·Original Article·

Diagnostic value of amplitude-integrated electroencephalogram in neonatal seizures

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Abstract: **Objective**   To investigate the accuracy of amplitude-integrated electroencephalography (aEEG) in detecting full-term neonatal seizures. **Methods**   Conventional EEG (cEEG) and aEEG were simultaneously applied to 62 full-term newborns with seizures and results were analyzed with different methods. **Results**   Of 876 seizures confirmed by cEEG, 21% were detected by clinical observation, 44.4% by aEEG and 85.7% by aEEG plus C3/C4 raw EEG. Of 531 seizures with a frequency higher than 5 times/h, 52.5% were detected by aEEG and 96.8% by aEEG plus C3/C4 raw EEG. Of 510 seizures lasting longer than 60 s, 50.6% were diagnosed by aEEG and 84.1% by aEEG plus C3/C4 raw EEG. Of 509 seizures originating in the central region, 57.9% were detected by aEEG and 90.9% by aEEG plus C3/C4 raw EEG. **Conclusion**   Combination of aEEG with cEEG offers more accurate diagnosis, especially for detecting high-frequency, long-lasting and central region-generated seizures.

Keywords: electroencephalography; cerebral function monitoring; amplitude-integrated electroencephalography

1   Introduction

Term infants with seizures have very poor outcomes[1], which have been shown in animal experiments[2] and clinical observations[3]. Approximately 20% of the infants with seizures die in the neonatal period and survivors have a 28%–35% probability of having severe neurodevelopmental disabilities and a 20%–50% probability of having epilepsy[3].

Before the application of electrophysiological examination in neonatal intensive care unit (NICU), seizures could only be diagnosed through clinical observation. Bedside long-term electroencephalography (EEG) monitoring

is a common method to diagnose seizures in NICU[4]. It remains a gold standard for seizure detection and also the best way to identify, quantify and classify neonatal seizures[5]. However, it is labor-intensive to both set up conventional EEG (cEEG) and interpret the results. Many NICUs have tried to adopt amplitude-integrated EEG (aEEG) as an alternative way to identify electrographic seizures. aEEG is a non-invasive cerebral function monitor method that shows a reflection of the EEG background. Signals collected from the parietal (or central) of the skull are highly filtered, processed, and compressed to show an envelope of lower and upper amplitudes of the EEG signal at a speed of 6 cm/h. However, aEEG has not been routinely applied in most NICUs in China. The aim of the present study was to compare the accuracy of cEEG and aEEG in neonatal seizure detection through simultaneous monitoring, and to improve the application skills of aEEG.

2   Material and methods

2.1 Patient information   Between Jan 2006 and Jan 2010, cEEG was immediately applied to all full-term newborns, who were suspected of having clinical seizures, to detect the electrographic seizure. Once an electrographic seizure was confirmed, monitoring was extended immediately, and aEEG was activated simultaneously. Totally 62 cases were included for analysis. All the patients were not sedated during monitoring. General information of patients was listed in Table 1. Parameters were shown as percentage or presented as mean ± SD. The study was approved by the Medical Ethics Committee of Huazhong University of Science and Technology.

Table 1. General information of patients (n = 62)

Parameters	Statistics
Conceptional age (week)	38.6±1.6
Male percentage	56.5% (35/62)
Weight (kg)	3.4±0.8
Length of monitoring (hour)	11.5±3.6
Age in days when monitoring (day)	3.4±0.9
Diagnosis	
Hypoxic-ischemic encephalopathy	32(51.6%)
Intracranial infection	11(17.7%)
Metabolic disturbance	9(14.5%)
Intracranial hemorrhage	5(8.1%)
Unknown	5(8.1%)

2.2 Monitoring method   Monitoring was carried out by an experienced EEG technician with a bedside polyparameter digital EEG equipment (EBNEURO, Italy). A prewired EEG cap containing 11 recording electrodes (P3 and P4 were added additionally) was used for monitoring. The recording electrodes, which were placed according to the modified 10–20 system for neonates, were Fp1/Fp2/C3/Cz/C4/P3/P4/O1/O2/T3/T4, along with 1 ground electrode (Fig. 1). Polyparameters were obtained from a pair of electromyogram electrodes, bilateral eye electrodes, a pair of respiratory electrodes and a pair of electrocardiographic electrodes. All recordings were synchronized.
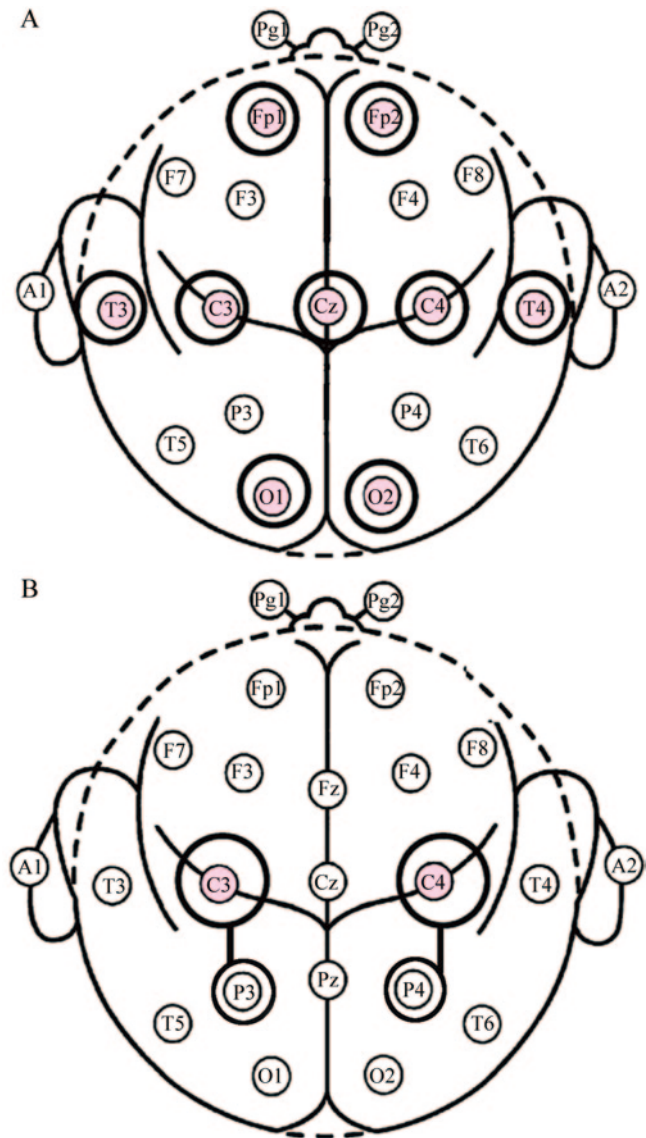
Fig. 1 A: Placement of EEG electrodes by the 10–20 system modified for neonates. B: Amplitude-integrated EEG was derived from the C3-P3/C4-P4 raw signal.

2.3 Analysis method   aEEG was derived from the C3-P3/C4-P4 raw EEG signal (low frequency filter 2 Hz, high frequency filter 15 Hz, speed 6 cm/h), and was transformed through a fast Fourier transform (FFT). The background pattern and epileptiform activity on the aEEG tracings were assessed visually according to the criteria by Toet *et al*[6]. Background pattern was classified as continuous normal voltage (continuous activity with voltage of 10–50 µV), discontinuous normal voltage (mainly continuous normal

voltage with periods of more discontinuous intermittent low voltage activity, without burst suppression), burst suppression (discontinuous background pattern where periods of very low voltage, or inactivity, intermixed with bursts of higher amplitude), continuous extremely low voltage (continuous background pattern of very low voltage of around or below 5 μV), or flat tracing (very low voltage, mainly inactive, isoelectric, tracing with activity below 5 μV). Epileptiform activity, where present, was classified as a single seizure, repetitive seizures, or status epilepticus. The presence or absence of sleep-wake cycling (changes in the width of the trace) on aEEG tracings was also noted. In healthy newborns, the trace is wider during sleep and narrower when they are awake. cEEG, aEEG and aEEG+C3/C4 raw signal were obtained from the same recording. The last 2 were derived directly from the first one. EEG results of each group were interpreted by 2 independent analyzers, who were blind to the patient information and to the other groups.

2.3.1 Clinical observation Two neonatologists with over 5 years of working experience evaluated only the video part of the recording to locate the suspected clinical seizures and documented the duration and manifestation of the seizures.

2.3.2 aEEG Another 2 expert neonatologists evaluated only real-time aEEG to locate the suspected seizures and documented the duration of the seizures. These neonatologists had no special knowledge of EEG and no previous experience in reading the cerebral function monitor (CFM) traces.

2.3.3 aEEG+C3-P3/C4-P4 raw signal Two electroencephalographers with 5-year experiences evaluated aEEG plus C3-P3/C4-P4 raw signal after the recordings were finished to locate seizures, and documented the duration of the seizures.

2.3.4 cEEG Another 2 expert electroencephalographers evaluated cEEG plus synchronized video information to locate seizures and documented the seizure onset, evolution, termination and duration of the seizures. cEEG results were taken as the final standard. An electrographic seizure was defined as a sudden, repetitive, evolving, and stereotyped ictal pattern having clear beginning, middle, and end, with an amplitude of ≥ 2 μV and a minimum duration of 10 s[6]. Individual seizures separated by a minimum of 10 s were counted as separate events. Tonic-spasm and myoclonic seizures were not included in this study. The average number was documented when inter-observer disagreement occured.

2.4 Statistic methods Data of 4 different methods were expressed as diagnostic percentage. McNemar test was used to compare the diagnostic rate of aEEG with the rate of aEEG plus C3/C4 raw EEG group. $P < 0.05$ was considered to be statistically significant.

3   Results

Among the 154 neonates suspected of having clinical seizures, 62 of them were confirmed by cEEG and were included in further monitoring (Table 2).

As shown in Table 2, a total of 876 electrographic seizures were detected by cEEG from the 62 patients. Only

Table 2. Seizure detection by clinical observation, aEEG, aEEG+C3/C4 raw EEG, and cEEG

|	Clinical observation	aEEG	aEEG+C3/C4 raw EEG	cEEG
Patients with seizures	62(100%)	11(17.7%)*	44(70.9%)	62(100%)
Individual seizures	184(21%)	389(44.4%)*	751(85.7%)	876(100%)
Seizure frequency > 5 per hour	145(27.3%)	279(52.5%)*	514(96.8%)	531(100%)
Seizure frequency < 5 per hour	39(11.3%)	110(31.9%)*	237(68.7%)	345(100%)
Seizure duration > 60 s	105(20.6%)	258(50.6%)*	429(84.1%)	510(100%)
Seizure duration < 30 s	12(7.6%)	6(3.8%)	13(8.3%)	157(100%)
Seizure from central origination	131(25.7%)	295(57.9%)*	463(90.9%)	509(100%)
Seizure from other origination	53(14.4%)	94(25.6%)*	288(78.5%)	367(100%)

*$P < 0.05$ *vs* aEEG+C3/C4 raw EEG group. Data were expressed as the percentage to that in cEEG group.

21% of the 876 individual seizures were detected by clinical observation, and aEEG recording detected 17% of the 62 patients and 44.4% of the individual seizures respectively. Besides, 70.9% of the 62 patients and 85.7% of the individual seizures were detected by aEEG+C3/C4 raw EEG, which were higher than the rates in aEEG group. These results showed that a large number of seizures would be ignored by clinical observation or simple aEEG monitoring, but aEEG combined with C3/C4 raw EEG significantly improved this situation.

3.1 Seizures with different frequencies The detection rates of seizures with different frequencies by the above 4 methods were analyzed. The majority of the 876 seizures (531 seizures) had higher frequencies (> 5 attacks hourly). The detection rates of these seizures were 27.3% and 52.5% by clinical observation and aEEG respectively. When aEEG was combined with C3/C4 raw EEG, the detection rate of high-frequency seizures increased to 96.8%, almost the same as that in cEEG group. For the

seizures with lower frequencies (< 5 attacks hourly), the diagnostic rates by clinical observation and aEEG recording decreased to 11.3% and 31.9%, respectively. When aEEG was combined with C3/C4 raw EEG, the diagnostic rate was significantly increased to 68.7%. These results demonstrated the advantage of aEEG plus C3/C4 raw EEG recording in detecting high-frequency seizures (Fig. 2).

3.2 Seizures with different durations The detection rates of seizures with different durations were analyzed. Among the total 876 individual seizures, 510 lasted for over 60 s. The detection rates for these seizures were 20.6%, 50.6% and 84.1% by clinical observation, aEEG and aEEG plus C3/C4 raw EEG respectively. The detection rates of seizures lasting for less than 30 s were lower than 10% by the above 3 recording methods. There was no statistic difference between aEEG group and aEEG plus C3/C4 group. The results showed that seizures with longer durations are more easily to be captured by aEEG plus C3/C4 raw. There was no effective way to detect the briefer seizures except
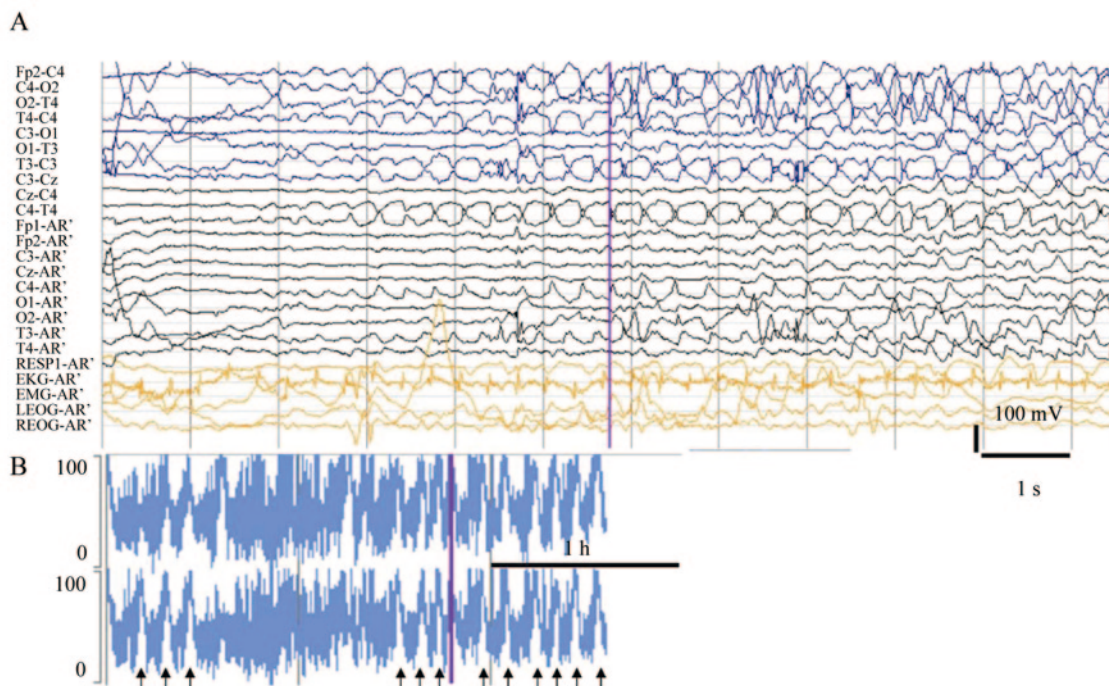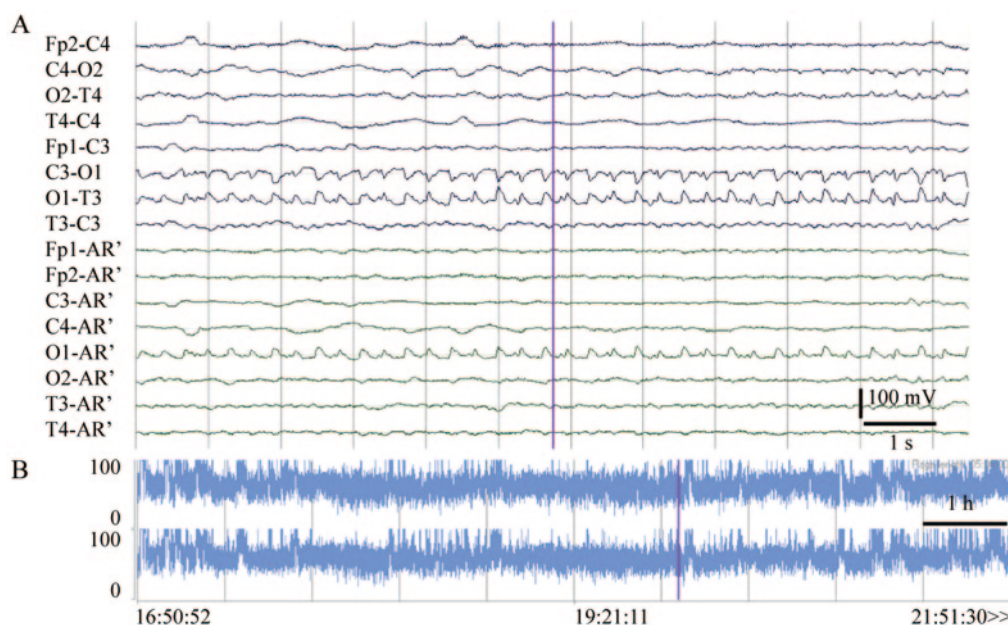

Fig. 2 Amplitude-integrated EEG (aEEG) had better detection for high-frequency seizures. A: A representative full conventional EEG (cEEG) recording. The seizures originating from the right central part (C4) with a frequency higher than 5/h were detected. B: A representative 3-h aEEG from the same patient. It displayed the repetitive high-frequency seizures during 3 h. The purple vertical lines represented simultaneous time cursors in cEEG and aEEG. Arrows indicated the seizures.

cEEG.

3.3 Seizures with different origination About 58.1% of the seizures (509 of 876) originated from the central part (C3/C4/Cz), and 41.9% seizures (367 of 876) were from the other parts of brain. As shown in Fig. 3, aEEG showed only the seizures with central origination or involved. For the seizures originating from the central part, the detection rates by clinical observation, aEEG and aEEG plus C3/C4 were 25.7%, 57.9%, and 90.9% respectively. The rates in the former 2 groups were obviously lower than that in cEEG group. For the seizures originating from the other parts of the brain, clinical observation and aEEG were less effective, and the detection rates were 14.4% and 25.6% respectively. The detection rate by aEEG plus C3/C4 was 78.5%, which was significantly higher than that by aEEG. These results demonstrated the advantage of aEEG+C3/C4 raw EEG in detecting both central- and other part-originating seizures.

Fig. 3 Seizures of different origination were revealed by conventional EEG (cEEG) (A) and amplitude-integrated EEG (aEEG) (B). A: The seizures originating from the left occipital (C3-O1, O1-T3, O1-AR) were detected by cEEG. B: A 10-h aEEG of the same patient. Localized seizures in left occipital shown in cEEG were not recorded by aEEG. No single seizure could be recognized from the aEEG trace. The purple vertical lines represented simultaneous time cursors in cEEG and aEEG.

4   Discussion

A prolonged bedside cEEG with concurrent video recording is considered the only accurate and timely diagnostic standard for neonatal seizures[7]. However, although this technique has been utilized in many NICUs, it highly relies on the apparatus and techniques[8]. In contrast, aEEG needs less electrodes (1 or 2 recording electrodes) and is convenient for long-time recording and simple to analyze. Studies have shown that aEEG correlates well with cEEG, and is even more advantageous than cEEG in background pattern's acquirement and classification[9]. cEEG is easily influenced by sedatives and aEEG has a less extent of influence by sedatives because it mainly reflects the background pattern[10]. Due to the above reasons, aEEG use is becoming popular in clinics.

Both aEEG and cEEG have been used extensively in the NICUs in the US and Europe. Similar to the situation in our study, cEEG is mainly interpreted by neurophysiologists whereas aEEG is usually interpreted by neonatologists. Most of the staff were not confident in their ability to

interpret EEGs despite the fact that they used monitoring routinely, and even half received no formal training in EEG[8]. The lack of training programs in EEG methodology and EEG interpretation for neonatologists has restricted the diagnostic value of aEEG in NICUs.

We found in the beginning of this study that only 40% of the patients (62/154) with observed seizures could be confirmed and 21% of seizures of the 62 patients were properly diagnosed by clinical observation. These results indicate that even the diagnoses made by "experienced experts" are problematic.

In our study, all simultaneous aEEG and cEEG traces from 2006 to 2010 were analyzed. Compared with the other studies, one advantage is the longer monitoring time [(11.5 ± 3.6) h]. In fact, longer simultaneous monitoring of aEEG and cEEG is difficult to achieve. We observed and analyzed the 4-year data retrospectively and found that no matter how experienced the neonatologists or EEG staff were, aEEG and clinical observation were not reliable in diagnosing neonatal seizures. When aEEG was combined with unprocessed C3/C4 EEG traces, more seizures were found and the diagnose value was close to cEEG. The majority of the found seizures had a high frequency (> 5/h) and a long duration (> 60 s), and were central originating.

aEEG alone is not sufficient to detect seizures and sometimes it may cause overdiagnosis of neonatal seizures[11]. On the other hand, Rennie et al.[12] have reported that over half of the neonatal seizures are missed during aEEG by non-experts. Whether a seizure can be recorded by aEEG depends on if there are amplitude changes on the recording channels. A seizure originating from and localized on the other channels besides C3/C4 cannot be recorded. The theoretical seizure detection value of aEEG which is predicted from the number and the duration of seizure on C3/C4 of cEEG is relatively high, but the practical rate is much lower. In the present study, we analyzed the missing seizures and tried to explain this low relevance ratio of aEEG. The results showed that the seizures with non obvious amplitude changes were difficult to be recognized on aEEG trend even if there were changes in the 2 raw EEG channels from which aEEG was derived. aEEG reflects the amplitude information. Seizures without obvious changes were easily ignored if aEEG was not combined with C3/C4 unprocessed EEG signals. The brief seizures were also easily ignored, since a 30-s seizure length shown on the aEEG trend was only 0.5 mm with a recording speed of 6 cm/h, and a 60-s seizure length is only 1 mm.

In a similar study of Lawrence R et al.[13], 12-h aEEG and cEEG were simultaneously recorded, and a software-based seizure event detector was used to diagnose neonatal seizures. Approximately 55% of the individual seizures and 87% of the seizures longer than 60 s were detected by an aEEG detector. The corresponding detection rates in our study were 44.4% and 50.6% respectively. When aEEG was combined with C3/C4 unprocessed raw EEG, 85.7% of individual seizures and 84.1% of seizures longer than 60 s were detected. It seems that this method is effective for all seizure recognition and the software-based seizure event detector has a better detection rate for longer seizures.

In conclusion, aEEG cannot serve as a substitute for cEEG to detect neonatal seizures. The detection rate by aEEG increases when aEEG is combined with raw EEG signals. cEEG remains as an exclusive method to diagnose seizures with low frequency and low duration.

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波幅整合脑电图对新生儿惊厥的诊断价值

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摘要：**目的** 观察波幅整合脑电图(aEEG)诊断足月新生儿惊厥的准确性。**方法** 对62名有惊厥表现的足月新生儿同时进行传统脑电图(cEEG)和aEEG检查，并将检查结果用不同方式进行分析。**结果** cEEG检查发现的876次惊厥中，有21%是通过临床观察发现的，44.4%可由aEEG诊断，85.7%可由aEEG附加C3/C4原始图诊断。在531次发作频率超过5次/小时的惊厥中，aEEG诊断了52.5%而aEEG附加C3/C4原始图诊断了96.8%。在510次持续60秒以上的惊厥中，aEEG诊断了50.6%而aEEG附加C3/C4原始图诊断了81.4%。在中央区起源的509次惊厥中，aEEG诊断了57.9%而aEEG附加C3/C4原始图诊断了90.9%。**结论** 结合cEEG的aEEG才能对新生儿惊厥，尤其是发作频率高、持续时间长以及中央区起源的惊厥提供更准确的诊断。

关键词：脑电图；脑功能监测；波幅整合脑电图