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Electroencephalography and brain injury in preterm infants

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Abstract

Electroencephalography (EEG) is a sensitive method for detection of brain injury in preterm infants. Although the acute and chronic EEG changes are mainly non-specific regarding type of injury, they correlate with later neurological and cognitive function. In infants developing periventricular hemorrhagic or ischemic brain injury, acute EEG findings include depression of background activity and presence of epileptic seizure activity. The chronic EEG changes associated with white matter injury and abnormal neurological development include delayed maturation, and presence of abundant rolandic sharp waves. Suboptimal cognitive development in preterm infants has been associated with changes in various sleep measures in EEG's recorded at full term. Continuous EEG-monitoring during neonatal intensive care shows that cerebral electrical activity during this vulnerable period can be affected by several extracerebral factors, e.g. cerebral blood flow, acidosis and some commonly used medications. For diagnosis of brain injury in preterm infants with neurophysiological methods, a combination of early continuous EEG monitoring during the initial intensive care period and full EEG, performed at later stages, is probably optimal.

Key words: EEG, aEEG, Cerebral Function Monitor, preterm, brain injury

The normal EEG of the very preterm infant

Our knowledge about what can be considered as a normal early postnatal EEG in an extremely preterm infant has increased considerably during the last few years. Such studies of extremely preterm infants are methodologically difficult to perform, not least due to the vulnerability of these infants during the first days of life, and the study populations are consequently relatively small. Nevertheless, a few studies have managed to include very immature infants with no intracranial pathology on cranial ultrasound or magnetic resonance imaging and with normal long-term follow up. Postconceptional age (PCA) is a commonly used term in EEG studies for describing the infant's degree of maturation. It is often defined as gestational age (GA) in weeks at delivery plus postnatal age in weeks. However, some authors use other terms, e.g. conceptional age and postmenstrual age. In this review we have chosen to use the authors' own terminology regarding the infant's maturity. Extrauterine life is not a normal condition in preterm infants, and therefore data on "normal" postnatal development of EEG in extremely preterm infants is lacking. Serial EEG's of preterm infants without brain lesions and who developed normally give the closest approximation of normal EEG development. However, some studies from healthy preterm infants indicate that some features of the EEG, especially regarding sleep-state variables, at full-term may differ from the EEG's of newborns born at normal gestations^{1,2}. Magnetoencephalography (MEG) is an advanced non-invasive method that can be performed on normal intrauterine fetuses. It is likely that MEG-data in the future can add knowledge on the normal neurophysiological development in fetuses during the last trimester. Furthermore, MEG also opens new perspectives regarding evaluation of fetal cerebral function in pregnancies with complications affecting the fetus, e.g. intrauterine growth restriction³.

A dominating feature of the extremely preterm infants EEG is discontinuity, i.e. the EEG contains periods with bursts of activity mixed with periods with attenuated low-voltage activity (interburst interval, IBI) ⁴. Several studies have shown that the duration of EEG bursts increase with gestational age and that IBI decrease with increasing gestational age in preterm infants ⁵. This seems to be relevant also for the most immature infants, as shown by a study of 15 infants with EEG's recorded at 21 to 26 weeks postconceptional age ⁶.

In 10 infants, born at 24 to 26 gestational weeks, EEG's were recorded during the first five days. Nine of the infants had normal outcome at 3 years of age. The EEG was discontinuous

in all infants, and dominated by bursts of high voltage delta activity. The bursts were mainly synchronous, bursts with amplitude > 50 μ V could last for periods up to 83 seconds. No infant had maximum burst intervals (amplitude < 15 μ V) exceeding 1 minute. Crude sleep-state organization was present at 25 weeks gestation ⁷. In another study, including 17 slightly more mature infants recorded at a 26-28 weeks conceptional age, EEG background was also mainly discontinuous. Synchronous bursts of activity (amplitudes \geq 30 μ V) appeared with up to 3 minutes duration, and there was an occipital predominance of activity. No infant had interburst intervals exceeding 46 seconds. The dominating EEG frequency was delta activity with superimposed alpha, beta and theta. Sleep state differentiation could be seen at 26 weeks conceptional age ⁸.

Some maturational EEG features can be considered as normal at some gestational ages, but abnormal if present at later stages. Rhythmic theta activity appearing in the temporal regions "temporal sawtooth" is associated with normal outcome when present at 27 to 30 weeks postmenstrual age, but an abnormal EEG feature if present a few weeks later ⁹. Temporal sharp waves may also appear in the EEG during the first weeks of life in infants born at 31-32 weeks gestation. However, if abundant, or persisting, they are associated with brain injury, figure 1 ¹⁰. There are also other EEG features that have been observed and associated with normal or abnormal outcome in preterm infants.

Perinatal morbidity and preterm EEG

Perinatal infection and inflammation is a common cause of preterm delivery, and fetal inflammation has been shown in several studies to correlate with development of white matter injury in preterm infants. There is very little data on the relation between perinatal infection and postnatal EEG. We are aware of only one small study investigating a possible relationship between endotoxin exposure and early EEG in preterm infants, and the results were inconclusive ¹¹.

Changes in cerebral blood flow are associated with development of brain injury in preterm infants. There seems to be a relation between early EEG activity in preterm infants and global cerebral blood flow (CBF), measured with 133 Xenon clearance. Lower CBF correlated with increasing discontinuity in the EEG; EEG activity was present when CBF was as low as 5

ml/100g/min¹². In hypotensive preterm infants, volume support increased arterial blood pressure, CBF (measured with Doppler flow velocity in the internal carotid artery) in 10 of 12 infants, but resulted in increased EEG burst rate in only 5, as evaluated by amplitude integrated EEG monitoring (aEEG)¹³. Arterial hypotension is common in infants with persistent ductus arteriosus (PDA), although the presence of a PDA does not seem to influence on the EEG, as evaluated before and after closure of the ductus arteriosus¹⁴.

One study in ventilated preterm infants also indicated that metabolic and respiratory acidosis is associated with depressed cerebral activity. The EEG depression was reversible in 21 of 32 acidotic events with cerebral activity returning to pre-acidosis levels after correction ¹⁵. Several medications, including surfactant and opioids, may transiently depress EEG activity in preterm infants and this must be considered when interpreting the EEG ^{16, 17}. However, one study failed to show a correlation between blood levels of phenobarbital and IBI in 46 very low birth weight infants ¹⁸.

Correlation between EEG abnormalities and brain injury

Background activity

Acute changes in the EEG/aEEG background are powerful, but non-specific, markers of brain dysfunction. Increased discontinuity, amplitude depression, presence of epileptic seizure activity and loss of sleep wake cycling are some of the more important EEG features that may emerge during and after an acute hypoxic-ischemic event. These are consequently common acute findings in preterm infants developing intraventricular hemorrhages (IVH) and periventricular leukomalacia (PVL), figures 2 and 3. A postmortem evaluation of preterm infants with IVH showed that the degree of EEG background abnormality correlated with the extent of brain injury ¹⁹.

EEG and intraventricular hemorrhage

Several studies evaluating both the EEG and the aEEG have shown that electrocortical background activity is depressed in infants developing IVH. Although the EEG/aEEG is of little diagnostic value it is a good predictor of outcome. The degree of background depression correlates with best with the extent of brain injury and also with the grade of IVH ^{18,19,20,21}. Electrographical seizure activity, often subclinical, is common and affects approximately 60-70 % of infants during the development of IVH ^{20, 21, 22}. Although many previous studies

indicated that an association between PRSW and IVH, some studies showed that PRSW did not seem to be associated with IVH and were more often observed with white matter injury PVL²⁰. It now seems clear that PRSW are markers of white matter injury. There seems to be no specific EEG features associated with IVH in preterm infants.

EEG and periventricular leukomalacia

Development of PVL is also associated with EEG depression and epileptic seizure activity ²³. In a study involving 288 preterm infants of which 49 developed PVL, it was suggested that a combination of EEG and cranial ultrasound increased the sensitivity and specificity for diagnosing PVL ²⁴. In a recent study, spectral analysis of the EEG showed a clear association between white matter brain injury and decreased spectral edge frequency ²⁵.

Positive rolandic sharp waves (PRSW) are early markers of white matter injury and PVL. They first appear in the EEG at around one week postnatal age and their occurrence may precede the development of cysts on ultrasound ²⁶. Several studies have shown that there is a clear correlation between the amount of PRSW and risk for cerebral palsy. Marret et al concluded, in a study of 300 preterm infants, that absence of PRSW in neonatal EEG's of preterm infants correlated with favorable motor outcome in 98%, and that presence of more than 2 PRSW per minute was highly associated with development of spastic diplegia ²⁷. The sensitivity of the appearance of PRSW in the neonatal EEG for predicting impairment in preterm infants is further supported by a study of infants with diagnosed PVL. It was shown that if the EEG of an infant with PVL contains no more than 0.1 PRSW per minute, there is a high probability that the infant will develop normally or with only mild impairment ²⁸.

Prediction of outcome

As discussed above, acute EEG abnormalities are strongly associated with neurological outcome in both preterm and full term infants. Presence of seizure activity usually occurs with abnormal EEG background, and is associated with abnormal outcome in both full term and preterm infants. However, most acute EEG abnormalities are transient and resolve later. Early postnatal EEG recordings, performed during the first days of life, are usually the most sensitive for prediction of neurological outcome. In a large study including 295 preterm infants of 27 to 32 weeks gestation, the best correlation between EEG and severity of cerebral palsy was present in EEG's recorded on postnatal days 1-2. The sensitivity for prediction of

outcome from EEG was significantly lower already after 3 days ²⁹. In a study of infants with large IVH's (grade 3-4) the maximum burst rate per hour during the first 24-48 postnatal hours was predictive of gross neurological outcome ³⁰. However, neurodevelopmental outcome in extremely preterm infants may be affected by several other factors including e.g. late onset sepsis and development of bronchopulmonary dysplasia. Therefore it can be expected that early EEG's have lower accuracy for prediction of outcome than EEG's in full-term infants. Tharp et al performed serial EEG's during the neonatal period in 81 preterm infants ³¹. Normal serial EEG's were closely associated with normal outcome, while the presence of a markedly abnormal EEG was associated with poor outcome. The study also showed that the abnormal EEG's were not always the first EEG's to be recorded in an infant. This must be considered in preterm infants deteriorating at later stages.

The chronic EEG changes include disorganized patterns and delayed maturation. Prolonged EEG dysmaturity or delayed maturation >2 weeks at full term is associated with development of later handicaps in preterm infants ^{1, 32}. Mild prolonged depression in early EEG's and dysmaturity in later recorded EEG's seems to be associated with impaired cognitive development in preterm infants ³³. As mentioned above, presence of PRSW are highly correlated with development of cerebral palsy ²⁷.

Presence of early, during the first week of life, sleep wake cycling in aEEG recordings in preterm infants with large IVH's (grade 3-4) is associated with better outcome ³⁰. Sleep measures in EEG's performed at full term in prematurely born infants seem to be sensitive predictors of developmental performance. A decreased amount of discontinuous tracé alternant pattern during quiet sleep was associated with lower IQ in prematurely born infants ³⁴. Advanced sleep measures performed on digitally acquired EEG recordings seem to be sensitive predictors of cognitive development ³⁵. New interesting methods for evaluating sleep in preterm infants include quantitative analysis of the frequency content of the discontinuous EEG activity during quiet sleep QS ³⁶, and analysis of very slow wave components that are not detectable with conventional EEG recording techniques ³⁷. However, a possible correlation between these measures and preterm brain injury has not been evaluated.

Functional integrity of the brain can be analyzed with EEG coherence. It was recently shown that infants treated with Newborn Individualized Developmental Care Program (NIDCAP) had higher EEG coherence between frontal and occipital brain regions indicating a higher

level of maturity as compared to matched controls ³⁸. However, there are at present no published data on correlation between EEG coherence, preterm brain injury and later outcome.

Diagnosing brain lesions with EEG/aEEG

Continuous EEG monitoring during the initial intensive care treatment increases the chance for detecting brain lesions preterm infants, sometimes before clinical symptoms and imaging methods reveal abnormalities. A clinical EEG-monitor has to be developed and adapted for the intensive care environment, and the monitoring should neither disturb the patient nor the medical care of the patient. Since the early 1980's, aEEG monitoring has proved to be useful in newborn infants of all gestational ages. New developments of equipment, including digitally stored signals and display of raw-EEG, allow more accurate evaluation. The aEEG is excellent for early detection of acute electrocortical background disturbances, e.g. deteriorating brain function during hypoglycemia. The aEEG is easy to learn for the neonatologists, but support from neurophysiologists increases the chances for accurate evaluations. The use of aEEG does not exclude standard EEG recordings, instead aEEG monitoring reveals so many, for the brain potentially hazardous, events that it usually leads to an increased need for the more detailed and accurate EEG, figure 4. The more subtle and chronic abnormalities can't be diagnosed with aEEG. The use of more advanced EEG methods, including sleep analysis and coherence, at full term are extremely promising.

Conclusions

Electroencephalography is a sensitive method for detecting acute and chronic brain dysfunction in preterm infants. Several studies have shown that abnormality of EEG correlates with brain injury and that EEG is sensitive for prediction of outcome. Continuous EEG-monitoring during neonatal intensive care, e.g. with amplitude integrated EEG, increases the chance of detecting acute background abnormalities, and evaluate effects from medical interventions. At least in some infants timing of brain injury is possible with EEG ³⁹. Most EEG changes are non-specific indicators of brain injury and not diagnostic for a certain type of injury. The only exception to this are PRSW, which are sensitive indicators of white matter injury and predictive of cerebral palsy.

Interpretation of very preterm infants' EEG needs special training. New digital EEG recording systems with possibilities for various filter and trend settings may increase the chance for early detection of abnormality. Future development of self-referential neural networks may assist in this development with automatic detection of EEG abnormalities in high-risk infants ⁴⁰.

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Legend to Figures

Figure 1a (left) and 1b (right).

This infant had a gestational age of 24 weeks and developed a right-sided intraventricular and intraparenchymal hemorrhage (IVH 4), and later frontal PVL on the right side. The EEG was recorded at 28 weeks gestational age showing abundant positive temporal sharp waves over the right hemisphere (left), and a short bifrontal seizure (right).

Figure 2 a (left) and 2 b (right).

This infant was born at 28 weeks gestation and needed surgery for necrotizing enterocolitis with bowel perforation. The first EEG (figure 1 a) was performed three days after surgery, at 32 gestational weeks. The EEG is discontinuous with high amplitude negative and positive sharp wave complexes over both hemispheres. The postoperative course was complicated, and the infant developed cystic PVL. Cerebral palsy was suspected at four months of age. The second EEG (right) was recorded when the infant was 10 months old (7 months corrected for prematurity) and admitted for infantile spasms. The EEG now had developed into hypsarrhythmia.

Figure 3 a (left) and 3b (right).

This hydropic infant had a cardiac malformation and was born at 31 gestational weeks. Early neuroimaging showed extensive bilateral cystic PVL indicating antenatal onset. The EEG was recorded at day 5 of age and is severely depressed and discontinuous with lack of synchronization between hemispheres. The aEEG (right) was recorded from birth and shows four hours of low amplitude burst-suppression with interburst intervals up to 60 seconds on postnatal day 2, but no seizure activity. The figure also shows two other trend measurements, interburst interval (IBI) and spectral edge frequency (SEF). The asynchronous burst activity can neither be seen in the single-channel EEG nor in the trends.

Figure 4 a (left) and 4 b (right)

This infant was born at 28 gestational weeks, and developed severe respiratory distress with pulmonary hypertension. Amplitude-integrated EEG was recorded from birth. On the left is the aEEG from the second day of life. The 4-hour aEEG tracing shows a discontinuous background with four brief electrographical seizures. The single channel-EEG below the aEEG shows the onset of a seizure, corresponding to the vertical line through the aEEG

tracing. Although difficult to see on this image, there is some very low amplitude interference in the EEG from high-frequency ventilation. On the third day of life bilateral IVH 3 was diagnosed, and the EEG was recorded (right). The EEG showed high-amplitude sharp-wave activity but no seizures.

Figure 1a

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