The prognostic value of amplitude-integrated electroencephalography in neonates with hypoxic-ischemic encephalopathy

Prognostička vrednost elektroencefalografije integrisanih amplitude kod novorođenčadi sa hipoksičko-ishemijskom encefalopatijom

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Abstract

Background/Aim. Diagnosis of perinatal hypoxic-ischemic encephalopathy (HIE) and early prediction neurological outcome is important and difficult. The aim of this study was to determine the prognostic value of amplitude-integrated electroencephalography (aEEG) for abnormal neurodevelopment outcome in a neonate with HIE.

Methods. A total of 90 neonates > 32 gestational age (GA) with HIE were enrolled prospectively. All neonates with HIE were categorized into three grades according to the Sarnat and Sarnat clinical scoring system (mild HIE, moderate HIE and severe HIE). aEEG traces were recorded with a cerebral function monitor (CFM) during the first 72 h of life. The neurodevelopment outcome was assessed at 12 months of age of corrected gestational age.

Results. The pattern of aEEG correlated with the severity of HIE (p < 0.0001) and subsequent neurodevelopment outcome (p < 0.001). We found that aEEG background patterns exhibited superior prediction of abnormal outcomes at 12 months of age (sensitivity of 91.7% and specificity of 94.3%, positive predictive value of 78.6% and negative predictive value of 98.1%) when compared to aEEG seizure (sensitivity of 94% and specificity of 48%, positive predictive value of 57% and a negative predictive value of 92%). Electroclinical dissociation seizure was detected in 28% of the neonates with HIE.

Conclusions. Our results confirm that aEEG is simple and accurate bedside diagnostic method for assessing extension of hypoxic-ischemic brain damage and early identification of neonates with perinatal HIE who are at high risk of neurodevelopmental impairment.

Key words: elektroencefalografija; intensive care units, neonatal; hypoxia-ischemia, brain; infant, premature; infant, newborn; prognosis.

Apstrakt

Uvod/Cilj. Dijagnoza perinatalne hipoksično-ishemičke encefalopatije (HIE) i prognoza kasnijeg neurološkog ishoda je važna i, istovremeno, vema teška. Cilj ove studije bio je da se utvrdi prognostički značaj elektroencefalograma integrisanih amplitude (aEEG) za utvrđivanje neurološke prognoze kod novorođenčeta sa HIE.

Metode. Ovom prospektivnom studijom bilo je obuhvaćeno 90 novorođenčadi > 32 gestacijskoj zrelosti na rođenju. Neurološka procena ispitivane dece sprovedena je u uzrastu od 12 meseci i korigovana je prema gestacijskoj zrelosti na rođenju.

Rezultati. Registrirana aEEG aktivnost bila je u korelaciji sa težinom HIE (p < 0,0001) i kasnijim razvojem neuroloških sekvleta (p < 0,001). Naši rezultati ukazuju da je aEEG jednostavna i precizna dijagnostička metoda za procenu ekstenzivnosti hipoksično-ishemičkog moždanog oštećenja i ranu identifikaciju novorođenčadi sa HIE.

Zaključak. Naši rezultati ukazuju da je aEEG jednostavna i precizna dijagnostička metoda za procenu ekstenzivnosti hipoksično-ishemičkog moždanog oštećenja i ranu identifikaciju novorođenčadi sa HIE.
Introduction

Perinatal hypoxic-ischemic encephalopathy (HIE) is a common cause of neonatal morbidity and mortality and neurological disabilities among survivors. Each year 1.2 million neonates die and about 1 million infants have permanent neurological disability caused by HIE. Determination of severity of perinatal HIE by the clinical criteria and appropriate neuroimaging or neurophysiologic techniques remains the main prognostic tool. Neonates with mild HIE have a uniformly good prognosis and those with severe HIE a very high risk for early death or severe disabilities. Thus, especially for the neonates with moderate HIE, neuroimaging and neurophysiological examinations have a great value. Unfortunately, the predictive values of neuroimaging techniques (i.e. magnetic resonance imaging, computerized tomography and ultrasound) are limited during the first days of life. In contrast, neurophysiological examinations of functional integrity of the brain have been shown to be useful also during the first days of life. High predictive values have been reported for evoked potentials (somatosensory, visual and auditory), conventional encephalography (EEG) and amplitude-integrated encephalography (aEEG). Both serial registration of conventional EEG and measurement of evoked potentials in a neonatal intensive care unit (NICU) require considerable technical skill, time and expertise in interpretation and may not be rapidly available in most hospitals. An alternative technique is aEEG recorded with a cerebral function monitor (CFM), designed for long-term monitoring brain activity at bedside. CFM is a simplified single- or two-channel electroencephalogram monitor. A signal is obtained from a single pair of electrodes placed at the P3 and P4 position of the 10–20 International System, i.e. in the left and right parietal region. A guard or reference electrode positioned anterior to the vertex was also used to reduce the effects of electrical interference. The use of two channels (two pair of bilateral frontoparietal electrodes) has the advantage of defining laterality in unilateral lesions, not available in the single channel devices. The signal is amplified and passed through an asymmetrical band filter which attenuates activity below 2 Hz and above 15 Hz in order to minimize artefacts from muscle activity and electrical interference. Additional processing includes semi logarithmic amplitude compression, rectification and time compression. A signal is presented electronically on the device monitor and can be recorded on paper with a semi-logarithmic scale at slow speed (6 cm/hr). A second trace continuously records the electrode impedance. EEG waveform can also be displayed on the monitor. The bandwidth in aEEG traces reflects variations in upper and lower margins of activity or patterns of aEEG, both of which depend on the maturity and severity of the illness of a newborn infant.

In this study we prospectively evaluated the prognostic value of aEEG for assessing extension of hypoxic-ischemic brain damage and early identification of neonates with perinatal HIE who are at high risk of neurodevelopmental impairment.

Methods

Our study was performed from January 2007 to January 2009 and was approved by the Ethical Committee for Medical Research of the Medical Faculty at the University of Belgrade. Our institute serves as a referral center for high-risk pregnancies, with delivery numbers of 7,000–7,500 per year. We studied 90 neonates under 32 weeks gestational age (GA) with perinatal HIE admitted to neonatal intensive care units (NICU) at the Institute of Gynecology and Obstetrics, Clinical Center of Serbia, Belgrade. Written consent was obtained from all parents. Perinatal HIE was diagnosed if fetal distress (meconium staining of liquor or abnormal fetal heart rate), metabolic acidosis [pH < 7.20, base excess (BE) ≥ 10 mmol/L and lactate > 3mmol/L in arterial cord blood within 60 min of birth], immediate neonatal depression Apgar score (AS) ≤ 6 at 5 min and/or delayed spontaneous respiration, necessitating artificial ventilation at 5 min, and early neonatal encephalopathy (within the first 24 of life) were presented. All the neonates were resuscitated according to the guidelines of the Newborn Resuscitation Program of the American Academy of Pediatrics and American Heart Association.

A complete obstetrical history and physical examinations were obtained on admission. Perinatal HIE was categorized into three stages according to the Sarnat and Sarnat clinical scoring system. Head sonograms were performed on all the neonates before enrolment.

aEEG recordings started after initial stabilization in all 90 neonates with HIE. aEEG was recorded during the first 72 h of life using the Cerebral Function Monitor Olympic 6000 (Olympic Biomedical, USA) from biparietal adhesive electrodes and displayed on the integral printer at 6 cm/h. Handling of the neonates, observed clinical seizures, and administration of anticonvulsants or sedatives were recorded by the nursing staff. We excluded any aEEG records within 30 minutes of anticonvulsant administration. The CFM also recorded the impedance across the electrodes which was always below 10 kΩ.

Evaluation of aEEG recording should begin with the background pattern and then proceed to the presence or absence of seizures. aEEGs were described with either voltage criteria, using the upper and lower margins of activity or patterns of aEEG.

Different aEEG background patterns (Figure 1) in a postasphyctic period were classified as: 1) normal aEEG background patterns (the upper margin of the trace is above 10 μV and the lower margin is greater than 5 μV. In healthy full term neonates the trace alters in width according to the awake and sleep state of the neonate); 2) moderately abnormal aEEG background patterns (the upper margin of the trace is greater than 10 μV and the lower margin is less than 5 μV). This pattern can be seen in neonates with moderately severe encephalopathy or immediately after administration of drugs such as anticonvulsants and sedatives. Excessive background discontinuity pattern (“dysmature pattern”) may also be seen in very preterm neonates; 3) severely abnormal aEEG background patterns (the upper margin of the trace is...
less than 10 μV and the lower margin is usually less than 5 μV. A severely abnormal trace is characterized by a general suppression of amplitude and this pattern may be accompanied by brief bursts of higher voltage spikes which appear as single spikes above the background activity – “burst suppression”. A severely abnormal trace is usually seen with severe encephalopathy and is often accompanied by seizure activity.

In addition, any of these three groups could be accompanied by seizures. Seizures were manifested as periods of sudden increase in voltage accompanied by narrowing of the band of aEEG activity and followed by a brief period of suppression (Figure 2). Arousal during care procedures may be misinterpreted as seizures. It is therefore important that all the procedures are documented to facilitate correct interpretation of aEEG. Administration of anticonvulsants or sedatives or handling of the neonates was recorded by the nursing staff. Status epilepticus often looks like a ‘saw tooth’ pattern but a continuously raised background may also be seen. Correct interpretation is only possible when simultaneous raw EEG is also available.

Neurodevelopment outcome was assessed at 12 months of corrected gestational age by the neonatologist and pediatric neurologist using the Denver Developmental Screening Test (DDST). Neurodevelopment outcomes were classified as normal, mild motor abnormality (slight abnormality in muscular tone or mild delayed of motor development) and severe adverse outcome [cerebral palsy (CP), epilepsy or if died in follow-up period].

We excluded neonates with congenital malformations, chromosomal abnormalities, inherited metabolic disorders, congenital or acquired neonatal infections and maternal drug addiction.

Statistical Package for Social Science software 11.5.1 for Windows (SPSS Inc., Chicago, IL, U.S.A.) was used for
Results

We studied 90 neonates (≥ 32 GA) with perinatal HIE. The majority of neonates in our study developed mild HIE (Table 1). Birth weight (BW) and gestational age were similar, while gender distribution was different among the neonates with mild and advanced clinical stage of HIE (p < 0.05) (Table 1). At term, the incidence of HIE ranged from 3 to 4 per 1,000 live births during our study period. Predictive capacities AS at 1 and 5 min and arterial blood cord values of pH, BE and lactate for severity of HIE and abnormal outcomes were shown in Table 1. Apgar scores at 1 min (W = 166; p < 0.05) and AS at 5 min (W = 181; p < 0.01) and pH values of arterial blood cord (W = 184; p < 0.001), BE (W = 167; p < 0.05) and lactate (W = 51; p < 0.05) correlated well with severity of HIE. Arterial cord blood pH measured by assessing the predictive value of abnormal aEEG background activity alone and/or seizure aEEG activity.

Clinical and biochemical characteristics at birth in neonates with different stage of hypoxic-ischemic encephalopathy

<table>
<thead>
<tr>
<th>Parameters</th>
<th>HIE</th>
<th>HIE I</th>
<th>HIE II</th>
<th>HIE III</th>
<th>NS</th>
</tr>
</thead>
<tbody>
<tr>
<td>GA (cm)</td>
<td>36.6 ± 2.6</td>
<td>36.4 ± 2.5</td>
<td>37.4 ± 2.6</td>
<td>36.2 ± 3.1</td>
<td>35.8 ± 2.7</td>
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<tr>
<td>BW (g)</td>
<td>2711 ± 810</td>
<td>2699 ± 775</td>
<td>2889 ± 796</td>
<td>2311 ± 1000</td>
<td>2450 ± 93</td>
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<tr>
<td>M (%)</td>
<td>62.38</td>
<td>54.46</td>
<td>67.33*</td>
<td>100/0*</td>
<td>67/33*</td>
</tr>
<tr>
<td>AS (1min)</td>
<td>3.4 ± 1.4</td>
<td>4.1 ± 1.1</td>
<td>2.6 ± 1.3</td>
<td>1.3 ± 0.7*</td>
<td>2.5 ± 1.6*</td>
</tr>
<tr>
<td>AS (5min)</td>
<td>5.5 ± 1.7</td>
<td>5.6 ± 0.5</td>
<td>4.3 ± 1.2</td>
<td>2.7 ± 1.0*</td>
<td>3.8 ± 1.8**</td>
</tr>
<tr>
<td>pH</td>
<td>7.09 ± 0.11</td>
<td>7.15 ± 0.05</td>
<td>7.03 ± 0.11**</td>
<td>6.88 ± 0.09***</td>
<td>6.97 ± 0.14***</td>
</tr>
<tr>
<td>BE (mmol/L)</td>
<td>-13.1 ± 4.2</td>
<td>-11.0 ± 1.7</td>
<td>-15.5 ± 4.5**</td>
<td>-19.7 ± 3.9***</td>
<td>-16.5 ± 5.1*</td>
</tr>
<tr>
<td>Lactate(mmol/L)</td>
<td>7.4 ± 4.4</td>
<td>5.4 ± 2.9</td>
<td>9.6 ± 4.6*</td>
<td>13.9 ± 3.9*</td>
<td>11.0 ± 5.1*</td>
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<table>
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<tr>
<th>NDO</th>
<th>HIE</th>
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<th>HIE III</th>
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<th>TERM</th>
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<tr>
<td>Normal NDO (%)</td>
<td>73.9</td>
<td>91.3**</td>
<td>54.2**</td>
<td>0**</td>
<td>62.7</td>
<td>84.4*</td>
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<tr>
<td>M (%)</td>
<td>12.5</td>
<td>7</td>
<td>29.2**</td>
<td>0*</td>
<td>16.3</td>
<td>8.9</td>
</tr>
<tr>
<td>CP (%)</td>
<td>10.2</td>
<td>17**</td>
<td>12.5</td>
<td>71.4**</td>
<td>14*</td>
<td>6.7</td>
</tr>
<tr>
<td>EPI (%)</td>
<td>3.5</td>
<td>0</td>
<td>4.1</td>
<td>28.6**</td>
<td>13.3</td>
<td>0</td>
</tr>
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</table>

Values are expressed as mean± standard deviation (SD) or percentages (%). Kruskal-Wallis χ² test and Wilcoxon rank sum test with continuity correction. Significance *p < 0.05 or **p < 0.01 or ***p < 0.001. BW = birth weight; AGA = appropriate BW for gestation age; SGA = small BW for gestation age and LGA = large BW for gestation age; GA = gestational age; M = male and F = female; AS = Apgar score; BE = base excess; Lactate(mmol/L) = lactate values; BE and lactate or AS at 1min and 5 min in preterm and term neonates.

A relation between aEEG patterns and severity of HIE and neurologic outcome is summarized in Figure 3. There was a close relationship between the findings on aEEG patterns and severity of HIE (p < 0.0001) (Figure 3). The aEEG patterns in the first 72 h of life also had high predictive value for abnormal outcome (p < 0.001) (Figure 3). All neonates with normal aEEG patterns had good outcome while neonates with severely abnormal aEEG patterns (low voltage or inactive isoelectric background activity) either died or subsequently had an abnormal neurologic outcome. All the three HIE groups could be accompanied by seizures (Figure 3). Electrographic seizures without clinical correlates were detected on the CFM in 28% of the neonates with HIE (Figure 4). In the neonates with seizures, we found that the interictal aEEG activity correlated with the subsequent outcome. Severely abnormal aEEG patterns accompanied with seizures had a poor outcome. We detected no significant difference among aEEG patterns in preterm and term neonates.

Neurodevelopmental outcome at 12 months of corrected gestational age corresponded well with severity of HIE (p < 0.01) and gestation age (p < 0.05) (Table 2). All the infants with severe HIE developed neurological sequelae (cerebral palsy or epilepsy). Two preterm neonates with severe HIE died, one within the early neonatal period because of multiorgan failure, the other later because of respiratory dysfunction. In determining the prognostic value of aEEG, we included death and neurodevelopmental impairment as a single outcome group. Incidences of neurological sequelae were significantly higher in preterm infants (p < 0.05). We found that aEEG background pat-
terns exhibited superior prediction of abnormal outcomes at 12 months of age (sensitivity of 91.7% and specificity of 94.3%, positive predictive value of 78.6% and negative predictive value of 98.1%) when compared to aEEG seizure (sensitivity of 94% and specificity of 48%, positive predictive value of 57% and negative predictive value of 92%) (Table 3).

**Discussion**

Outcome prediction after perinatal asphyxia is important and difficult. Despite vast advances in neonatal intensive care the incidence of HIE continues to have a significant impact on the perinatal morbidity and mortality. The incidence of perinatal HIE varies at different gestational ages. At term, the incidence ranges from 3 to 5 per 1,000 live births and an incidence approaching 60% in premature newborns. In our study the incidence of perinatal HIE was similar. The age-dependent vulnerability to hypoxic-ischemic insults seen in the immature brain can be explained by the high density of N-methyl-D-aspartate (NMDA) receptors and neuronal nitric oxide synthase (nNOS)-positive cells. The immature brain is especially sensitive to oxidative damage relative to the mature brain are poor antioxidant capabilities and a high concentration of free iron and lipids.

In our study males had higher incidence of long term developmental disabilities than females. A recent analysis of a European database of 4,500 children with CP found that the incidence of CP was 30% higher in males than females.
Basic research of the causes of CP has revealed that gender may influence the pathogenesis of developmental brain injury. Sex differences in the immature brain appear to be strongly influenced by intrinsic differences between male and female cells and this is influenced by sex chromosomes and sex hormones.\(^{15,16}\)

The Apgar scoring system, first devised in 1952, has been used to assess a newborn’s condition and to reflect the need for resuscitation.\(^{17}\) Over time, the Apgar score has also been used to define asphyxia, which is inappropriate, as many other conditions (e.g., congenital anomalies, prematurity, maternal drug administration) can result in low scores that are not reflective of asphyxia.\(^{18}\) On the other hand, another study stated that low Apgar scores at 5 min are associated with death or cerebral palsy, and this association increased if both Apgar scores at 1 and 5 minute were low.\(^{19}\) Our results also showed that the Apgar score at 5 minute remained a valid predictor of neonatal mortality, but using it alone to predict long-term outcome was inappropriate.

The incidence of long-term complications depends on the severity of hypoxic-ischemic encephalopathy which is in concordance with our results. In adults, neuronal necrosis and apoptosis after global ischemia are slow, and last for several hours to several days. Studies in neonatal experimental model suggest a quicker cellular destruction and energy substrates in the neonatal brain continue to run down for 12 h to 48 h after perinatal hypoxia.\(^{20}\) Therefore, neuroprotective intervention might be effective 6 h to 8 h after perinatal hypoxic-ischemic insult.\(^{18}\) Intervention and treatment following perinatal asphyxia may not be free of risk.

A CFM could be useful for selecting those neonates who might benefit from early intervention after perinatal asphyxia, avoid unnecessary risks related to treatment for those neonates that do not need intervention.\(^{21,22}\) A CFM provides a continuous real-time display of cerebral electrical activity at bedside to assist the clinician in making immediate treatment decisions and in identifying high-risk neonates, which requires closer attention. The benefit of CFM in a NeuroCare Unit (NCU) setting is its simplicity and ease of interpretation. It can be applied rapidly by nursing staff at any time of the day. We showed that aEEG correlates closely with neurologic outcome in neonates with HIE. The ability of aEEG background abnormalities to predict abnormal outcome has been previously studied in asphyxiated neonates.\(^{21}\) Our study showed that neonates with normal aEEG patterns within the first 72 h of life were likely to survive without sequelae, by contrast, neonates with severely abnormal aEEG patterns or worse pattern were at a risk of death or neurological sequela. These findings are in accordance with previous studies.\(^{24}\) Our data also show that normalization of abnormal background patterns is associated with normal neurologic outcomes, whereas severely abnormal aEEG patterns that persisted beyond the age of 72 h are associated with adverse outcomes. These findings are in accordance with previous studies.\(^{25}\)

Diagnosis of seizures in a neonate has been based on clinical recognition of repetitive, stereotypic motor activity or behavioural phenomena. All neonates with either clinical or silent seizures were treated with antiepileptic drugs (phenobarbital as drug of first choice). Treatment with antiepileptic drugs has never changed a normal pattern into a severely abnormal one, although in some infants, the pattern became transiently more discontinuous than before, for 30 to 60 min. By excluding from analysis the parts of the records that were associated with drug administration or handling of the neonates we minimized possible confounding effects. A CFM aids in the detection of seizures and displays their severity, duration and frequency in real time.\(^{26}\) In neonates with seizures, we found that the interictal aEEG activity correlated with a subsequent outcome. The neonates with seizures and a normal-amplitude aEEG had a normal outcome, whereas the neonates with seizures and moderately abnormal or suppressed amplitude aEEG had a poor outcome. A CFM also helps to evaluate response to anticonvulsive therapies and to identify subclinical seizures. Electrographic seizures without clinical correlates are common in neonates with HIE. From previous studies, it is estimated that >50% of seizures identified on EEG or aEEG in neonates may be silent.\(^{27}\) However, there are studies with the opposite results, reporting a rate of electroclinical dissociation seizure of approximately <30%–50% in neonates with HIE, which is in accordance with our findings. Moreover, once anticonvulsant therapy is initiated, electrographic seizures may persist well after cessation of clinical seizure activity.\(^{28}\) The importance of electrographic seizures is underscored by recent data showing that electrographic seizures with or without clinical correlates may have detrimental effects on the neonatal brain. Animal and human data indicate that seizures in the developing brain may be harmful, at least in the short term, considering disturbances in cerebral blood flow, energy metabolism, and excitotoxic amino acids. This suggests that anticonvulsant therapy that suppresses clinical but not electrographic seizures may not be fully effective in preventing brain injury and that an appropriate goal of anticonvulsant therapy is to suppress both clinical and electrographic seizures. Brief seizure activity may be missed, and neonatologists with limited experience in reading aEEGs may misinterpret the presence or absence of seizures.\(^{29}\) These studies stress the fact that experience is required to be able to interpret aEEG traces, and one should also be aware of the limitations of the technology. The long duration of aEEG recording outweighs the limitations of obtaining detailed information during much shorter, 30–40 min of full montage EEG recording. Newer systems provide access to raw EEG, and may offer 2 to 4 channels of recording. The use of these two modalities in conjunction is likely to provide the best information at the current state of the technology.\(^{30}\)

A CFM is a useful tool in deciding when to initiate neuroprotective interventions and it can aid in evaluating the progress or recover from hypoxic-ischemic brain injury.\(^{31}\) The CFM identifies neonates that require further neurological assessment by MRI or multi-lead EEG.\(^{32}\) We did not investigate very preterm infants. Interpretation of aEEG is more difficult in preterm neonates because of EEG changes related to gestational age: a burst suppression pattern observed in extremely preterm neonates changes to a discontinuous pattern in more mature neonates. Therefore, it is
very unlikely that immaturity influenced our results. Our study shows that when CFM is used in combination with standard neurologica1 examination, it enhances the clinician’s ability to identify neonates at risk for poor long-term neurodevelopment outcome. Just like monitoring of respiratory, heart rate, and saturation is routine in neonatal intensive care settings for high risk neonates, continuous aEEG recording to monitor brain function may be appropriate for neonates with HIE and may be considered a standard care.

Conclusion

In conclusion, our findings confirm that continuous aEEG is a simple and accurate bedside diagnostic method for assessing extension of hypoxic-ischemic brain damage and early identification of neonates with perinatal HIE who are at high risk of developmental delay. aEEG improves our ability to detect neonates at risk of hypoxic-ischemic brain injury at an earlier stage, when the window for therapeutic action is still open, optimize timing and assessment of neuroprotective treatment at the same time.

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