Amplitude-integrated Electroencephalography in Full-term Newborns without Severe Hypoxic-ischemic Encephalopathy: Case Series

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Aim To assess the diagnostic value of amplitude-integrated electroencephalography (EEG) in comparison to standard EEG in newborns without severe hypoxic-ischemic encephalopathy who were at risk for seizures.

Methods The study included a consecutive series of 18 term newborns without severe hypoxic-ischemic encephalopathy, but with clinical signs suspicious of epileptic seizures, history of loss of social contact, disturbance of muscle tone, hyperirritability, and/or jitteriness. Amplitude-integrated and standard EEG tracings were assessed for background pattern, epileptiform activity, and sleep-wake cycling.

Results Amplitude-integrated EEG and standard EEG recordings of 15 newborns were suitable for analysis. Only two different background patterns were seen on amplitude-integrated EEG and standard EEG, with the absence of severely abnormal background patterns. Of 15 newborns, epileptiform discharges were present on amplitude-integrated EEG in 3 newborns, and on standard EEG in 6 newborns. Sensitivity of seizures discharges on amplitude-integrated EEG to correspond with epileptiform discharges on standard EEG was 50%; specificity 100%,positive predictive value 100%, and negative predictive value 75%. Of 4 newborns suspected of having sleep myoclonus, amplitude-integrated EEG correctly identified the newborn who had epileptiform activity on standard EEG.

Conclusion The diagnostic value of amplitude-integrated EEG monitoring of term newborns without severe hypoxic-ischemic encephalopathy is limited, but could have a role in evaluating presence or absence of epileptiform activity and in differentiating non-epileptic movement from seizures.

Amplitude-integrated electroencephalography (EEG) has been used for monitoring cerebral function of newborns for more than two decades (1). The interest of previous amplitude-integrated EEG studies has been mainly focused on newborns who experienced severe forms of hypoxic-ischemic encephalopathy, while newborns with milder forms of hypoxic-ischemic encephalopathy or even without hypoxic-ischemic encephalopathy received less attention. The amplitude-integrated EEG monitoring of newborns with hypoxic-ischemic encephalopathy has been used for the assessment of background pattern, detection of seizures, evaluation of the effects of anticonvulsive drugs, selection of patients for neuroprotective intervention, and prediction of neurodevelopmental outcome as early as in the first hours after birth (2-7).

Seizures are the most distinctive sign of neurologic disease in the neonatal period (8). By clinical observation, the incidence of epileptic seizures in neonatal period is from 0.5% in the term newborns to 22.2% in the preterm newborns (9). Because of central nervous system immaturity, the clinical signs of epileptic seizures in newborns are frequently subtle or even clinically silent, and the generalized tonic-clonic seizures are rare (8,10). Furthermore, normal motor or autonomic behaviors of healthy newborns are sometimes difficult to distinguish from epileptic seizures (11). There is increasing number of studies suggesting that untreated neonatal seizures, either clinical or subclinical, are associated with increased mortality and adverse outcome (10,12-16). Seizures are frequently experienced by newborns with moderate or severe hypoxic-ischemic encephalopathy (17). By definition, seizures do not characterize mild hypoxic-ischemic encephalopathy, but newborns with mild hypoxic-ischemic encephalopathy or without hypoxic-ischemic encephalopathy may experience seizures of other etiology, such as intracranial hemorrhage, central nervous system infection, congenital brain anomalies, or inborn errors of metabolism or transient metabolic disturbances (18,19).

The aim of this study was to assess the value of amplitude-integrated EEG monitoring in comparison to standard EEG for detection of seizures in newborns without severe hypoxic-ischemic encephalopathy, and to identify other possible indications for amplitude-integrated EEG monitoring in these newborns.

Subjects and methods

Subjects

Between February 2001 and March 2003, 18 consecutive term newborns were enrolled in this prospective study. The inclusion criteria were absence of severe hypoxic-ischemic encephalopathy as described by Sarnat (17) and presence of clinical signs suspicious of epileptic seizures, history of loss of social contact, disturbance of muscle tone, hyperirritability, or jitteriness. There were no antenatal signs of fetal distress, cardiotocographic findings were normal, and amniotic fluid was clear in all cases. All newborns had an uneventful birth, Apgar scores at 1 minute after birth and later were ≥7, the newborns were not resuscitated after birth, and did not need oxygen supplementation. No newborn presented signs of severe hypoxic-ischemic encephalopathy in the following days. Three newborns were subsequently excluded from the study due to proven chromosomopathies (Prader-Willi syndrome, trisomy of chromosome 13, and partial trisomy on p-arm of chromosome 4).

Informed parental consent was obtained in all cases. The study was approved by the medicoethical committee of the Republic of Slovenia.

Amplitude-integrated electroencephalography

The amplitude-integrated EEG recording was started within 72 h after the admission to the unit. The amplitude-integrated EEG was recorded with the cerebral function monitor

(CFM 4640, Lectromed Devices Ltd, Hertfordshire, UK). Skin was cleaned with a dermabrasive cream and covered with collodium before disc electrodes were placed and fixed in their positions (P3, P4, and reference Fz). Single-channel amplitude-integrated EEG was derived from biparietal electrodes and recorded on the paper at slow speed (6 cm/h) at the cot side. A second tracing continuously recorded the electrode impedance. The upper limit of tolerated impedance was 10 kΩ. All nursing procedures were marked on the amplitude-integrated EEG tracing. The amplitude-integrated EEG tracings were reviewed by 2 clinicians who were blinded to the perinatal data.

The background pattern and epileptiform activity on the amplitude-integrated EEG tracings were assessed visually according to the criteria by Toet et al (3) as follows: 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 amplitude-integrated EEG tracings was also noted. In healthy newborns, the trace is wider during sleep and narrower when the newborn is awake.

Standard electroencephalography

Standard EEG recordings were performed preferably within 24 h before or after amplitude-integrated EEG recordings. Serial EEG recordings were performed in several infants, but only the EEG recording closest in time to the amplitude-integrated EEG recording was used for the purpose of this study.

Standard EEG was recorded with a digital EEG device Nicolet AllianceWorks (Nicolet Biomedical, VIASYS Healthcare Inc., Madison, WI, USA). The recordings were performed by an experienced neurophysiology technician. For placement of the electrodes, an Infant Electro-Cap system was used (Infa-Cap I, Electro-Cap International Inc., Eaton, OH, USA), which has the international 10-20 electrode placements (10 electrodes: Fp1/2, T3/4, O1/2, C3/4, Cz, and the ground). The EEG signal was sampled digitally at a frequency of 1500 Hz. From the electrodes of the Electro-Cap system, 10 bipolar EEG channels were derived, with two additional channels, one for electrocardiogram and the other for respirogram. A bandwidth of 1-70 Hz was used for the assessment. The duration of the recording was 20 minutes in all newborns.

For background and epileptiform activity categorization, the categories modified after Holmes and Lombroso (20) and Ortibus et al (13) were used. Background activity was classified as normal activity; discontinuous activity; burst-suppression pattern; low voltage, undifferentiated activity; or isoelectric activity. Epileptiform activity, where present, was classified as interictal unifocal (duration of epileptiform activity <6 s, single focus); interictal multifocal (duration of epileptiform activity <6 seconds, ≥2 foci); ictal unifocal (duration of epileptiform activity ≥6 seconds, single focus); ictal multifocal (duration of epileptiform activity ≥6 seconds, ≥2 foci); or status epilepticus.

When patterns of epileptiform activity were clearly recognized on standard EEG recording, phenobarbital was administered. Clinical seizures were noted, when observed by the attending personnel.

Statistical analysis

Both amplitude-integrated and standard EEG traces were analyzed off-line and independently interpreted by two investigators who were unaware of the clinical condition of the newborns. Amplitude-integrated EEG interpreters were blinded to the standard EEG tracings and vice versa. The two interpreters reached consensus on the tracings on which they had previously disagreed. Sensitivity, specificity, positive predictive value, and negative predictive value were calculated for comparisons between amplitude-integrated EEG and standard EEG tracings by use of SPSS 12.0 for Windows (SPSS Inc, Chicago, IL, USA).

Results

The inclusion criteria were met by 15 newborns (5 girls and 10 boys). The median gestational age was 39 weeks (range, 37-40), median birth weight was 3410 g (range, 2860-4500), and median Apgar scores at 1 and 5 minutes were 8 and 9, respectively (Table 1). The median time interval between birth and amplitude-integrated EEG recording was 7 days (range, 2-22 days). The median length of the amplitude-integrated EEG recordings was 370 minutes (range, 150-840).

On amplitude-integrated EEG tracings, two different background patterns were observed: 12 newborns showed continuous normal voltage, whereas 3 newborns showed discontinuous normal voltage pattern (Table 1). Similarly, on standard EEG 12 newborns showed normal background activity, whereas 3 newborns showed discontinuous activity.

In 3 newborns, epileptiform discharges were seen on both amplitude-integrated and standard EEG, ie, repetitive epileptiform discharges were seen on amplitude-integrated EEG tracings in all 3 newborns, whereas on standard EEG interictal epileptiform discharges were seen in 2 newborns, and ictal epileptiform discharges in one newborn. No epileptiform discharges were seen on amplitude-integrated EEG tracings in the remaining 12 newborns. In 9 of these newborns, there were no epileptiform discharges seen on standard EEG either, whereas in the remaining 3 newborns epileptiform discharges were seen only on standard EEG in the form of interictal epileptiform discharges in 2 newborns and ictal epileptiform discharges in one newborn (Table 1).

Table 1. Clinical and electroencephalographic (EEG) findings in 15 newborns*

		Clinical findings					EEG				
		Apgar score					amplitude-integrated			standard	
Patient No.	Gestational age (weeks)	at 1 min	at 5 min	diagnosis	clinical seizures	phenobarbital treatment	background pattern	epileptiform activity	sleep-wake cycling	background pattern	epileptiform activity
1	40	8	10	convulsions	yes	yes	DNV	NP	NP	discontinuous	ictal unifocal
2	37	8	9	hypotonia, prolonged jaundice	no	no	DNV	NP	NP	normal	interictal multifocal
3	39	9	10	sleep myoclonus	yes	no	CNV	repetitive seizures	NP	normal	interictal multifocal
4	39	9	10	convulsions	yes	no	CNV	repetitive seizures	P	discontinuous	ictal unifocal
5	40	9	9	sleep myoclonus	yes	no	CNV	NP	P	normal	NP
6	38	8	9	sleep myoclonus	yes	no	CNV	NP	P	normal	NP
7	38	9	9	sudden life threatening event	no	no	CNV	NP	P	normal	NP
8	40	8	9	intracranial hemorrhage, convulsions	yes	yes	CNV	repetitive seizures	P	discontinuous	interictal multifocal
9	38	9	9	convulsions	yes	no	CNV	NP	P	normal	NP
10	39	7	9	myoclonus, ventriculomegaly	yes	no	DNV	NP	P	normal	NP
11	40	7	10	hypotonia	no	no	CNV	NP	P	normal	NP
12	39	8	9	sleep myoclonus, sudden life threatening event	yes	no	CNV	NP	NP	normal	NP
13	39	9	9	hypotonia, tremor	no	no	CNV	NP	P	normal	interictal multifocal
14	40	8	9	hypotonia, poor spontaneous movement	no	no	CNV	NP	P	normal	NP
15	39	7	8	hypotonia, convulsions	yes	no	CNV	NP	P	normal	NP

*Abbreviations: DNV – discontinuous normal voltage; CNV – continuous normal voltage; NP – not present; P – present.

The sensitivity of epileptiform discharges on amplitude-integrated EEG to correspond with epileptiform discharges on EEG (ictal or interictal) was 50%, specificity 100%, positive predictive value 100%, and negative predictive value 75%.

Clinical signs suggesting seizures were found in 10 newborns. In 6 of them, no epileptiform activity was found on either standard or amplitude-integrated EEG. In 3 newborns epileptiform activity was present on both amplitude-integrated and standard EEG. In one newborn with clinical signs of seizures, epileptiform activity was seen on standard EEG (ictal activity), but not on amplitude-integrated EEG. Sleep-wake cycling was found on amplitude-integrated EEG tracings in 11 newborns.

Discussion

Our study findings suggest that continuous amplitude-integrated EEG monitoring could detect epileptiform activity and help differentiating benign non-epileptic movement from true epileptic seizures in newborns without severe hypoxic-ischemic encephalopathy. The clinical gain of amplitude-integrated EEG monitoring was limited in these newborns because of relatively normal background activity and absence of severe forms of epileptiform activity. However, continuous amplitude-integrated EEG monitoring may be recommended in newborns without severe hypoxic-ischemic encephalopathy, if a newborn is at risk of having seizures.

Status epilepticus, which is often seen in newborns with severe hypoxic-ischemic encephalopathy, was not found on amplitude-integrated or standard EEG tracings in any of the newborns included in our study. Nevertheless, these newborns did present electrographic seizures. Although amplitude-integrated EEG detected only 50% of newborns who had epileptiform discharges on standard EEG, all of the epileptiform discharges detected by amplitude-integrated EEG were confirmed by standard EEG. The relatively low sensitivity of amplitude-integrated EEG for detection of epileptiform discharges was probably influenced by the fact that amplitude-integrated EEG and standard EEG were not recorded simultaneously, which is a limitation of this study. Lower sensitivity was also partly expected, because short (<30 s) or focal epileptiform activity cannot be detected by amplitude-integrated EEG (3,21). However, one of the main advantages of amplitude-integrated EEG over standard EEG is the continuity of monitoring. Newborns can easily be monitored for hours or even days with amplitude-integrated EEG, while standard EEG recording is usually 20 minutes in duration. Newborns without severe hypoxic-ischemic encephalopathy can experience seizures that are detectable by amplitude-integrated EEG, which implies that amplitude-integrated EEG can be of use as a screening method in newborns at risk of seizures to help identify those who should be further evaluated with standard EEG. Newer amplitude-integrated EEG monitors that simultaneously present the raw EEG and the amplitude-integrated EEG signal could prove to be of greater value than the Lectromed monitor we used in our study.

Background pattern can be severely depressed in newborns with severe hypoxic-ischemic encephalopathy (22). The evaluation of the background pattern on amplitude-integrated EEG was not found to be of use in newborns included in this study, because all had either normal (continuous normal voltage) or only mildly discontinuous (discontinuous normal voltage) background activity. Newborns with hypoxic-ischemic encephalopathy presenting these two background patterns shortly after birth usually have a favorable outcome (7). A more detailed prediction of outcome based on the differentiation between the continuous and discontinuous normal voltage background pattern on amplitude-integrated EEG is unlikely, although this was not investigated in this study. It has been re-

ported that anti-convulsive drugs, including phenobarbital, which was administered in some of the newborns included in our study, can lead to transient deterioration of the amplitude-integrated EEG background pattern, and that this deterioration depends on the severity of the preceding insult to the brain (6,7). Therefore, the effect of phenobarbital on the background activity in the newborns studied was most likely minimal.

Hellström-Westas et al (23) found that differentiating epileptic seizures from non-epileptic movements, such as sleep myoclonus, in severely ill newborns was possible with the use of amplitude-integrated EEG. Our results are in agreement with their findings. Our study included 4 newborns because they were suspected of having sleep myoclonus, but epileptic seizures had to be excluded to confirm the diagnosis. In 3 newborns, there were no epileptiform discharges either on amplitude-integrated or on standard EEG, but in one newborn repetitive seizures were seen on amplitude-integrated EEG tracing and interictal multifocal epileptiform discharges were seen on standard EEG.

The limitation of this study is a small number of newborns included, and larger studies are needed to further confirm our findings. Also, the value of amplitude-integrated EEG in our study was not compared with video EEG monitoring, which is a well-established method for differentiating epileptic seizures from non-seizure movements.

Sleep-wake cycling was found in 11 of 15 newborns in our study. In a study on term newborns with hypoxic-ischemic encephalopathy, sleep-wake cycling was more often present in newborns with milder forms of hypoxic-ischemic encephalopathy than in those with a more severe form of hypoxic-ischemic encephalopathy (24). One could expect to find sleep-wake cycling in a higher percentage in the newborns without severe hypoxic-ischemic encephalopathy. In our study, the newborns were monitored for approximately 6 h and a larger proportion of newborns would have likely present sleep-wake cycling, had they been monitored for a longer period of time.

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