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Amplitude-integrated electroencephalogram in newborn infants for clinical and research purposes

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Amplitude-integrated electroencephalogram (aEEG) monitoring with the Cerebral Function Monitor (CFM) is used increasingly in neonatal intensive care. The method has been available for more than 30 y since Maynard, Prior and Scott presented the first CFM in the late 1960s (1). The CFM was originally designed for adults but has been used in neonatal care for at least 25 y (2–4). The simplicity of the method, including the single- or two-channel recording makes it feasible for “round the clock” recording. The aEEG method is easy to apply and to interpret and the attending neonatal intensive care unit (NICU) staff can continuously follow changes in the electrocortical background and responses to medical interventions. The aEEG has been used in a number of clinical and experimental neonatal settings including routine clinical monitoring of brain activity in patients in the NICU, detection of epileptic seizure activity, prediction of outcome and as a research tool. Normal values for moderately preterm infants and full-term infants have been published by Verma et al. and by Thornberg and Thiringer (4, 5). Other methods for continuous EEG monitoring have also been used successfully in newborn infants, especially the Medilog EEG tape-recorder, on which several publications on normative data and abnormal findings during intensive care have been recorded (6, 7). However, this commentary focuses on the pros and cons of using the CFM method for clinical and investigational purposes.

In the NICU the aEEG is used for monitoring cerebroelectrical background activity in severely ill neonates. In this group of infants, deterioration of the electrocortical background activity can precede clinically obvious deterioration (8). It is obvious that major changes in cerebroelectrical activity may occur without clinical signs in ill newborn infants. One example is the marked temporary depression of background activity that may occur after surfactant administration in preterm infants (9). The reason for this reaction has still not been explained. Some medications, such as phenobarbitone, morphine and diazepam, are known to produce EEG depression. They may also affect the aEEG background and this must be considered when the aEEG is interpreted (10).

The aEEG can also be used for diagnosing epileptic seizure activity in newborn infants and is feasible for following the effects of antiepileptic treatment. The clinical manifestations of neonatal seizures are often subtle and may be difficult to distinguish from immature movements. The aEEG method revealed that subclinical seizure activity is relatively common in NICU patients (11), and also that epileptic seizure activity is common in preterm infants developing germinal matrix and intraventricular haemorrhages (12). The aEEG findings were supported by other EEG monitoring techniques (7). Later, EEG studies confirmed that a majority of neonatal seizures actually are subclinical

and hence not possible to detect through clinical observation only (13).

The reason that the aEEG has recently gained more widespread use in NICUs is probably its sensitivity in predicting outcome after birth asphyxia. Several studies have shown that the aEEG is sufficiently sensitive for prediction of outcome as early as in the first hours of life (14–16). If the electrocortical background is normal, there is a good chance that the infant will recover without sequelae, but if the background is abnormal there is a high risk of adverse outcome. Previous studies have shown that the standard EEG has a high predictive sensitivity after birth asphyxia if performed during the first week of life. Since the aEEG is based on the standard EEG, it is reasonable to believe that the standard EEG would also have the same sensitivity for prediction of outcome. However, we are not aware of any comparable early studies on serial EEG and continuous aEEG after birth asphyxia. Yet, in a recent study only 6 out of 9 asphyxiated infants were correctly predicted by an early EEG that was performed within the first 8 h of life (17).

The aEEG is excellent for continuous long-term monitoring of background activity and can be used for several days and weeks if necessary. When using the aEEG one must, however, be aware that this is a simplified method for monitoring general electrocortical background activity and that it subsequently has limitations. Comparisons between simultaneous aEEGs and EEGs have shown good correlation between general background activity. However, even though most epileptic seizure activity is detected by the aEEG, some short or localized seizures may be missed (18, 19). Since the aEEG interpretation is based on pattern recognition without the possibility of EEG verification of seizure activity, on some occasions there may be uncertainty whether the pattern really represents seizure activity or other activity. It should also be remembered that the aEEG does not give detailed information on electrocortical activity. For this reason we recommend that at least one standard EEG should be recorded in monitored infants; the only exemption in our unit is extremely preterm infants who have an aEEG as routine clinical monitoring during intensive care. A complementary standard EEG may reveal some subtle features that are impossible to detect with the aEEG, e.g. localized sharp-wave activity. After the first week of life, the EEG is probably more sensitive than the aEEG for detecting abnormalities and prediction of outcome. In an EEG study of preterm infants, abundant positive rolandic sharp-wave activity was predictive of cerebral palsy (20). This type of activity is not possible to detect with the aEEG.

The study by Groenendaal et al. in this issue of *Acta Pædiatrica* (21) highlights the question of during what clinical circumstances we might expect to find changes in the aEEG and when we should not expect any changes, and also the question of when other methods

might be more appropriate for our investigative purposes. Severe hypoglycaemia depresses cerebral activity, which can also be seen in the neonatal aEEG (8). Cerebral effects from moderate hypoglycaemia in newborn infants may be compensated for by using other metabolic substrates, e.g. lactate and ketone bodies. Consequently, moderate neonatal hypoglycaemia did not produce any measurable changes in the aEEG (22). In newborn infants, progressive hypoxia is associated with an increase in EEG slow activity before the amplitude is depressed (23). However, hypoxia in the experimental situation was associated with stable electrocortical brain activity until arterial blood pressure dropped (24). Consequently, it cannot be assumed that the aEEG should be able to detect the early changes due to progressive hypoxia. However, blood exchange transfusions in newborn infants produce measurable aEEG changes associated with changes in mean arterial blood pressure (25). The aEEG has been used for following cerebral recovery and effects from postasphyctic interventions in the experimental situation. In asphyxiated infants, intervention with allopurinol, a free radical scavenger, preserves but does not ameliorate aEEG amplitude during a 4-h observation period, in comparison with control infants where the aEEG deteriorates (26). Postasphyctic intervention with deferoxamine in newborn lambs produces measurable changes in aEEG amplitude within 3 h, and the aEEG amplitude also correlates with $\text{Na}^+\text{-K}^+\text{-ATPase}$ activity (27). On the second day of life in asphyxiated newborn infants, aEEG background correlates with cerebrospinal fluid levels of neuron-specific enolase (28). It is consequently reasonable to investigate whether postasphyctic intervention in newborn infants produces measurable changes in electrocortical activity that reflect effects on the brain. The excitatory amino acid glutamate plays a major role in postasphyctic neuronal injury. One of the effects of glutamate is to induce opening of the N-methyl-D-aspartate (NMDA) channel, thereby allowing excess intra-neuronal entry of calcium ions. The NMDA receptor is gated by magnesium ions. Administration of magnesium sulphate blocks the NMDA channel to calcium entry, which theoretically could reduce postasphyctic neuronal injury.

In a preliminary study of newborn infants comparing two doses of magnesium sulphate for postasphyctic intervention, no changes in aEEG or Medilog EEG were found. However, the study was not blinded and the aEEG/EEG findings were not described in detail (29). The present study by Groenendaal et al. (21) is justified because it is rational to hypothesize that adequate blocking of the NMDA channel with magnesium sulphate in the early postasphyctic period would produce some electrocortical recovery. Furthermore, more information is needed on early neurophysiological recovery and the effects of intervention in asphyxiated newborn infants. The study investigated aEEG background patterns, and aEEG burst-density but did not

find any effects of the magnesium sulphate compared with placebo. The authors discuss possible reasons for the lack of effects from the magnesium sulphate. Yet another explanation is that their method of evaluation, the aEEG method with the CFM, is too crude for the purpose. With the newly increased interest in neonatal EEG monitoring, new flexible equipments are being developed with the possibility of combining the aEEG, with e.g. frequency analysis from several channels, when needed, simultaneously with continuous recording of the raw EEG.

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