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Acute neonatal encephalopathy and seizures recurrence: A combined aEEG/EEG study

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ABSTRACT

Purpose: To evaluate amplitude-integrated EEG (aEEG) in comparison with conventional (cEEG) for the identification of electrographic seizures in neonates with acute neonatal encephalopathies.
Methods: Thirty-one conventional cEEG/aEEG long-term recordings from twenty-eight newborns were reviewed in order to assess the electrographic seizure detection rate and recurrence in newborns. Two paediatric neurologists and one neonatologist, blinded to the raw full array cEEG, were asked to mark any events suspected to be an electrographic seizures on aEEG. They were asked to decide if the displayed aEEG trace showed the pattern of a single seizure (SS), repetitive seizures (RS) or status epilepticus (SE). Their ability to recognize electrographic seizures on aEEG was compared to seizures identified on full array cEEG.
Results: 25 of the 31 long-term cEEGs recordings showed electrographic seizures. The two paediatric neurologists and the neonatologist identified SE in 100% of the reviewed traces using aEEG alone while they identified 49.4% and 37.5% of electrographic seizures using aEEG alone. Overall, the correct identification ranged from 23.5% to 30.7% for SS and 66% for RS. The inter-observer agreement (k) for the identification of SE for the two paediatric neurologists and the neonatologist was 1.0. Overall the inter-observer agreement (k) for the detection of SS, RS and SE of the two paediatric neurologists was 0.91.
Conclusions: In our study the observers identified SE in 100% of the reviewed traces using raw aEEG alone, thus aEEG might represent a useful tool to detect SE in the setting of NICU. SS may not be reliably identified using aEEG alone. Simultaneous recording of the raw cEEG/aEEG provides a good level of sensitivity for the detection of neonatal electrographic seizures.

1. Introduction

Epileptic seizures are more frequent in the neonatal period than at any other time during life. They commonly occur in the setting of an encephalopathy and can have a wide range of etiologies.[1,2] Noteworthy, seizure burden is an important issue because a high seizure frequency may worsen the previous brain impairment.[1] Clinical detection of neonatal epileptic seizures is difficult because not all the infants show overt clinical manifestations of seizures and the detection of them represents a particular diagnostic challenge in the neonatal intensive care unit (NICU): seizures frequently present just with subtle signs, or are entirely non-convulsive, with no clinical manifestation.[2–4] In this setting, seizures may be only detectable by electroencephalography (EEG) and the long term EEG recording is the method commonly used to detect the presence and burden of electrographic seizures. The use of conventional multichannel EEG (cEEG), sometimes including video recordings, is considered the best method for this purpose. However, it is a cumbersome technique in the NICU that needs specialized personnel for both application and interpretation. For these reasons, amplitude integrated EEG (aEEG) technology has been increasingly used in the NICU.[5] Amplitude integrated EEG depicts time-compressed and rectified EEG amplitude on a semi-logarithmic scale, and is now commonly employed to monitor cerebral function in neonates.[6] Of note, their use in the NICU requires minimal training. While aEEG provides an accurate

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measure of neonatal EEG background, its utility for seizures identification remains a matter of debate.[7] For this reason aEEG monitoring technique has been used to improve electrographic seizures identification rate using multichannel recordings.[5] The aim of this study was to assess the electrographic seizures occurrence and recurrence in the setting of acute neonatal encephalopathy using long-term aEEG monitoring as compared to cEEG.

2. Methods

All infants were studied at the NICU of "Vittore Buzzi" Hospital, Milan. Our hospital's IRB approved this study and granted a waiver of informed consent.

We identified all neonates with an encephalopathic condition by means of a continuous cEEG/aEEG monitoring from March 2009 to August 2012. The simultaneous conventional/aEEG recording was used in order to compare seizure detection. Recording of aEEG in our unit was indicated for all infants at high risk for neurological insult (e.g. infants after severe birth asphyxia, infants with suspected clinical seizures, infants with intracerebral haemorrhage). In this retrospective analysis we included only cEEG/aEEG recordings of at least a 12 h duration that were performed as per the following indications: suspicion of non-convulsive seizures in a patient deemed to be at risk; to investigate the evolution of the cEEG/aEEG background during therapeutic hypothermia or to characterize clinical events suspected to represent seizures.

2.1. EEG recordings

EEG electrodes were applied to the scalp at F1, F2, C3, C4, T3, T4, O1, O2, and CZ (according to the international 10–20 system of electrode placement, as modified for neonates.

A Micromed EEG monitor (Micromed SystemPlus, Mogliano Veneto, Italy) was used to record continuous EEG recordings. This device has software which also displays raw aEEG in real time. EMG activity, EKG and abdominal respiration were monitored.

The aEEG was derived from a two-channel recorder (C3-T3, C4-T4) and was displayed on a conventional semi-logarithmic scale (linear from 0 to 10 μV and logarithmic from 10 to 100 μV). The signal was then compressed to a rate of 6 cm/h.

According to Scher et al.,[8] an electrographic seizure was defined as an event of at least 10 s, characterized by a series of abnormal repetitive discharges with demonstrable onset, time course, and conclusion with respect to EEG frequency, waveform morphology, electrical field and amplitude. Periodic epileptiform discharges, defined as repetitive sharp transients, either occurring in isolation or in repetitive runs without evolution into discrete electrographic seizures, were not scored as seizures. An electrographic seizures in the aEEG was categorized as an abrupt rise in the minimum amplitude accompanied by a rise in the maximum amplitude.[9] Repeated seizures were identified as repeated peaks in the aEEG trace and described as a "sawtooth pattern". Status epilepticus was depicted as continuous increase of the lower and upper margin.[9,10] In order to detect electrographic seizures each aEEG recording was scored for epochs of 30 min and classified as: (1) single seizures (SS): 1 electrographic seizure per each epoch; (2) repetitive seizures (RS): more than 1 electrographic seizure per epoch but less than 1 electrographic seizure over a 10 min period.

We are aware of the lack of a clear consensus regarding the definition of status epilepticus (SE) in the neonate.[11] Noteworthy, SE is defined in two ways: (a) continuous seizure activity for at least 30 min, or (b) recurrent seizures for ≥50% of the recording time ranging from 1 to 3 h.[8] We used these temporal criteria to define SE. Moreover, according to Mizrahi,[12] since our recordings were ≥12 h, we also defined SE as a continuous electrographic seizure longer than 15 min and/or more than 1 electrographic seizure over a 10 min period.[11]

A "missed seizure" was defined as a seizure detectable by raw cEEG but not recognizable by aEEG.

2.2. Assessment method

Amplitude-integrated EEG recordings were assessed independently by two paediatric neurologists (VB and IF) with neonatal cEEG and aEEG expertise and by a senior neonatologist (PF) with no prior experience using aEEG device. The neonatologist first underwent 10 h of training, during which she was introduced to the theoretical basis of aEEG, followed by extensive hands-on training on the recognition of electrographic seizures and various artefacts, employing a training set of 12 continuous EEG recordings performed in the NICU. During the training, the neonatologist had the opportunity to review aEEG displayed simultaneously with the underlying raw EEG. Following the training, the neonatologist was evaluated on her ability to identify electrographic seizures using aEEG display. The two paediatric neurologists and the neonatologist were informed that the purpose of the study was to determine their ability to identify seizures from artefacts using raw aEEG, without the raw cEEG traces for those channels available, and they were asked to make a decision if aEEG showed a pattern of SS or RS or SE. The investigators were blinded to cEEG data.

The senior paediatric neurologist (MM) simultaneously reviewed aEEG/cEEG traces to assess the correspondence between the two EEG devices.

2.3. Analysis

The ability for seizure identification and the false positive rate were calculated by comparing the suspected electrographic seizures on aEEG device, marked by the two paediatric neurologists and the neonatologist, with the seizures identified by the gold standard analysis of the raw EEG. Correct identification were recognized when a mark was placed on a seizure or within 30 s of the seizure onset or offset. False-positive were defined as a mark placed anywhere else in the recording. Observers were asked to identify seizures from non-epileptic events on aEEG display. Each EEG recording was presented in a different random order.

A Kappa statistic was used to measure inter-observer agreement and agreement with the correct response. Kappa (k) is the proportion of agreements after agreement by chance is excluded. Values range from +1 to −1. If there is perfect agreement the Kappa coefficient will be equal to 1. A negative Kappa indicates that the observers agree less frequently than by chance.

All values were considered significant at $p < 0.05$. All statistics were implemented using Statistica v 8.0 (Statsoft, USA).

3. Results

A total of 28 neonates were monitored using aEEG/cEEG recordings from March 2009 to August 2012. All of the infants were admitted directly to the NICU at the V. Buzzi Hospital of Milan. Overall the infants were enrolled at birth, and the mean (SD) time from birth to commencement of EEG monitoring was 5.7 (2.3) hours. Apgar scores of ≤5 at 5 min occurred in 15 of the 28 neonates. An initial pH of ≤7.0 occurred in 9 patients while BD less than −15 mEq/L or more occurred in 13 out of 28 neonates.

The most common indication for continuous EEG monitoring was the suspicion of non-convulsive seizures and SE. Diagnoses among patients undergoing EEG monitoring were various, the most common being hypoxic-ischaemic encephalopathy (HIE) (Table 1).

Table 1
Demographic characteristics of study subjects.

Patient	28
Gestational age (wk) and birth	39.4 ± 1.6
Sex (M/F)	18M/10F
Birth weight (g)	3250 ± 705
Primary diagnosis (*n*)	
HIE	9
Epilepsy	6
Intracranial haemorrhage	5
Meningitis/encephalitis	4
Genetic/metabolic disease	4
Total no. of EEG recordings	31
Duration of recording (h)	15.5 ± 3.0
No. of EEG recordings	31
No. of recordings containing seizures	25
Seizure types (*n*; %)	
Status epilepticus	(7; 22.6)
Repetitive seizures	(12; 38.6)
Single seizures	(6; 19.4)
No seizures (*n*; %)	(6; 19.4)

HIE: hypoxic-ischaemic encephalopaty.

Thirty-one long-term aEEG/cEEG recordings were analyzed and, of these, 25 contained electrographic seizures. Seven neonates had SE; RS was observed in twelve patients; six patients showed a SS pattern and six neonates had no epileptic seizures (Table 1). Status epilepticus and prolonged seizures appeared on aEEG trace as a continuous increase of the lower and upper margin and as a sawtooth pattern as well (Fig. 1). This was completely subclinical (i.e. non-convulsive) in six neonates. Overall the six patients without electrographic seizures were diagnosed as having HIE (all grade 2 according Sarnat and Sarnat). In 11 out of the 28 infants the first recorded clinical seizures consisted of apnoea, lip smacking or limb cycling. In five patients, clonic limb jerking was recorded.

The use of antiepileptic drugs (AEDs) was reviewed. Five infants, with subclinical seizures only, received no medication. Eleven received phenobarbital as first-line AED and nine infants received phenytoin as a second-line AED. Two infants received pyridoxine.

A total of 1240 seizures were recorded in our study. The two paediatric neurologists and the neonatologist identified 49.4% and 37.5% of seizures respectively by using aEEG. Interestingly, all the three investigators identified SE on aEEG device in 100% of the reviewed traces (Fig. 1). Correct identification ranges from 23.5% to 30.7% of SS and 66% of RS (Fig. 2). Overall 50–60% of the seizures were completely missed by all 3 reviewers on aEEG display. Missed seizures fell into two categories: (i) the seizures were of short duration (<20 s) and (ii) the amplitude was less than 40 mcV (Fig. 3). Some of the missed seizures not diagnosed by the neonatologist were suspected on the aEEG traces but discarded. Moreover, seizures that occurred in the context of abundant interictal epileptiform discharges were also missed.

False positive rates did vary among the 31 individual recordings. Overall, these false-positive rates were quite low, corresponding to 1 false-positive per 15 h of aEEG displayed. Two EEG recordings resulted in particularly high median false positive rates due to movement or electrode artefact mimicking electrographic seizures with no clear changes on cEEG.

Interestingly, overall the observers showed an excellent concordance to detect artefacts on aEEG traces (Table 2).

The inter-observer agreement (k) for paediatric neurologists was 0.91 ($p < 0.0001$). The agreement with correct responses between the two paediatric neurologists and the neonatologist was >0.7 ($p < 0.0001$).

4. Discussion

The aim of our study was to compare aEEG and cEEG techniques for seizures detection and recurrence in neonates with acute encephalopathy. Our results showed that: (i) SE and prolonged electrographic seizures can be easy disclosed by aEEG device; (ii) overall the observers missed approximately half of the short SS using aEEG alone.

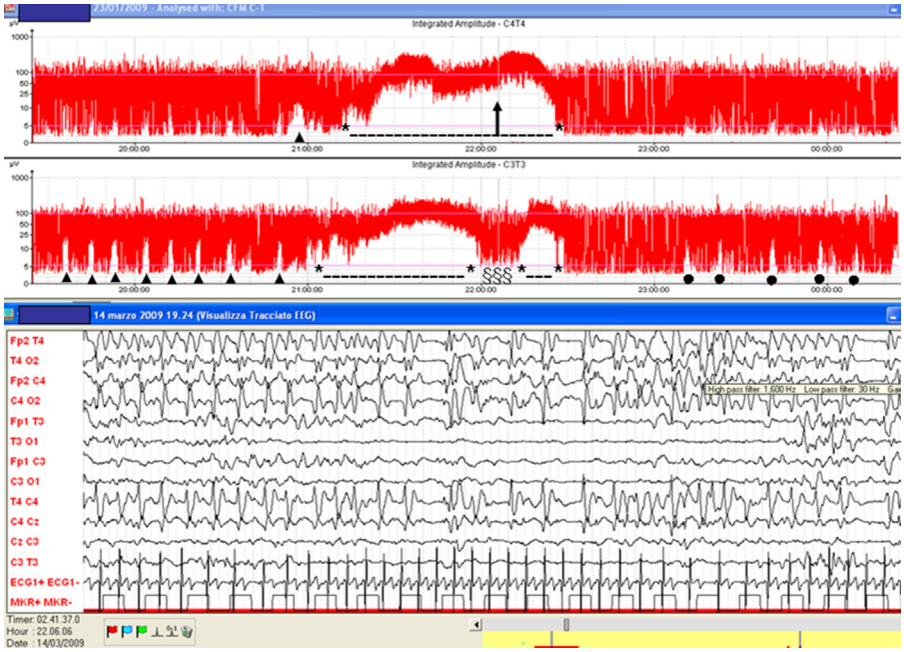

Fig. 1. "Status epilepticus" (SE) aEEG pattern (more than 1 discharge each 10 min of recording and/or a continuous discharges for equal or more than 15 min): after 90 min with repetitive seizures (▲) on the left side (less evident in the right hemisphere), a continuous independent bilateral discharge occurs, lasting more than 60 min (*———*); at 22.06 SE persists on the right side (*–↑—*) while stops in the left side (§§§), to recur here after 10 min with left flat EEG. Single seizures occur (●). The aEEG background pattern can be classified as "severely discontinuous normal without sleep–wake cycling".

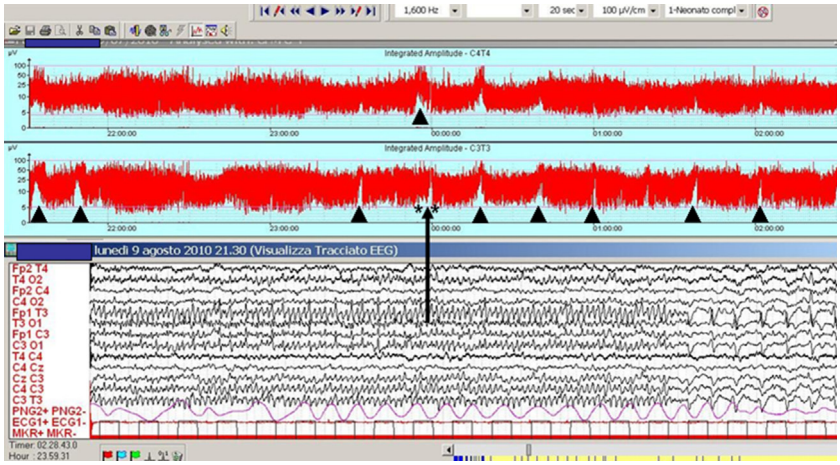

Fig. 2. "Repetitive seizures" (RS) aEEG pattern (more than 1 discharge during a 30 min epoch but not more than one event each 10 min): from 22.30 to 02.10, ten seizures (▲) recur, lasting 2–5 min each. At 22.59 one of these is shown (*↑*), lasting less than 2 min, strictly associated to a clear left ictal discharge on cEEG. The aEEG background pattern can be classified as "continuous normal voltage with sleep–wake cycling", with some short periods of discontinuity.

The reliability of aEEG as a tool for seizures detection has been questioned by several authors because aEEG is sensitive to amplitude changes and insensitive to frequency changes. Moreover, discharges without a substantial increase in amplitude were missed with aEEG.[4–7,9] Several studies in neonates have evaluated 1- or 2-channel aEEG displayed, reporting a wide range of sensitivities for seizures identification from 26% to 76%.[6,7,13–17] Our study confirms these findings, however we found that SE may be detected by using aEEG. There is growing evidence that electrographic seizures in human newborns with HIE exacerbate the initial hypoxic ischaemic injury.[1] Since it is recognized that seizures in neonates with HIE become more severe and frequent between 12 and 24 h of life,[18] with SE often being observed, our findings could be very useful even if aEEG does not identify all patients with SS.

This variability in results can be attributed to the level of experience of the aEEG reviewers, the number of aEEG channels and the length of recordings.[19] In our study, the major electrographic seizures that were missed included short duration of the seizures (less than 20 s), which is a well known limitation of aEEG due to time compression of the display.[9] Regardless the above mentioned limitations a recent study shows that using an 8-channel aEEG display the observers correctly identified 81.5% of seizures.[20] Thus, this finding suggests that in order to achieve a higher sensitivity it may be necessary to use more than 2-channel aEEG as used in our and in several previous studies.[14] The widespread use of aEEG monitoring is evident from the results of a recent survey among specialists in neonatal neurology or neonatal neurocritical care.[19] In this investigation, more than 90% of physicians endorsed detecting epileptic seizures with both aEEG/cEEG.

Interestingly, Lynch et al.[18] found that the period of maximum seizure burden is reached within a median of 5.9 h of the first recorded seizure in newborn with HIE. On this basis, given the unreliability of clinical signs associated with electrographic seizure and because neonatal seizure are difficult to detect using aEEG alone, continuous multichannel aEEG/cEEG recording could

Table 2
Concordance of seizures detection by aEEG versus cEEG.

	Kappa		*p* values	
	Seizures	Artefacts	Seizures	Artefacts
Neonatologist	0.48	0.88	0.0002	<0.0001
Paediatric neurologist 1	0.76	1.0	<0.0001	<0.0001
Paediatric neurologist 2	0.70	1.0	<0.0001	<0.0001

Fig. 3. "Missed seizures" (MS) on aEEG recording (*↓*), detected by cEEG traces in Cz-C3 (*——*): (i) the seizure lasts less than 15 s and (ii) the amplitude is less than 40 mcV. Ictal events of various lengths are recorded before and after the MS (▲). The aEEG background pattern can be classified as "continuous extremely low voltage".

represent a valuable diagnostic tool in NICU. Noteworthy, in addition to the aEEG trend, commercially available devices display the original cEEG signal with both present and past recordings which is crucial for easier recognition of seizures patterns and artefacts displayed on aEEG.

The main findings of the present investigation is that all the 3 reviewers identified SE in 100% of the reviewed traces using aEEG alone and we found a excellent agreement for SE detection between the two paediatric neurologists and the neonatologist even if the neonatologist had no prior experience in reviewing aEEG traces. Interestingly, in the NICU, aEEG traces are usually reviewed by the clinical neonatology team and it is common practice to treat seizures on the basis of clinical diagnosis alone.[21,22] Based on this, we agree that training neonatal staff in recording and reporting continuous aEEG/cEEG is necessary in order to avoid overuse or misuse of continuous electroencephalography monitor interpretation in the NICU.[23]

In conclusions, our study confirms that aEEG monitoring does not replace but it is complementary to cEEG for seizure detection in newborns with acute encephalopathy.[9] In this sense, our study shows that aEEG technique represents a valuable tool to detect SE in neonates.

In clinical practice, after a training of this technique, aEEG could be used as a screening tool in long-term monitoring to identify time-points of interest during a prolonged cEEG/aEEG recording that warrant closer inspection using the raw EEG alone. Further investigations are needed to establish the impact of incorporating aEEG in the critical care of neonates with seizures.

Conflict of interest statement

The authors do not have any conflict of interest and did not receive any fund for this study.

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