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Evoked potentials recorded during routine EEG predict outcome after perinatal asphyxia

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HIGHLIGHTS

- EEG with simultaneous evoked potential recording is valuable in asphyxic newborns.
- Somatosensory evoked potentials recorded during routine EEG predict outcome with 98% accuracy.
- EEG complemented with SEPs is more accurate than EEG alone in outcome prediction.

ABSTRACT

Objective: To evaluate the added value of somatosensory (SEPs) and visual evoked potentials (VEPs) recorded simultaneously with routine EEG in early outcome prediction of newborns with hypoxic-ischemic encephalopathy under modern intensive care.
Methods: We simultaneously recorded multichannel EEG, median nerve SEPs, and flash VEPs during the first few postnatal days in 50 term newborns with hypoxic-ischemic encephalopathy. EEG background was scored into five grades and the worst two grades were considered to indicate poor cerebral recovery. Evoked potentials were classified as absent or present. Clinical outcome was determined from the medical records at a median age of 21 months. Unfavorable outcome included cerebral palsy, severe mental retardation, severe epilepsy, or death.
Results: The accuracy of outcome prediction was 98% with SEPs compared to 90% with EEG. EEG alone always predicted unfavorable outcome when it was inactive ($n = 9$), and favorable outcome when it was normal or only mildly abnormal ($n = 17$). However, newborns with moderate or severe EEG background abnormality could have either favorable or unfavorable outcome, which was correctly predicted by SEP in all but one newborn (accuracy in this subgroup 96%). Absent VEPs were always associated with an inactive EEG, and an unfavorable outcome. However, presence of VEPs did not guarantee a favorable outcome.
Conclusions: SEPs accurately predict clinical outcomes in newborns with hypoxic-ischemic encephalopathy and improve the EEG-based prediction particularly in those newborns with severely or moderately abnormal EEG findings.
Significance: SEPs should be added to routine EEG recordings for early bedside assessment of newborns with hypoxic-ischemic encephalopathy.

Abbreviations: aEEG, amplitude-integrated electroencephalography; BE, base excess; CP, cerebral palsy; EEG, electroencephalography; EP, evoked potential; HIE, hypoxic-ischaemic encephalopathy; IBI, interburst interval; MRI, magnetic resonance imaging; NICU, neonatal intensive care unit; SEP, somatosensory evoked potential; VEP, visual evoked potential; TH, therapeutic hypothermia.

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1. Introduction

Hypoxic-ischaemic encephalopathy (HIE) due to perinatal asphyxia occurs in approximately 2,5 per 1000 live full-term births (Graham et al., 2008), and is one of the leading causes of neonatal deaths and severe neurodevelopmental compromise (Lai and Yang, 2011). Recent data show that even when treated with therapeutic hypothermia (TH), 40–50% of newborns with moderate-to-severe HIE will die or develop with severe handicap (Tagin et al., 2012).

Early recovery of the electroencephalography (EEG) background or amplitude-integrated EEG (aEEG) trend has, within the last decade, become a routine bedside method for early prognostication (Hellström-Westas et al., 1995; Toet et al., 1999; Murray et al., 2009). However, TH delays the aEEG recovery beyond the first 36–48 h, limiting its utility in early outcome prediction (Hallberg et al., 2010; Thoresen et al., 2010; Massaro et al., 2012; Csekő et al., 2013; Bonifacio et al., 2015). In terms of early prognostication, the newborns with moderate HIE are the most challenging (Gunn et al., 2008). This very same population may, however, gain the most from therapeutic interventions (Tagin et al., 2012). Hence, it is of high priority to improve the accuracy of outcome prediction at bedside to support individualized treatment decisions.

In addition to EEG, other neurophysiological methods, particularly somatosensory (SEPs) (Majnemer et al., 1990; Taylor et al., 1992; Eken et al., 1995; Scalais et al., 1998; Suppiej et al., 2010; Swarte et al., 2012; Kontio et al., 2013) and visual evoked potentials (VEPs) (Whyte et al., 1986; Muttitt et al., 1991; Taylor et al., 1992; Eken et al., 1995; Scalais et al., 1998; Suppiej et al., 2010) are known to predict clinical outcome after perinatal asphyxia. In the present paper, we set out to study whether recording SEPs and VEPs simultaneously with routine EEG could provide additional value in the early outcome prediction in term newborns with HIE, and whether their predictive yield is affected by TH, an essential part of modern neonatal intensive care.

2. Patients and methods

2.1. Patients (Table 1, Supplementary Table S1)

The study included 50 newborns (born between 36 + 7 and 42 + 2 gestational weeks; 23 females) treated for asphyxia/HIE at the tertiary level neonatal intensive care unit (NICU) of the Helsinki University Hospital during a four-year period (January 2011 — December 2014). Initially, we identified all asphyxiated/HIE newborns within the study period that underwent an EEG. Asphyxia was defined by the following criteria: pH < 7.10, BE ≤ -10 mmol, 5-min Apgar score $\leq$6, or primary mechanical ventilation and some other indication of asphyxia (e.g. abnormal cardiotocography, decreased fetal movements, or meconium in the amniotic fluid). We then excluded newborns with gestational age <36 weeks and those with diagnosed or suspected genetic abnormalities, inborn errors of metabolism, or major malformations. Only the earliest EEG of those newborns with several recordings was included. All of the final 50 EEG recordings included simultaneous SEPs and VEPs (in accordance with our in-house routine clinical neonatal EEG protocol). All neurophysiological recordings were performed for clinical indications. Of these 50 newborns, 28 received whole-body therapeutic hypothermia (target temperature 33–34 degrees) for 72 h as part of their treatment strategy and 15 of the 28 were still under hypothermia during the EEG and EP recording. Cooling was initiated according to the criteria of the TOBY study (Azzopardi et al., 2008) with the exception that in certain situation cooling was initiated without a preceding aEEG trace (e.g. if aEEG was not available).

The Ethics Committee for Pediatrics, Adolescent medicine, and Psychiatry, Hospital District of Helsinki and Uusimaa, approved the study protocol. Parental consent form was received for the use of the photograph in Fig. 1A.

2.2. Decisions on withdrawal of treatment

Decisions to withdraw intensive care were based on a combination of poor clinical condition including severe HIE, poor EEG, and severe MRI findings. Decisions were made after discussions with parents.

2.3. EEG, SEP, and VEP recording (Fig. 1A and B)

The EEG and EPs were recorded between 15 h and 10 days postnatally, following our in-house developed clinical routines (Nevalainen et al., 2015). We collected the EEG and SEP signals at 2000 Hz using the NicoletOne EEG system (Cardinal Healthcare/Natus, USA; acquisition bandwidth 0.053–500 Hz), Cz reference, and 21 channel EEG caps (sintered Ag/AgCl electrodes; Waveguard, ANT-Neuro, Germany). An additional electrode was placed over the C7 vertebra to record the cervical SEP. We stimulated each median nerve at the wrist at 0.5 (n = 7) or 1 Hz (n = 43) rates using two disk electrodes and a battery powered portable electrical peripheral nerve stimulator (Micromed Energy Light stimulator; Micromed, Italy) and pulse width of 0.2 ms. If standard stimulation was not possible due to intravenous lines, we stimulated the median nerve at the palm (n = 7) or elbow (n = 1). One newborn only underwent unilateral stimulation because no suitable stimulation site was accessible on one side. The stimulation current was individually adjusted to just above the motor threshold. VEP stimulations were delivered using a stroboscopic flash at 1 or 2 Hz. We aimed at recording all the evoked potentials during sleep (or quietness in case normal vigilance states could not be identified). However, in each EP condition (right hand SEP, left hand SEP, VEP) three newborns did not fall asleep within the recording time slot or woke up during the recording and were, thus, recorded while awake.

2.4. EEG background grading

Two EEG experts (PN and VM) blinded to the clinical information scored all EEGs independently using previously described criteria (Murray et al., 2009). In case of disagreement, a third EEG expert (LL) scored the given EEG, and the final score was reached by consensus. EEG grade 4 indicated inactive trace (background activity <10 μV or severe discontinuity with interburst interval (IBI) >60 s), grade 3 severe abnormality (discontinuous activity with IBI 10–60 s, severe attenuation of background patterns, no sleep-wake cycle), grade 2 moderate abnormality (discontinuous activity with IBI < 10 s, or clear asymmetry or asynchrony), grade 1 mild abnormality (continuous activity with slightly abnormal activity: e.g., mild asymmetry, or mild voltage depression), and grade 0 normal EEG.

2.5. Analysis of evoked potentials

We averaged the EPs offline in BESA® software (BESA GmbH, Germany) for epochs from −100 to 800 ms relative to stimulus onset without further filtering (Fig. 1C). Author PN visually evaluated all EPs using bipolar montages and electrical field maps (Fig. 1D–E). Cervical SEP was identified in the cervical electrode (C7, referenced to Fz) between 8 and 20 ms. Cortical SEP was observed as a salient response beginning within 100 ms from the stimulation in the contralateral centroparietal area coupled with a topographic pattern of electrical field that indicated a source at the contralateral primary somatosensory cortex i.e. a parietal