with raw trace, a total of 47 infants in the EOEE group were detected of
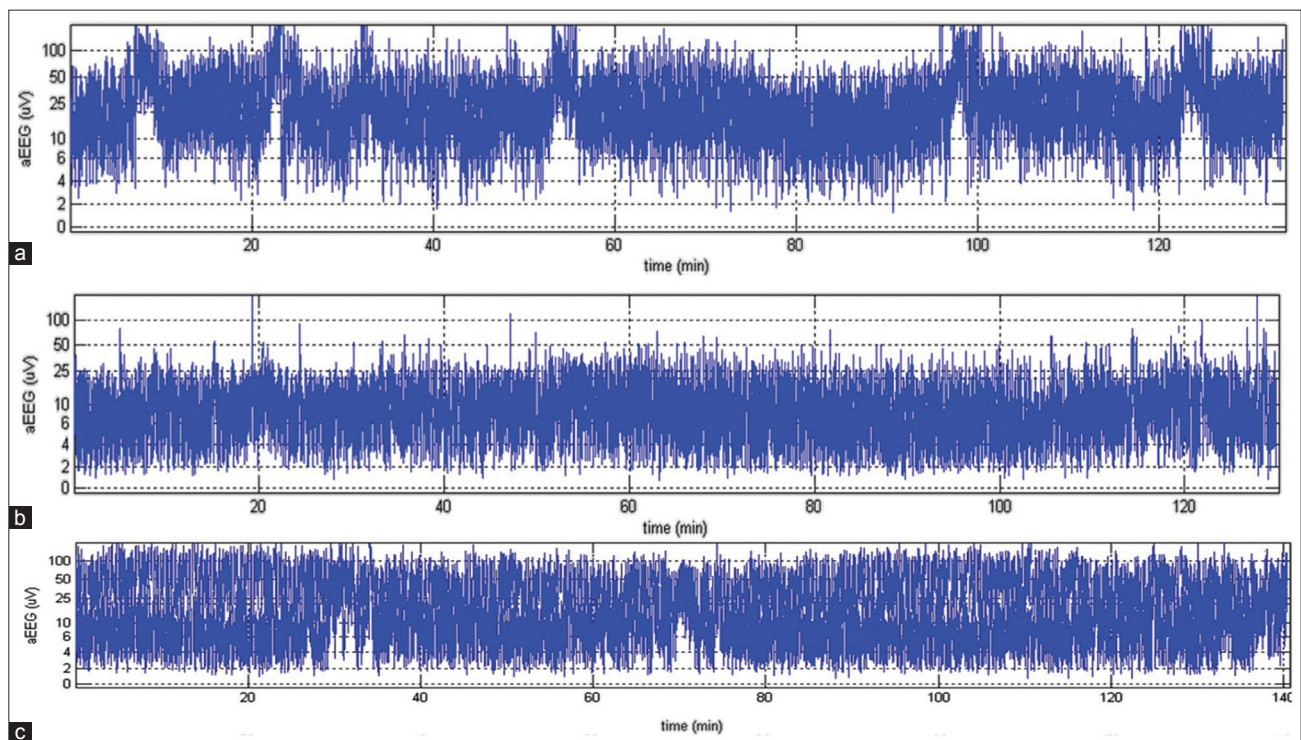

Figure 1: Characteristics of amplitude-integrated encephalogram recorded when seizures occurred in the neonatal period in infants with early-onset epileptic encephalopathy (a) continuous normal voltage background pattern, mature sleep-wake cycling, repetitive seizures detected during recording. (b) Discontinuous normal voltage background pattern, immature sleep-wake cycling, lower margin without variability, only upper margin with identifiable variation, seizure detected during recording. (c) Burst suppression background pattern, very low voltage of lower margin (2 μV), high upper margin voltage (>50 μV), dramatically broad bandwidth, absence of sleep-wake cycling, seizure detected during recording.

Table 2: Characteristics of aEEG compared between EOEE group and nEOEE group

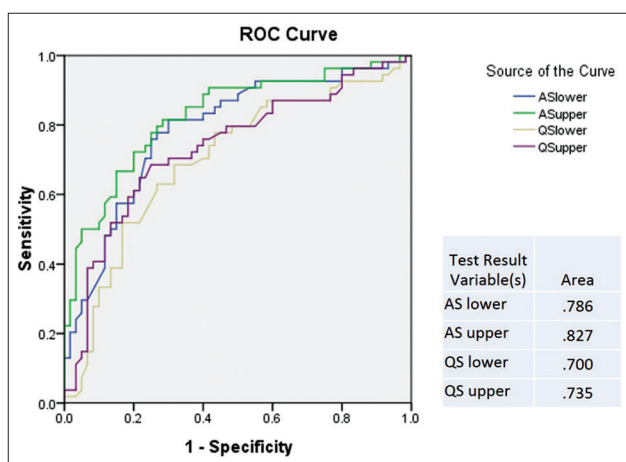| Characteristics	EOEE	nEOEE	χ^2	P
N	66	62		
Background pattern			24.470	<0.01
non-severe	40 (60.6%)	60 (96.8%)		
severe	26 (39.4%)	2 (3.2%)		
Swc			32.513	<0.01
absence	38 (57.6%)	6 (9.7)%		
existence	28 (42.4%)	56 (90.3%)		
Seizure			10.215	<0.01
with	41 (62.1%)	21 (33.9%)		
without	25 (37.9%)	41 (66.1%)		

Figure 2: Receiver operating characteristic curve and area under curve of amplitude-integrated encephalogram upper and lower margins of QS and AS.

seizures, with diagnostic sensitivity rising to 71.2%, while the corresponding outcome in the nEOEE group raised to 27 cases and 43.5%. Hence, aEEG with raw trace could improve the diagnostic sensitivity for identifying neonatal seizures and those who evolved into EOEE could be detected by aEEG more easily than those who did not.

Monitoring by aEEG with raw trace, a total of 108 times of seizure attacks were supervised in the 47 infants from EOEE group, 37 of them manifested seizures more than two times during the recording. Despite the occurrence of SC, the duration of single seizure ranged from 10 to 300 s (mean duration 60 s). While only 31 times of attacks in 27 infants from nEOEE group were recorded, two of them presented with more than two times of seizures, the duration of single seizure varied from 10 to 180 s (mean duration 51 s). Cases with seizure episodes more than two times in EOEE group were apparently more than that in nEOEE group ($\chi^2 = 19.8$, $P < 0.01$). However, there was no significant difference of single seizure duration between the two groups ($t = 0.939$, $P = 0.349$). Two main forms of seizures were showed on the aEEG of refractory seizure in EOEE group which were characterized by sudden increases of both the lower and upper margins

and a sudden burst of higher amplitude followed by a very low voltage, known as the burst-suppression pattern [Figure 3].

Among the aEEG data and parameters analyzed in our study, the difference of aEEG background pattern, cyclicity, detection of seizures, and whether more than two times of seizure attacks being recorded between the two groups had statistically significance. Severely abnormal aEEG background pattern, absence of cyclicity, detection of seizures, and more than two times of seizure attacks being detected could be considered as the characteristics of aEEG of EOEE originated within the neonatal period. Logistic multivariate regression analysis was performed and the result indicated that severely abnormal background pattern (odds ratio [OR] = 0.081, 95% confidence interval [CI]: 0.009–0.729, $P = 0.025$) and more than two times of seizures being detected ($OR = 0.158$, 95% CI: 0.043–0.576, $P = 0.005$) were the independent risk factors for the evolvement from neonatal seizure into EOEE.

Discussion

EOEEs are characterized by intractable epilepsy and developmental delay during the infantile period. Due to poor prognosis, EOEE is also intractable issues for clinicians. A few of EOEE patients originate with seizures in the neonatal period. However, it is difficult to be diagnosed as EOEE within the neonatal period since the developmental status or delay of newborns is not easy to evaluate. According to the findings of our study, only seven of all the 66 EOEE patients (10.6%) with onset within neonatal period got confirmed diagnosis in the neonatal period. By summarizing and analyzing the characteristics of clinical manifestations and aEEG of EOEE infants, we tried to present a useful approach to the early diagnosis of EOEE for pediatric clinicians, to make a contribution to the early treatment and prognosis prediction.

Previous studies have demonstrated that the causes, onset, seizure type, EEG background pattern, and AED types were associated with adverse outcomes including evolving to epilepsy, cerebral palsy, and/or neurodevelopmental retardation.[12,13] Our study finds that neonatal refractory seizures may terminally evolve to EOEE if they need more than two AEDs to control the convulsions and present as more than two seizure types together with high frequency of daily repetitive seizures. However, the onset time of seizure is not related with the adverse outcome of EOEE.

The main causes of EOEE infants started with neonatal seizures in our study are severe perinatal cerebral injury, congenital encephalodysplasia, and congenital metabolic diseases. As we know, severe perinatal cerebral injury includes severe HIE, IVH of degree IV, hypoglycemic brain damage with occipital lobe encephalomalacia, and bacterial meningitis complicated with hydrocephalus. Severe HIE, severe intracranial hemorrhage, encephalodysplasia, and congenital metabolic disorders are the main etiology of
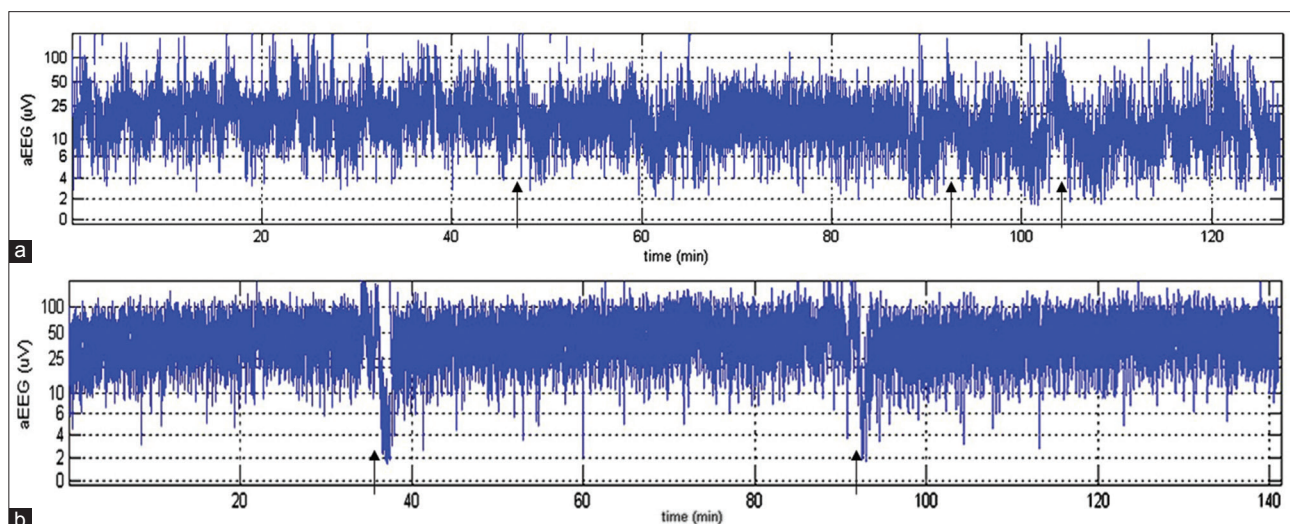
Figure 3: Amplitude-integrated encephalogram appearance of seizures of early-onset epileptic encephalopathy with onset within neonatal period. (a) Detection of repetitive seizures, presented as sudden increases of both lower and upper margins of the tracing. (b) Detection of seizure attacks twice, presented as a sudden burst of higher amplitude followed by a very low voltage, known as the burst-suppression pattern.

Table 3: Comparison of aEEG voltage (μV) between EOEE group and nEOEE group

aEEG voltage	EOEE (n = 66)	nEOEE (n = 62)	t	P	95% CI
AS lower margin	9.9 ± 3.7	6.7 ± 2.2	5.6	<0.01	2.1–4.3
AS upper margin	34.3 ± 13.6	21.3 ± 6.4	6.4	<0.01	9.0–17.1
QS lower margin	11.9 ± 4.4	9.4 ± 4.0	3.2	<0.01	0.93–4.04
QS upper margin	41.2 ± 15.1	30.4 ± 11.4	4.3	<0.01	5.78–15.8

neonatal seizures with unfavorable prognosis.[14,15] 74.2% of the infants' etiology enrolled in our study still remained unclear. Gene mutation is considered to be responsible for agnogenic EOEEs.[9] With the extensive application of next-generation sequencing (NGS) and whole exome sequencing, EOEE-related gene panels make for early and efficient diagnosis of EOEE patients and also help detecting more EOEE susceptibility genes.[10] STXBP1, ARX, SLC25A22, and KCNQ2 are some of the susceptibility genes for OS, while CDKL5, ALG13, and SCN1A are considered to be responsible for WS. The first infant enrolled in the study was in 2007; at that time, genetic mutation test was not widespreadly used in our clinical practice; thus, most of the agnogenic patients did not undergo gene testing. In recent years, we have tried to carry out more genetic tests with the consent of the patients' parents and successfully reported the first case of OS with STXBP1 gene mutation in China.[16] After detecting genetic mutation, we informed the parents with the etiology and prognosis and provided them with genetic counseling and prenatal diagnosis if they would like to conceive again.

aEEG is a method newly applied in bedside cerebral function monitoring for neonates. Compared to the conventional EEG (cEEG), fewer number of electrodes (only 3 electrodes) used and compressed complicated EEG graph make aEEG much more simply to handle and the results become more easily to interpret. It can be operated conveniently in the neonatal ward, and the neonatologists can give prompt interpretations by bedside, so the aEEG is applicable for real-time monitoring and flexible to all kinds of hospitals. The electrical background recorded by aEEG has been reported to correlate well with cEEG. It can be used to evaluate the cerebral function and degree of the brain injury and to judge the prognosis.[17,18] In neonates with seizures, abnormal aEEG background pattern could predict adverse outcome with a sensitivity of 85%, a specificity of 84%.[8,19] The neonates who evolve into EOEE suffer from much less favorable poor outcome. In our study, severely abnormal background pattern and absence of SWC were considered to be the characteristics of aEEG in the infants in EOEE group; thus, the results were consistent with the previous research. Instead of only applying qualitative data, quantitative parameters and analysis were also brought into our research. The upper and lower margins of AS and QS were calculated. Significantly increased voltage was identified as one of the aEEG characteristics in EOEE group. It may associate with frequent high amplitude electric activities during the ictal and interictal period in the research group. Among the four parameters (upper and lower margins of AS, upper and lower margins of QS), upper margin of AS owned the best diagnostic specificity and sensitivity for the prediction of evolving into EOEE. In the normal state, the QS margin was higher than AS margin, while in respect of seizure, the amplitude increased obviously in the AS because of the relatively lower baseline.
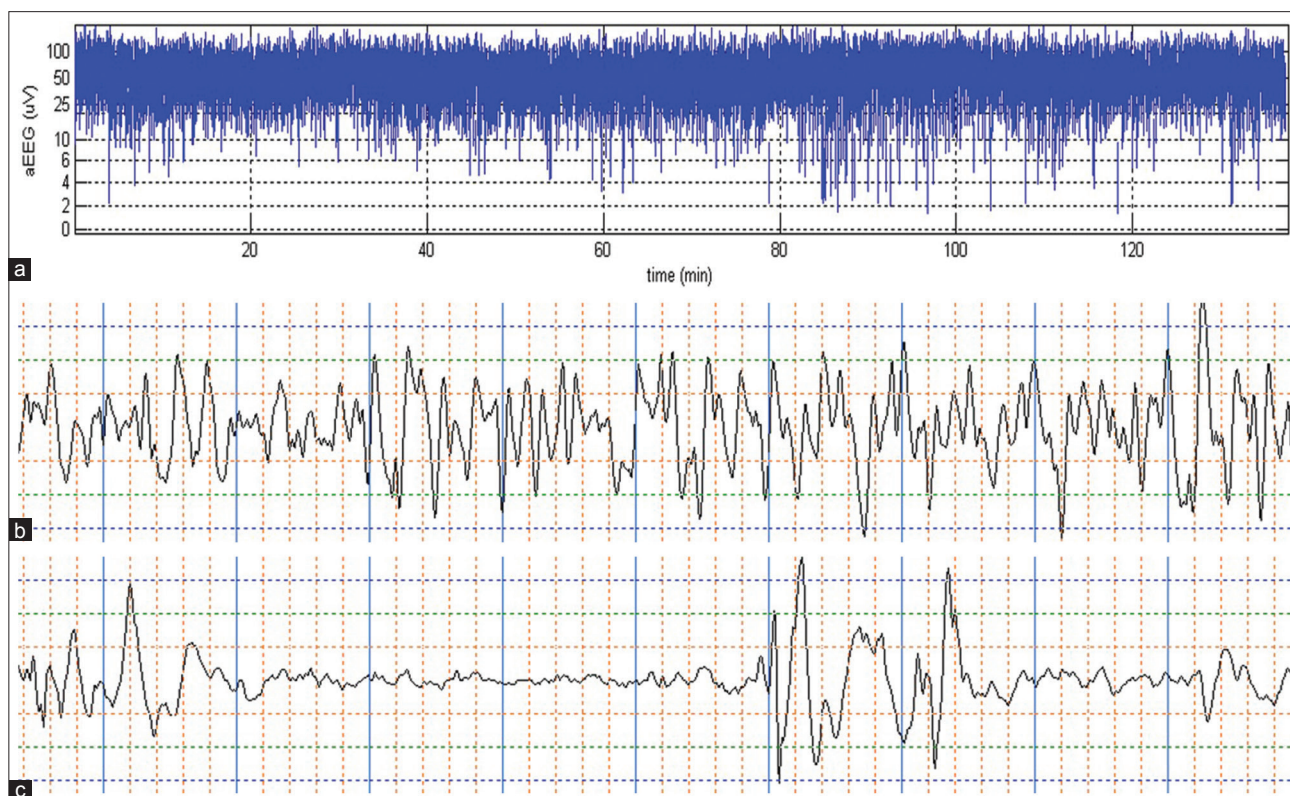
Figure 4: Appearance of amplitude-integrated encephalogram with hypsarrhythmia background pattern on video encephalogram. (a) The amplitude-integrated encephalogram background showed persistent high voltage with the absence of sleep-wake cycling. (b) The seizure activity presented on raw encephalogram while the amplitude-integrated encephalogram did not display simultaneously. The background of amplitude-integrated encephalogram among these infants showed persistent high voltage activities may cover up the real seizure attacks. (c) The burst suppression presented on raw encephalogram while the amplitude-integrated encephalogram did not display simultaneously due to the short duration of the suppression period lasting for only 4 s.

Recent studies have demonstrated that aEEG can be used for neonatal seizure screening. In respect of detecting individual seizures, using aEEG with raw trace, median sensitivity was 76% (range: 71–85%) and specificity 85% (range: 39–96%). When aEEG without raw trace was applied, the median sensitivity decreased to 39% (range: 25–80%) but with specificity increasing to 95% (range: 50–100%).[20] The diagnostic sensitivity in EOEE group was 62.1% with aEEG and rose to 71.2% with raw EEG, significantly higher than those in the nEOEE group. The positive detection rate of seizures via aEEG depended on the origination of the electric activity, frequency, duration, and voltage of the seizure and the interpreters' experience.[17,21,22] Seizure attacks more than two times during the aEEG examination was one of the aEEG characteristics in the EOEE group and may contribute to a higher detection rate. There were still seizure attacks missed in aEEG recording. In our study eight infants presented as hypsarrhythmia background pattern on vEEG, but the aEEG background of them showed persistent high voltage activities and covered up the actual seizure activities [Figure 4]. Two of these eight patients combined with BS background pattern on aEEG, and the presence of BS was also covered up because of the short duration of the suppression period lasting for 3–10 s [Figure 4]. According to these findings, it is critical that aEEG should be interpreted together with raw trace for patients with seizure. If the aEEG background manifests persistent high voltage of electric activities with the absence of SWC, a vEEG examination should be suggested to avoid missing the diagnosis of neonatal seizures.

The clinical characteristics of the neonatal seizure which terminally evolved into EOEE include the administration of more than two AEDs, high seizure frequency (daily attack), and presentation of more than two types of the seizures. Significant high voltage, severely abnormal background, and more than twice seizure attacks detected on aEEG are meaningful indicators for predicting EOEE. Severe perinatal brain damage, congenital encephalodysplasia, and congenital metabolic disorders are common causes of EOEE. If certain causes could not be found, genetic testing for these EOEE infants should be performed to determine the etiology and prognosis.

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Conflicts of interest

There are no conflicts of interest.

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