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Early aEEG can Predict Neurodevelopmental Outcomes at 12- To 18- Month of Age in VLBWI with NEC: A Cohort Study

Si Chen
Second Affiliated Hospital & Yuying Children's Hospital of Wenzhou Medical University
Xiuman Xiao
Second Affiliated Hospital & Yuying Children's Hospital of Wenzhou Medical University
Su Lin
Second Affiliated Hospital & Yuying Children's Hospital of Wenzhou Medical University
Jianghu Zhu
Second Affiliated Hospital & Yuying Children's Hospital of Wenzhou Medical University
Lidan Liang
Second Affiliated Hospital & Yuying Children's Hospital of Wenzhou Medical University
Minli Zhu
Second Affiliated Hospital & Yuying Children's Hospital of Wenzhou Medical University
Zuqin Yang
Second Affiliated Hospital & Yuying Children's Hospital of Wenzhou Medical University
Shangqin Chen
Second Affiliated Hospital & Yuying Children's Hospital of Wenzhou Medical University
Zhenlang Lin
Second Affiliated Hospital & Yuying Children's Hospital of Wenzhou Medical University
Yanli Liu (254340319@qq.com)
Second Affiliated Hospital & Yuying Children's Hospital of Wenzhou Medical University

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Abstract

Background Studies have shown that neurological damage is not uncommon in NEC survivors. The purpose of the study was to investigate the predictive value of amplitude integrated electroencephalogram (aEEG) for neurodevelopmental outcomes in preterm infants with neonatal necrotizing enterocolitis (NEC).

Methods Infants with NEC (n=13) were selected, and the control group was selected according to 1:1-2 pairing by gestational age. We performed single-channel (P3-P4) aEEG in two groups. The Burdjalov score system was evaluated and compared between the two groups. Cranial magnetic resonance imaging (MRI) was performed at term equivalent age. And the neurological outcomes at 12-18 month of age were compared with Gesell Developmental Schedules (GDS).

Results There was good consistency between the two groups in general conditions, except for the highest C-reactive protein (CRP) and incidence of thrombocytopenia. In the 1st aEEG examination, the incidence of retardation in Co (7/10:0/16), Cy (8/10:0/16), LB (6/10:0/16), B (8/10:0/16) and Total score(9/10:0/16) were significantly increased in the NEC group ($p \leq 0.01$). Cranial MRI in NEC group revealed widened inter-parenchymal space with decreased myelination. The Gesell Developmental Schedules (GDS) assessment indicated that NEC children had inferior performance and lower mean scores in the sub-domains of gross motor (73.12±10.742:94.13±10.366, P<0.001), fine motor (68.15±10.323:100.04±12.608, P<0.001), adaptive behavior (74.79±9.774:100.24±12.175, P<0.001), language (68.59±12.593:96.37±11.493, P<0.001), personal-social responses (82.36±16.013:97.58±11.834, P=0.010) and in overall DQ (73.08±8.901:98.02±9.289, P<0.001). The results of the logistic binary regression analysis revealed that NEC patients had a significantly increased risk of neurodevelopmental retardation compared to no NEC patients (aOR = 27.00, 95% CI 2.561 – 284.696, P = 0.006). Confirmed by Spearman's rank correlation analysis, the neurodevelopmental outcome was significantly affected by 1st aEEG Burdjalov score (r=0.603, p=0.001). The abnormal 1st Burdjalov score has predictive value for neurodevelopmental retardation with high specificity (84.62%) and positive predictive value (80.00%).

Conclusions Early aEEG in NEC patients suggested inhibition of brain function. NEC children are more likely developing neurodevelopmental delay. And there're high specificity and PPV of the early aEEG in predicting neurodevelopmental retardation.

Introduction

In the past two decades, with the development of neonatal intensive care technology, the survival rate of premature infants, especially those ELBW, has been greatly improved, and the incidence of necrotizing enterocolitis (NEC) increased significantly. The incidence of NEC in very low and extremely low birth weight infants is as high as 5%, and the mortality rate exceeding 25%[1]. NEC seriously endanger the

health of premature infants. Studies have shown that neurological damage is not uncommon in NEC survivors. But little research has been done on how to assess neurological damage early in NEC patients.

Amplitude integrated electroencephalogram (aEEG) is the third generation of brain function monitoring technology designed by Maynard in the late 1960s[2], and has been applied in neonatal intensive care units since the 1980s[3]. aEEG is an amplitude integration of the original EEG, and output 6cm/h, reflecting the background activity. aEEG can also be used in children on ventilation or mild hypothermia therapy. At present, the application of aEEG in neonatal intensive care unit includes hypoxic ischemic encephalopathy (HIE) and mild hypothermia therapy[4][5], neonatal convulsion[6], intracranial hemorrhage[7], severe congenital heart disease[8], metabolic diseases[9] and bilirubin encephalopathy[10]. However, the application of aEEG in brain function monitoring of premature infants is still in its infancy. Studies have shown that preterm aEEG background was associated with gestational age and corrected gestational age, and the postnatal brain function of preterm infants showed catch-up development[11][12]. And early aEEG examination can predict prognosis of premature neural development[13][14]. Abnormal aEEG tracings such as discontinuous low voltage, low voltage, the outbreak-inhibition (BS) activities, lack of sleep-wake cycles, were confirmed with brain damage by ultrasound and head magnetic resonance imaging (MRI) in the later follow-up. However, most newborns with normal aEEG background do not have such abnormalities. The purpose of this study was to analyze the relationship of aEEG tracing and neurological prognosis of preterm infants with neonatal NEC.

Methods

A total of 13 preterm NEC infants who admitted in a level III NICU of the second affiliated hospital of Wenzhou Medical University between October 2017 and October 2018, were enrolled in the study. So the selected cases were the patients who admitted to the same NICU unit during the same period, excluding the interference of nursing and environmental factors. In all enrolled infants, the infants with the following diseases happened before aEEG examination were excluded: intrauterine distress, neonatal asphyxia, intracranial hemorrhage (III degree and above), hydrocephalus, periventricular leukomalacia (PVL), HIE, bilirubin encephalopathy, intracranial infection, hypoglycemic encephalopathy, brain malformations, severe chronic lung disease (sCLD), intrauterine growth retardation, complex congenital heart disease, chromosomal disorders and genetic metabolic diseases. All the cases were not treated with sedative or analgesic medications within 24h before aEEG recordings. A total of 10 patients were finished follow-up. A control group with 16 normal preterm infants of the same gestational age with NEC group was set up according to 1:1–2 pairing. In the no NEC infants, aEEG recordings were performed at the same gestational age as well as the corrected gestational age in each group.

Necrotizing enterocolitis was defined clinically, radiologically or histologically according to modified Bell's staging criteria[15]. Medical NEC was diagnosed as Bell's stage II or lower. Medical management included withdrawal of feeds, antibiotic usage and symptomatic support measures. Infants were classified as surgNEC as Bell's stage III and operation was performed. In NEC group, 6-h aEEG recording was conducted in the following four time periods: 24 to 72 hours (1st), 1week (2nd), 2week (3rd) and 3week

(4th) after surgery in surgNEC or after diagnosis in medNEC. In the control group, aEEG examination was completed synchronously at the same age of correction day.

The aEEG recording (NicoletoneTM Monitor) was conducted by neonatologist. According to the international 10–20 system of electrode placement, P3 and P4 were selected as the one-channel electroencephalogram from 2 parietal needle electrodes to gain aEEG tracing. Only recordings with an impedance < 10 kΩ were analyzed. The frequencies were between 2 ~ 30Hz and the signal were displayed on a semi-logarithmic scale at a speed of 6cm/h.

The aEEG tracings were reviewed by two neonatologists who had many years of aEEG interpretation and were blinded to the clinical data. Background activity classification was carried out according to the scoring system developed by Burdjalov and colleagues[16], which consists of Co (continuity of the recording), Cy (presence of sleep-wake cycle (SWC)), LB (lower border amplitude score), and B (bandwidth), to assess objectively the developmental maturation of the premature infants, in order to facilitate the assessment of premature infants at different gestational age.

Each subject underwent a complete cranial MRI at term equivalent age. Plain cranial MRI scans were performed by using a head coil in a 1.5 Tesla whole-body imaging system (Philips Gyroscan Intera, Best, the Netherlands.). The MRI sequences included axial T1-weighted imaging (T1WI), T2-weighted imaging (T2WI), fluid attenuated inversion recovery (FLAIR) sequence transverse-sectional T2WI and diffusion-weighted imaging (DWI) sequence. T1WI scan was performed with T1-weighted spin-echo (195/5 [repetition time msec/echo time msec]) and T2WI scan was performed with T2-weighted spin-echo (transverse-sectional slices: 5350/134 or 3500/99). T2WI and DWI scan was performed with T2-weighted spin-echo (transverse-sectional slices: 8000/88). Thickness/spacing was 5.00/6.00mm or 4.00/4.40mm for transverse-sectional slices. Uncooperative infants were given chloral hydrate enema (0.5ml/kg) sedative before the exam. The MRI findings were evaluated by two radiologists who were blinded to the clinical data.

All the infants enrolled in the study were followed up by neurologist and physiotherapist blinded to clinical diagnosis in our hospital. Neurodevelopmental outcomes were assessed using Gesell Developmental Schedules (GDS) at 12- to 18- month of age. Neurodevelopmental outcomes were classified into 2 groups according to overall developmental quotient (DQ) score: delay if scores of DQ < 85 (DQ scores < 70 were defined as retardation, Scores of 70–84 indicated moderate delay), normal if DQ ≥ 85.

Statistical analyses were performed using IBM SPSS, version 25. Measurement data were expressed as median (SD), and t-test or Mann-Whitney U test were used to inter-group comparison. Categorical data were analyzed with Pearson's chi-squared test or Fisher's exact test(when the expected frequency was less than 5). Spearman's rank correlation analysis was used to analyze the correlations of aEEG to the prognosis of nervous system. We define Burdjalov score as normal when the score reaches the respective postconceptional age; otherwise we define abnormal. The risk factors of abnormal neurodevelopmental outcome were analyzed with logistic binary regression. The receiver operator characteristic (ROC) was

calculated to evaluate the predictive value of abnormal Burdjalov score in predicting neurodevelopmental outcome, and enable us to calculate the sensitivity, specificity, positive predictive value and negative predictive value.. $P < 0.05$ was considered as statistically significant.

Results

A total of 13 preterm infants with secondary NEC were enrolled in the NEC group, 1 patient was dead before discharge; 1 patient had severe secondary intracranial hemorrhage (IVH) discovered after operation, so the patient's aEEG recordings was analyzed separately, but was not included in the follow-up of this study. And another patient was lost to follow up due to accidental death. A total of 16 normal preterm patients completed follow-up study. In NEC group there were 9 surgNEC patients. All surgical procedures were uneventful, and the vital signs were maintained at normal levels during the perioperative period. None of the infants were given sedative and analgesic treatment after postoperative anesthesia. All surgNEC patients were given fasting, gastrointestinal decompression (mean 8.5 days), respiratory support (mechanical ventilation for 16 days in 1 case, and the others 4.5 days in average), anti-infective treatment (broad-spectrum antibiotics were used), and correction of anemia (suspended red blood cells were transfused in 7 cases). All cases were transfused with plasma, albumin and intravenous nutritional support, and given dopamine therapy. There was 1 medNEC patient, the medical management of which included withdrawal of feeds for 7 days, intravenous nutritional support, antibiotic usage and symptomatic support. In the control group, the infants were fed normally with intravenous nutrition, respiratory support and symptomatic therapy during aEEG recordings. The conditions of the two groups in gender, gestational age, birth weight, Apgar score, IVH, highest serum C-reactive protein (CRP), ibuprofen treatment rates in patent ductus arteriosus (PDA), incidence of retinopathy (ROP) and CLD were shown in Table 1. As can be seen from the table, male proportion and the highest CRP value in NEC group were significantly higher than those in the control group. The highest CRP of the 5 infants in the NEC group was greater than 200mg/l, which was calculated as 200mg/l in the statistics.

Table 1
Epidemiological data of the study group.

Clinical characteristics	NEC	No NEC	*P* value
Male	10/10	6/16	0.001[a]
Gestational age, weeks	28.90(SD = 1.194)	29.29(SD = 1.119)	0.899[b]
Birth weight, g	1223.00(SD = 148.926)	1323.75(SD = 157.729)	0.119[b]
Small for gestational age	0/10	0/16	/
Apgar-1min	8.00(SD = 1.160)	9.00(SD = 1.000)	0.336[c]
Apgar-5min	9.00(SD = 0.738)	10.00(SD = 0.512)	0.100[c]
IVH grade I or II	3/10	5/16	0.946[a]
IVH grade III or IV	0/10	0/16	/
Highest CRP(mg/l)	150.78(SD = 49.010)	10.89(SD = 8.462)	< 0.001[b]
PDA treated by Ibuprofen	1/10	3/16	1.000[a]
ROP	3/10	2/16	0.340 [a]
CLD	3/10	7/16	0.683 [a]

Values are presented as medians (SD) or number/total number. [a]Fisher's exact test, [b]T test and [c]Mann-Whitney U test were used. $P < 0.05$ was considered as statistically significant.

The aEEG features of NEC infants including discontinuous background not consistent with gestational age, absence of SWC and abnormal waveform like epileptic electrical activity. Here are two examples of the representative tracing analysis, which are shown in Figs. 1. The first infant (Fig. 1a) was 29 + 1 weeks' gestation, whose birth weight was 1230 g and Apgar scores were 9-9-9. He was diagnosed NEC after born 9ds and underwent surgery the next day. aEEG at 24 ~ 72h hours postoperatively indicated functional inhibition of the brain (discontinuous, no cycling). The lower part of the figure (Fig. 1a) displayed abnormal burst-suppression background pattern at 12s in raw EEG. In fact, aEEG in preterm infants with cGA of 30^{+6} w is characterized by continuous background, visible but incomplete cycles, elevated lower borders, and immature bandwidth. The second infant (Fig. 1b) was 30 + 5 weeks' gestation; birth weight was 1580 g and Apgar scores were 9-10-10. He was diagnosed NEC after born 6ds and underwent surgery on the same day. After surgery, he was found seizures, and his aEEG at 24 ~ 72h hours postoperatively indicated electrographic status epilepticus, and continuous low voltage was displayed in the following aEEG monitoring. The lower part of the figure (Fig. 1b) displayed epileptic electrical activity at 12s in raw EEG. Cranial MRI (corrected gestaional age (cGA) 41w) showed longer T1(a and b) and T2(c and d) abnormal signal changes, demonstrating severe cerebral hemorrhage in the right parietal temporal

lobe, left parietal temporal lobe and bilateral external capsule area, with hydrocephalus (see Fig. 2 online only). He was not included in the follow-up and correlation studies. We've got a patient with medNEC, and his first aEEG Burdjalov score was 2 at 31 + 4w of cGA.

According to the scoring system developed by Burdjalov and colleagues[16],the Burdjalov total scores and separate entities such as continuity, SWC and bandwidth were compared with the reference indicators, which were considered normal if the score met or exceeded the level of corrected gestational age, and abnormal if the score lagged behind the corrected gestational age. The results showed that compared with no NEC group, the incidence of abnormal Co (7/10:0/16), Cy (8/10:0/16), LB (6/10:0/16), B (8/10:0/16) and Total score(9/10:0/16) were significantly increased in the NEC group ($p \leq 0.01$). However, in 2nd aEEG, 3rd EEG and 4th aEEG recordings, the incidence of abnormal T (2/10:0/16; 2/10:0/16; 0/10:0/16) was not significantly different between both groups.

A total of 12 NEC infants had received cranial MRI examination, among which 5 cases presented widened inter-parenchymal space with cerebral tissue volume lessened (2 cases among these had decreased myelination). One of the infants was 28 + 1 weeks' gestation, birth weight was 1260 g and Apgar scores were 7-9-9. He was diagnosed NEC after born 10ds and underwent surgery the next day. aEEG at 24 ~ 72h hours postoperatively indicated functional inhibition of the brain (total score 3), and the Burdjalov scores at 1w, 2w and 3w were 4, 9, 13 separately. Ultrasonography indicated white matter and gray matter damage 5ds after surgery. The brain MRI (correct gestational age (cGA) 38 + 4w) showed brain retardation (like premature infants). Bilateral basal ganglia region, both cerebral cortical and subcortical diffuse patchy distribution of longer T1, longer T2 and lower Flair T2 abnormal signal changes, with local gyrus slightly swollen. This case was lost to follow up, for he died accidentally when he was 8-month old (see Fig. 3). In the control group, 16 infants received MRI examination, while no obvious abnormalities were found.

To assess intelligence and motor outcome, GDS were used on 10 NEC patients and 16 normal preterm infants at 12- to 18-month of age. The GDS DQ assessment indicated that NEC children had inferior performance and lower mean scores in the sub-domains of gross motor (73.12 ± 10.742:94.13 ± 10.366, $P < 0.001$), fine motor (68.15 ± 10.323:100.04 ± 12.608, $P < 0.001$), adaptive behavior (74.79 ± 9.774:100.24 ± 12.175, $P < 0.001$), language (68.59 ± 12.593:96.37 ± 11.493, $P < 0.001$), personal-social responses (82.36 ± 16.013:97.58 ± 11.834, $P = 0.010$) and in overall DQ (73.08 ± 8.901::98.02 ± 9.289, $P < 0.001$). In NEC group, there were 2 children with scores < 70, 7 children with scores 70–84, 1 child with normal score (= 85). In the contrast group, there were 2 children with scores of 70–84, 14 children with normal scores (≥ 85).

In this study, we found that among 13 infants with neurodevelopmental delay (DQ < 85), 9 (69.23%) infants had NEC; among 13 infants with normal neurodevelopmental outcome(DQ ≥ 85), 1 (7.69%) infant had NEC.The difference in the proportion of NEC among patients with normal neurodevelopmental outcome versus delay neurodevelopmental outcome was statistically significant ($P < 0.001$). Logistic binary regression analysis was performed for the influencing factors of poor neurodevelopmental

outcome. Considering the exclusive criteria in all enrolled infants: intrauterine distress, neonatal asphyxia, intracranial hemorrhage (III degree and above), hydrocephalus, periventricular leukomalacia (PVL), HIE, bilirubin encephalopathy, intracranial infection, hypoglycemic encephalopathy, brain malformations, severe chronic lung disease (sCLD), intrauterine growth retardation, complex congenital heart disease, chromosomal disorders and genetic metabolic diseases. Therefore, the factors included in the study were financial difficulties, parental education(below middle school), maternal age ≥ 35 years, male, hCRP, platelets < 100×10^9/l, and NEC. After univariate analysis, statistically significant factors were included in the logistic binary regression analysis, and the results revealed that NEC patients had a significantly increased risk of abnormal neurodevelopmental outcome compared to no NEC patients (aOR = 27.00, 95% CI 2.561–284.696, P = 0.006) after adjusting for male, hCRP > 50mg/l and platelets < 100×10^9/l.

Following Spearman's rank correlation analysis, there was a positive correlation between 1st Burdjalov score of aEEG and neurodevelopmental outcome ($r = 0.603$, $p = 0.001$), but no significant difference with the 2nd Burdjalov sore ($r = 0.337$, $p = 0.092$) and 3rd Burdjalov score ($r = 0.337$, $p = 0.092$). And the 4th Burdjalov scores all reached the normal level according to cGA in both groups.

When we worked on the assumption that infants with abnormal 1st Burdjalov scores to postconceptional age would be likely to suffer from neurodevelopmental delay, and infants with normal Burdjalov scores would be likely to be neurologically normal in later life, the area under the receiver operator characteristic curve(ROC) was 0.806 ($p = 0.010$), the sensitivity was 61.74%, the specificity was 84.62%, the positive predictive value was 80.00%, and the negative predictive value was 68.75%.

Discussion

Subjects were strictly included in this study. The infants enrolled in the two groups were preterm infants of appropriate gestational age whose GA < 32w. All the patients had a smooth birth process, with no history of intrauterine distress or asphyxia, and had ≤ degree I/II hemorrhage. In our study, the infants in the NEC group showed a significant increase in CRP level after secondary NEC, and even went through septic shock. Highest CRP level in the control group was significantly lower than that in the NEC group. As an acute phase protein and becomes raised in the inflammatory process, the serum CRP concentration is commonly used as a surrogate marker for infection. NEC can cause a severe overwhelming systemic inflammatory response. Several clinical studies have shown associations between infection and cerebral injury[17][18][19][20][21][22]. And studies have shown that inflammatory response generated in response to NEC can result in clinical decompensation with brain injury or death[23]. The preterm infants with surgNEC showed severe WMI on brain MRI[24].The mental and motor development of NEC survivors was significantly lower than that of normal premature infants[25][26][27][28]. A follow-up study at age 7 found that children with NEC had an increased incidence of cerebral palsy and hyperactivity, as well as impaired reading, writing, math and social skills[29]. In this study, Neurodevelopmental outcome was assessed at 12 to 18 months of age using GDS in the NEC group, and the DQ scores of gross motor, fine motor, adaptive behavior and language were significantly lower than those in the control group, indicating the existence of neurodevelopmental retardation. To assess the impact of NEC on preterm infants' brain

development at an early stage, we conducted aEEG examination at different time periods without using sedative or pain relief drugs postoperatively. Based on the study by Lisanne J S., recovery to preoperative brain activity occurred within 24 hours after cessation of anesthesia in most preterm infants[30]. The first examination was scheduled at 24 ~ 72h after surgery, with an average of 48h, and rechecked at 1w, 2w and 3w.

Burdjalov and colleagues[16] developed a scoring system which consists of Co (continuity of the recording), Cy (presence of SWC), LB (lower border amplitude score), and B (bandwidth), to assess objectively the developmental maturation of premature infants. The scores of premature infants with brain injury were lower than the corresponding gestational age or adjusted gestational age[31],[32]. Recent studies have pointed out a correlation of early aEEG parameters with short- and long-term neurological outcome[13][33][34]. Cerebral maturation measured by Burdjalov scores and onset of cyclicity during the early NICU course were associated with cerebral injury and other perinatal exposures[35]. Early amplitude-integrated EEG with moderate/severe abnormalities in the background is associated with severe structural lesions detected in imaging studies in very low birth weight infants[36]. In aEEG tracing, discontinuous background or BS pattern were the result of brain damage. The presence of SW cycling in preterm babies matures with age, which has been shown by multiple studies[37], and was another important parameter for evaluating the cerebral function. In our study, we discovered that a NEC patient with intracranial hemorrhage developed seizures. Unfavorable outcomes following seizures in preterm infants include death, epilepsy and neurodevelopmental impairment[38]. In this study, after diagnosis or 24 ~ 48h after surgery, most infants with NEC showed abnormalities such as voltage discontinuity, absence of sleep wake cycle, bandwidth enlargement or electrographic epilepticus, and the total scores using Burdjalov. scoring system decreased significantly. So aEEG was a useful tool for early detection of brain function.

Neurodevelopmental outcomes are of importance in these preterm NEC infants, but after discharge, these outcomes may be influenced by many factors such as nutrition, socioeconomic status, parents' education level and early intervention[39],[40],[41]. Indeed, some children become left-behind and were even unable to live with their parents. All the factors will affect children's cognitive and social abilities. However, cranial MRI at term equivalent age can avoid these factors and show brain development from the structural level. Neonatal brain development is in the period of glial cells maturation and white matter fiber myelin formation, during which brain biochemical composition and water content change greatly, and MRI signal changes are complex. Brain MRI in preterm infants is characterized by thin cortex, high water content in white matter (decreased myelination) and widened inter-parenchymal space. 4/10 NEC infants including the medNEC patient had the brain MRI image of some of the above anomalies, which may demonstrated neurodevelopmental retardation. In addition, one NEC patient was excluded from follow-up due to severe cerebral hemorrhage and hydrocephalus after surgery.

NEC patients had a significantly increased risk of abnormal neurodevelopmental outcome compared to no NEC patients after adjusting for gender, hCRP and platelets. As to gender, it was caused by coincidence and susceptibility that all the infants in NEC group were male. A study held by Spagnoli C.

suggested that male premature infants may be the high-risk factor for secondary NEC[38]. This suggests that gender may have some correlation with NEC. At the same time, we also compared the two groups of children in terms of economic factors, parental education, maternal age, and family income, and there was no significant difference.

Our study indicated that neurodevelopmental retardation was associated with 24-72h aEEG Burdjalov score. We found a high specificity of 84.62% and positive predictive value of 80.00% for abnormal early aEEG (24-72h) with respect to an adverse neurological prognosis.

The shortcoming of this study is that the sample size included in this study is relatively small. This is because of the gradual improvement of premature infant management in Wenzhou area, and of the remarkable achievements in the prevention and treatment of complication. In addition, NEC infants were not divided into the surgery group and the medicine group, and we suggested further studies in qualified units.

Conclusions

In summary, early aEEG during 24-72h after NEC diagnosis or operation suggested inhibition of brain function. Cranial MRI may reveal brain retardation or severe intracranial hemorrhage. Prognosis at 12- to 18-month age suggested that NEC children are more likely developing neurodevelopmental delay. And there’re high specificity and PPV of early abnormal Burdjalov score (24-72h) in predicting neurodevelopmental retardation.

Abbreviations

aEEG: Amplitude-integrated electroencephalography; NEC: neonatal necrotizing enterocolitis; GDS: Gesell Developmental Schedules; DQ: development quotient; CLD: chronic lung disease; CRP: C-reactive protein; MRI: magnetic resonance imaging

Declarations

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Availability of data and materials

The datasets generated and analysed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Authors' contributions

SC performed project design, medical records collection, and article writing. XXX and SL performed aEEG tracing interpretation and assisted in case collection. JHZ performed subject design guidance and paper modification. LDL performed Gesell scoring. MLZ, ZQY and SQC assisted in follow-up of the discharged patients. ZLL performed paper modification, and YLL performed quality control and statistical analysis. All authors read and approved the final manuscript.

Authors' information

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Ethics approval and consent to participate

Written informed consents have been obtained from the parents of subjects under 16 years of age for this study, and has got ethics approval and consent by Research Ethics Committee of the Second Affiliated Hospital of Wenzhou Medical University. The Ethical Approval Number was LCKY2019-287.

Competing interests

The authors declare that they have no competing interests.

Author details

[1]Department of Neonatology, [2]Children's Rehabilitation Department, the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Zhejiang,Wenzhou, China

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Figures

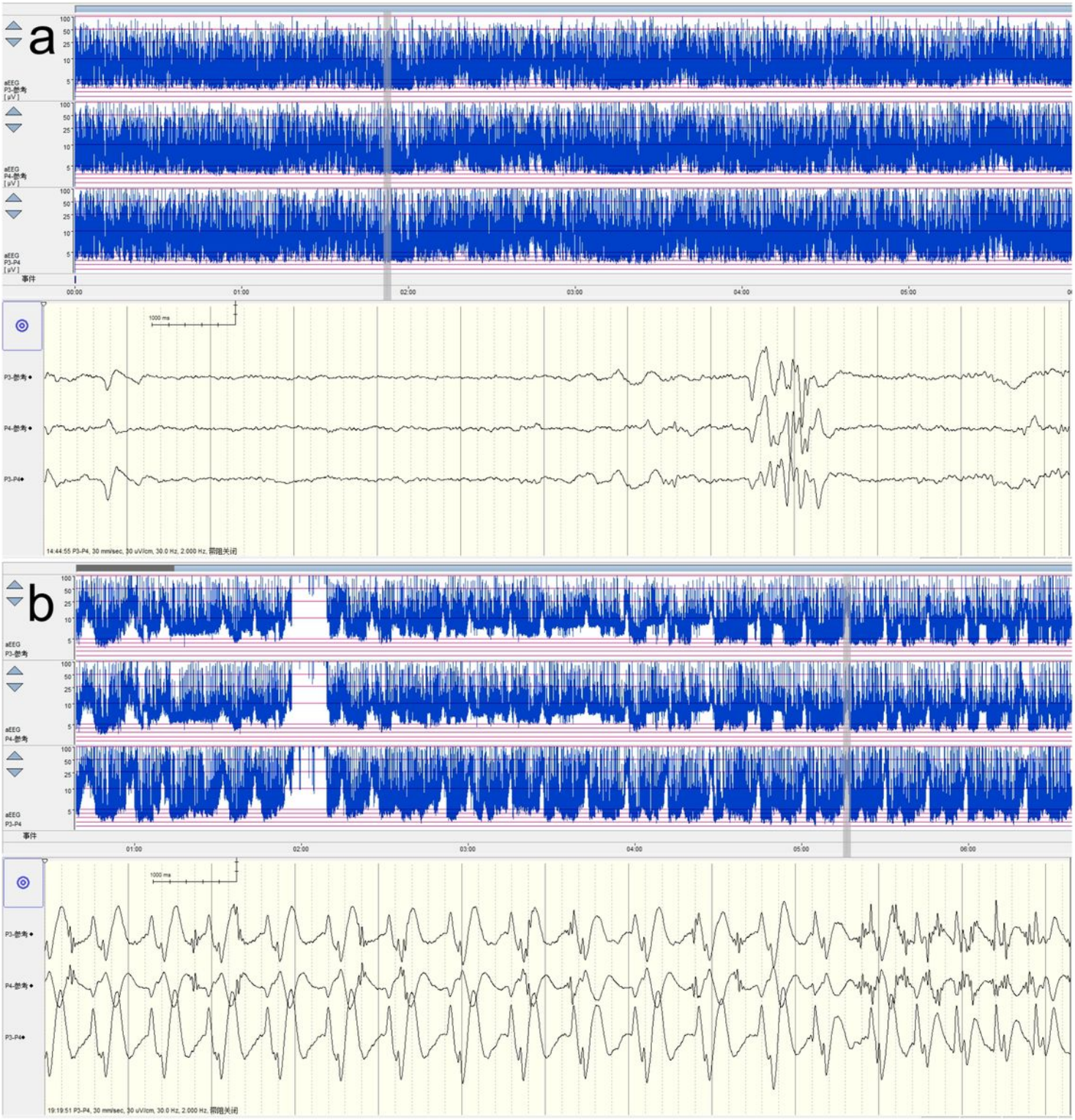

Figure 1

two examples of the representative tracing analysis of NEC infants.

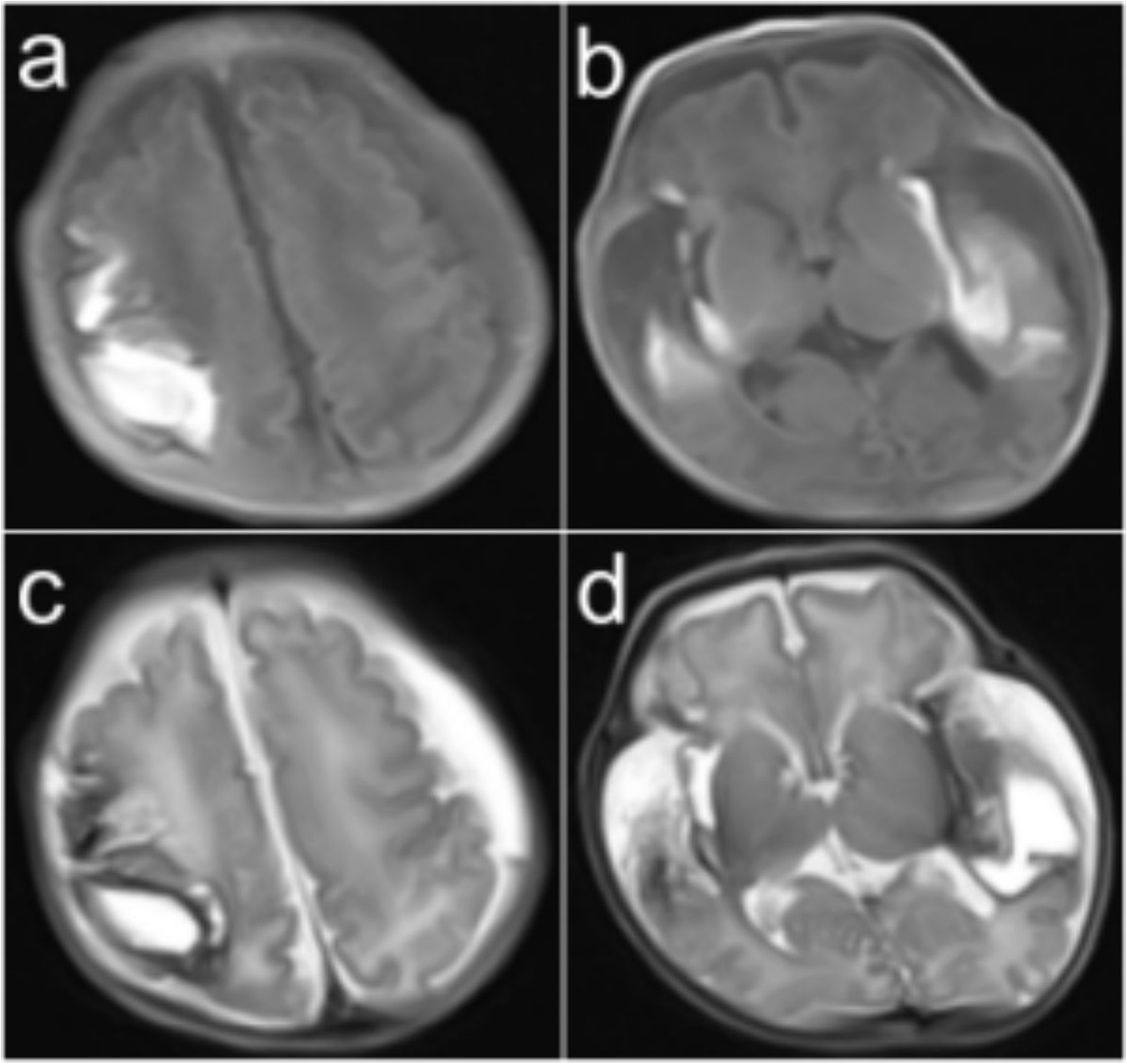

Figure 2

online only brain MRI of a NEC infant; longer T1(a and b) and T2(c and d).

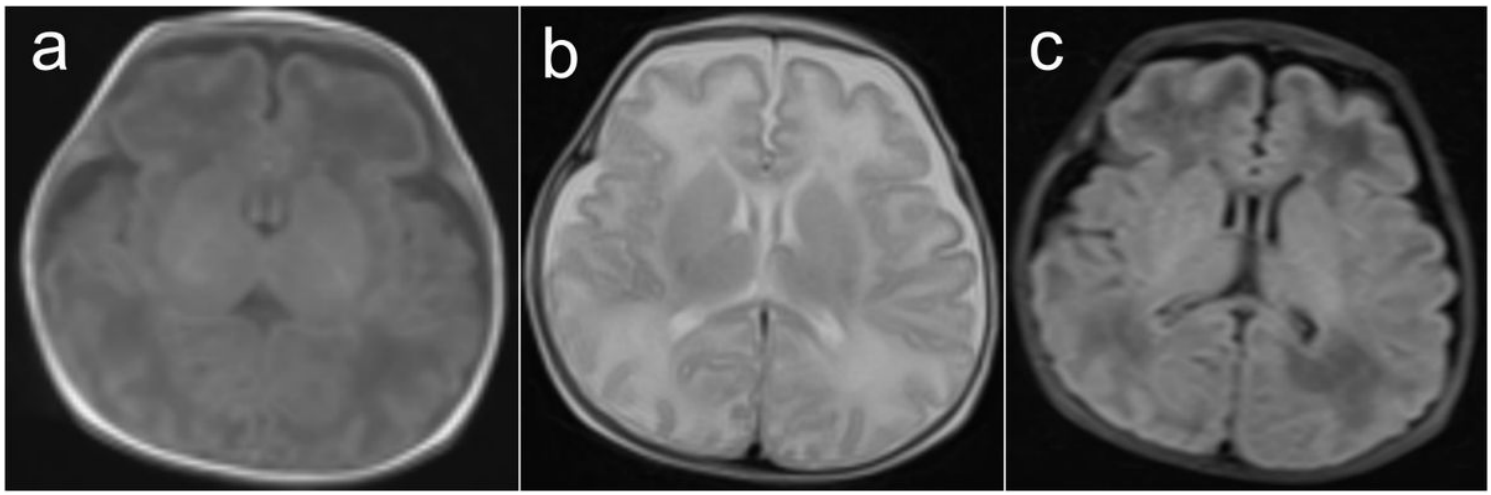

Figure 3

brain MRI of a NEC infant; longer T1(a), longer T2(b) and lower Flair T2(c).