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## REVIEW

## Role of cerebral function monitoring in the newborn

L S de Vries, L Hellström-Westas

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For many years, newborn infants admitted to neonatal intensive care units have had routine electrocardiography and been monitored for respiratory rate, heart rate, oxygen saturation, and blood pressure. Only recently has it also been considered important to monitor brain function using continuous electroencephalography. The role of cerebral function monitoring in sick full term and preterm infants is reviewed.

Whereas monitoring of respiratory rate, heart rate, oxygen saturation, and blood pressure has been well integrated into the routine care of any newborn infant admitted to a neonatal intensive care unit for many years, only recently was it considered important, or possible, to use continuous electroencephalography (EEG) to monitor brain function.

Maynard<sup>1</sup> originally designed the cerebral function monitor (CFM) in the late 1960s. The main clinical application, investigated by Prior,<sup>2</sup> was monitoring adult patients during anaesthesia and in intensive care after cardiac arrest, during status epilepticus, and after heart surgery. A description of the device and initial experiences with it have been compiled into a well known book.<sup>3</sup> The term amplitude integrated EEG (aEEG) is currently preferred to denote a method for electrocortical monitoring, whereas CFM is used to refer to specific equipment. The EEG signal for the single channel aEEG is usually recorded from one pair of biparietally placed electrodes (corresponding to P<sub>3</sub> and P<sub>4</sub> according to the international EEG 10–20 classification, ground F<sub>z</sub>). Both thin subdermal needle electrodes and disc and hydrogel electrodes have been used. Although application of needle electrodes is considered more invasive, it involves less handling, and the impedance usually remains below 5 k $\Omega$  for several days. The use of a single channel does not allow information about hemispheric asymmetry to be obtained. The use of two channels (bilateral frontoparietal electrodes) may be of clinical significance, especially in children with a unilateral brain lesion. The signal is amplified and passed through an asymmetrical band pass filter, which strongly attenuates activity below 2 Hz and above 15 Hz in order to minimise artefacts from such sources as sweating, muscle activity, and electrical interference. Additional processing includes semilogarithmic amplitude compression, rectification, and time compression. The signal is recorded on paper with a semilogarithmic scale at slow speed (6 cm/h) at the cot side (fig 1). A second trace continuously records the electrode impedance.

The band width in the output reflects variations in minimum and maximum EEG amplitude, both of which depend on the maturity and severity of illness of the newborn infant. The use of a semilogarithmic scale to plot the output means that changes in background activity of very low amplitude (<5  $\mu$ V) are enhanced. The cerebral function analysing monitor (CFAM; RDM Consultants Ltd, Uckfield, East Sussex, UK) is a further development of the CFM. aEEG monitoring can be carried out from two to four channels, and a frequency analysis can be performed and presented as percentage activity within each of the classic frequency bands.<sup>4</sup> More recently, several digital EEG monitoring systems have been developed which allow the raw EEG to be displayed and stored continuously with online trend analysis of the aEEG, using one, two, or more channels.

The first studies performed in newborn infants are from the early 1980s.<sup>5–7</sup> In most of the studies, aEEG was recorded with the CFM (CFM 4640 or 5330; Lectromed Devices Ltd, Letchworth, Hertfordshire, UK). In the initial studies, maturation of the background pattern was assessed in low risk preterm infants.<sup>6–8</sup> However, it quickly became clear that long term recordings in high risk, full term infants with neonatal encephalopathy was especially interesting.<sup>5, 9</sup>

#### RATIONALE FOR THE USE OF aEEG IN THE NEONATAL BRAIN

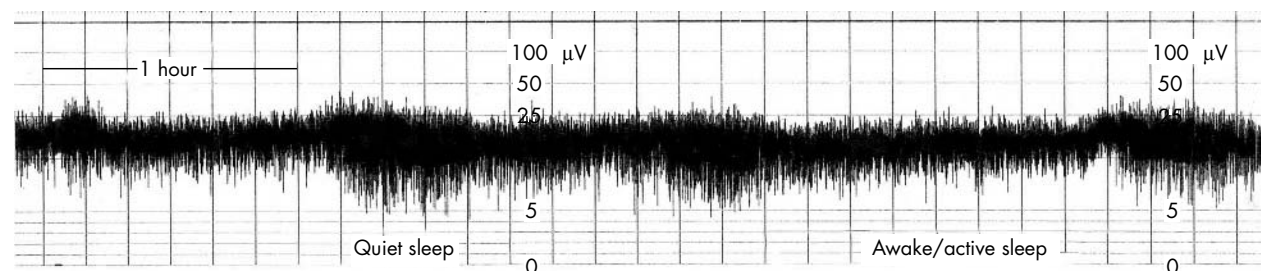
Interest in the neonatal brain has increased considerably during the last decade or so. This is in part due to better diagnostic methods in the acute and subacute stage. Magnetic resonance imaging provides important information about the presence and extent of structural lesions. Information on cerebral metabolism can be obtained during the same examination using magnetic resonance spectroscopy.<sup>10</sup> Although magnetic resonance imaging is now often performed within a few days of birth, information is preferably obtained within hours of delivery for selection of infants for early intervention studies, such as hypothermia.<sup>11</sup> aEEG provides information about the functional integrity of the brain and can be used immediately after admission or even in the referring hospital.

**Abbreviations:** aEEG, amplitude integrated electroencephalography; CFM, cerebral function monitor; EEG, electroencephalography; HIE, hypoxic-ischaemic encephalopathy

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**Figure 1** Continuous normal voltage background pattern with sleep-wake cycling recorded on a CFM 5330 (Lectromed).

## NEONATAL ENCEPHALOPATHY AND NEONATAL SEIZURES

Despite advances in obstetric and neonatal care, perinatal hypoxic-ischaemic encephalopathy (HIE) is still experienced by three to four infants per 1000 live term births, and is associated with death or an adverse neurodevelopmental outcome in a considerable number of these. aEEG monitoring of newborn infants with HIE has been used for assessment of aEEG background activity, early evaluation of brain function, detection of seizures, evaluation of the effect of anti-convulsive drugs, selection of patients for neuroprotective intervention, and prediction of neurodevelopmental outcome as early as the first hours after birth.

## ASSESSMENT OF aEEG BACKGROUND PATTERN

Assessment of the aEEG recording should start with the background pattern. Then the presence or absence of seizure activity should be noted.

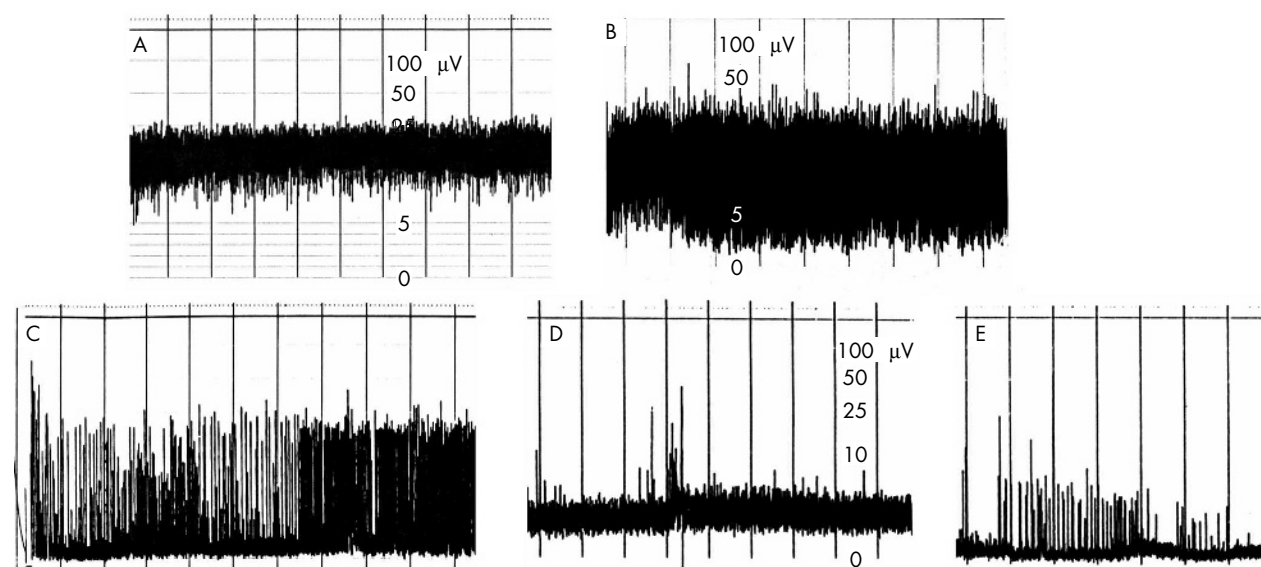
Different methods have been used to classify the variations in background pattern. Some describe the different patterns,<sup>12–14</sup> whereas others have made a distinction based on the voltage as level of the upper and lower margins of the activity.<sup>15</sup> The classification of background patterns distinguishes five different patterns in full term infants (fig 2):

- (a) the continuous normal voltage pattern is a continuous trace with a voltage of 10–25 (–50)  $\mu$ V (fig 2A);

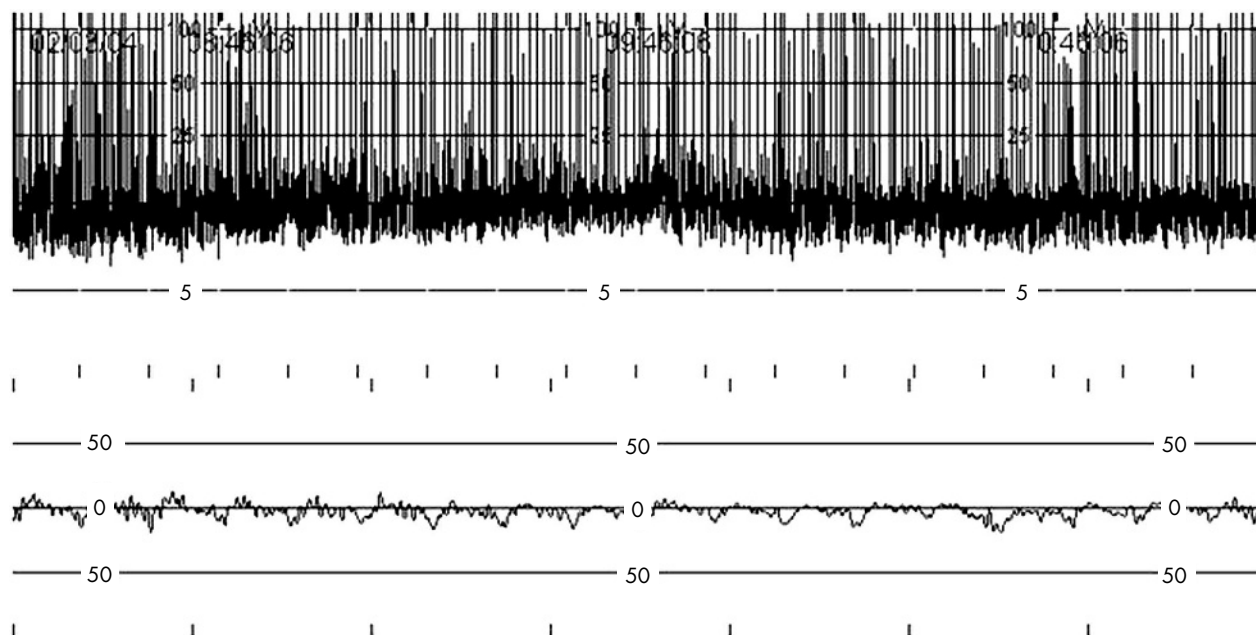
- (b) discontinuous normal voltage pattern is a discontinuous trace, where the low voltage is predominantly above 5  $\mu$ V (no burst suppression) (fig 2B);
- (c) discontinuous background pattern (burst suppression); periods of low voltage (inactivity) intermixed with bursts of higher amplitude (fig 2C);
- (d) continuous background pattern of very low voltage (around or below 5  $\mu$ V) (fig 2D)
- (e) very low voltage, mainly inactive trace with activity below 5  $\mu$ V (flat trace) (fig 2E)

There have been several studies in which aEEG and standard EEG were performed simultaneously to compare the two techniques. Overall there appeared to be a good correlation between the aEEG and EEG background pattern in the sick full term infant.<sup>16, 17</sup> In the presence of a discontinuous normal voltage background pattern, a mild discrepancy was sometimes noted, showing excessive discontinuity on the standard EEG.<sup>17</sup> Infants with this background pattern usually normalise within the first 24 hours, but some deteriorate and develop a burst suppression pattern. A standard EEG is therefore especially important in this intermediate group to obtain more detailed information, especially about possible intermixed electrical discharges (see below).

In the classification of al Naqeeb *et al*,<sup>15</sup> amplitude was classified as normal when the upper margin of the band of



**Figure 2** Different background patterns recorded on a CFM 5330 (Lectromed). (A) Continuous normal voltage; (B) discontinuous normal voltage; (C) burst suppression; (D) continuous low voltage; (E) flat trace.



**Figure 3** Full term infants with severe hypoxic-ischaemic encephalopathy. The infants started off with an isoelectric trace and subsequently developed electrical discharges on a severe burst suppression pattern. After some hours, a drift of the baseline is noted with a minimum voltage above 5  $\mu$ V even though a burst suppression pattern can still be recognised. The raw electroencephalogram appears to show a pulse waveform (Olympic 6000).

aEEG activity was  $>10 \mu$ V and the lower margin  $>5 \mu$ V (fig 2A), moderately abnormal when the upper margin of the aEEG band was  $>10 \mu$ V and the lower margin  $\leq 5 \mu$ V (fig 2B and latter half of 2C), and suppressed when the upper margin of the aEEG band was  $<10 \mu$ V (fig 2D, E). When the latter classification system is used, care should be taken with the so-called drift of the baseline, which can significantly raise the baseline, while still showing a burst suppression pattern. This drift of the baseline is especially seen in infants with a severely depressed background pattern and is probably due to interference from extracranial activity—for example, electrocardiography (fig 3). Both the pattern and the voltage should be considered to avoid incorrect classification of a background pattern into a “better” category. In addition, the underlying EEG signal should be examined to assist in the recognition of interference, which may cause the drift.

Over the years quite a number of groups have studied the relation between the background pattern recorded within 3–12 hours of birth and subsequent neurodevelopmental outcome.<sup>12 13 18 19</sup> The first studies assessed the aEEG during the first 12–24 hours, but with recent interest in early intervention, it has now been assessed as early as three to six hours after birth, to see whether it could play a role in

selection of infants at risk of developing neonatal encephalopathy. The predictive value of the presence of a poor background pattern (burst suppression, continuous low voltage, flat trace) for subsequent poor neurodevelopmental outcome was assessed in these different studies. The predictive values obtained by different groups were very similar (table 1). Both positive and negative predictive values were slightly lower when aEEG was assessed at three rather than six hours after birth, but they were still considered sufficiently high to use this technique for early selection in hypothermia intervention studies. A more recently published study indicates that the sensitivity and specificity can be increased further when early aEEG evaluation is coupled with a clinical evaluation.<sup>20</sup>

### DETECTION OF EPILEPTIC SEIZURE ACTIVITY

Epileptic seizures are common in full term infants admitted with HIE. Several studies have shown that, although the initial seizures are often clinical, subsequent seizures after administration of the first anti-epileptic drug are often subclinical.<sup>21 22</sup> This is referred to as electroclinical dissociation or “uncoupling”. Bye and Flanagan<sup>23</sup> showed evidence of reduced clinical features after sequential administration of anti-epileptic drugs. Using prolonged video/EEG monitoring, they found that 85% of all seizures were not associated with clinical manifestations. This phenomenon was recently also addressed by Sher *et al.*<sup>21</sup> They found that 58% of the infants with seizures persisting after treatment with phenobarbitone or phenytoin showed uncoupling of electrical and clinical seizures.<sup>3 21</sup> Boylan *et al.*<sup>22</sup> also found that electrographic seizures were common in infants with severe HIE after initial treatment with phenobarbitone. The aEEG can play an important role in the detection of these subclinical seizures. The effect of anti-epileptic drugs can only be assessed when continuous aEEG or standard EEG registration is used (fig 4).

Seizures are most often recognisable on the aEEG as a rapid rise in both the lower and upper margins of the trace. Arousal during care procedures often results in a transient rise in the aEEG background and may be misinterpreted as

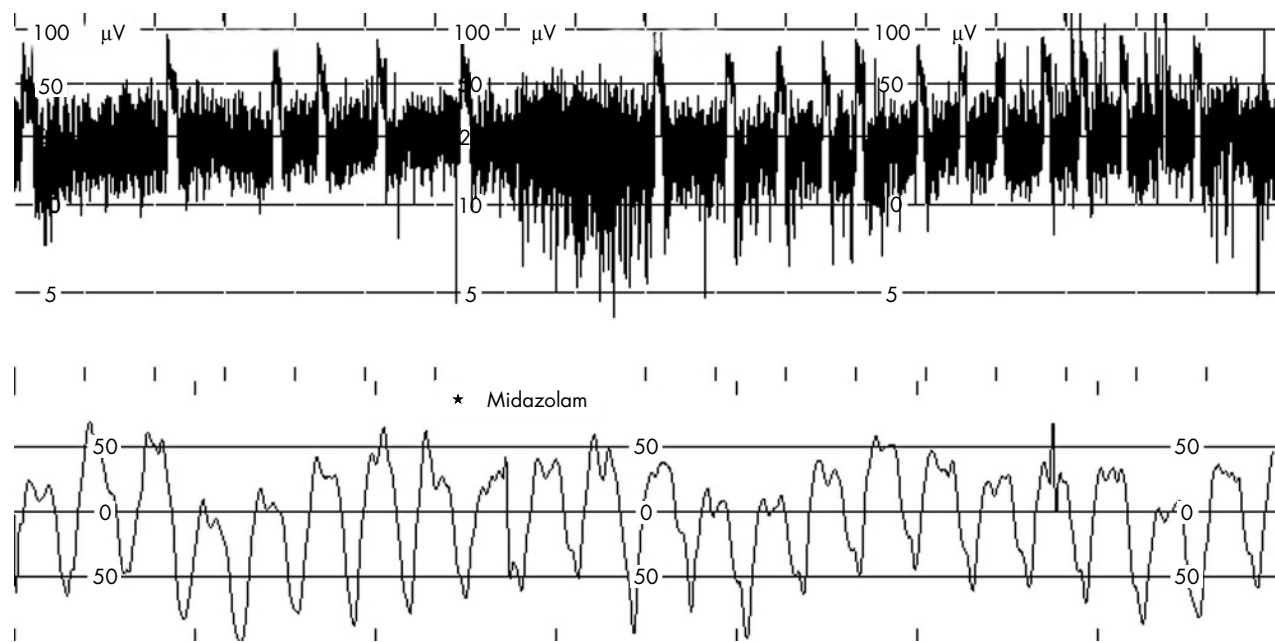
**Table 1** Predictive value of a poor background pattern (burst suppression, continuous low voltage, flat trace) for poor neurodevelopmental outcome in the neonatal period and infancy

Time after birth (h)	Sensitivity	Specificity	PPV	NPV
6 <sup>12</sup>	95	89	86	96
6 <sup>18</sup>	94	79	84	92
6 <sup>13</sup>	91	86	86	96
3 <sup>13</sup>	85	77	78	84

Values are percentages.

PPV, Positive predictive value; NPV, negative predictive value.



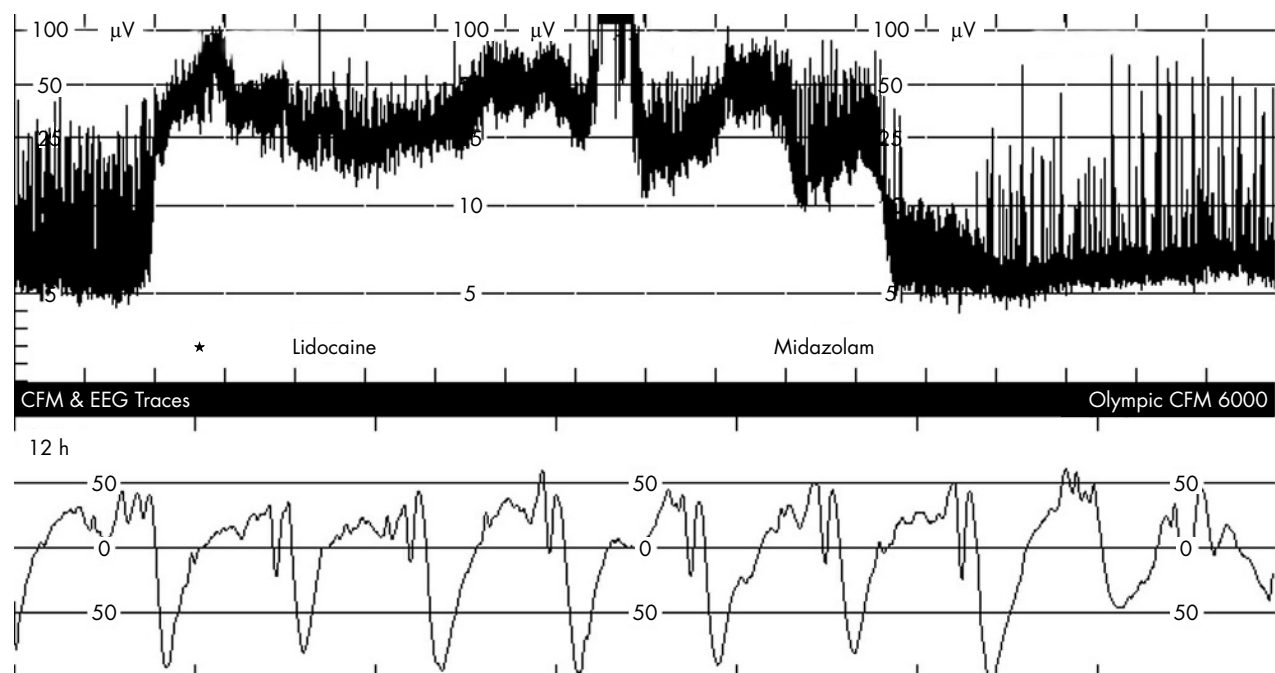


**Figure 4** Repetitive epileptic discharges on a continuous normal voltage background pattern. Raw electroencephalogram, shown at the asterisk, shows rhythmic activity. Midazolam is also given at this time. Repetitive discharges continued without any clinical signs (Olympic 6000).

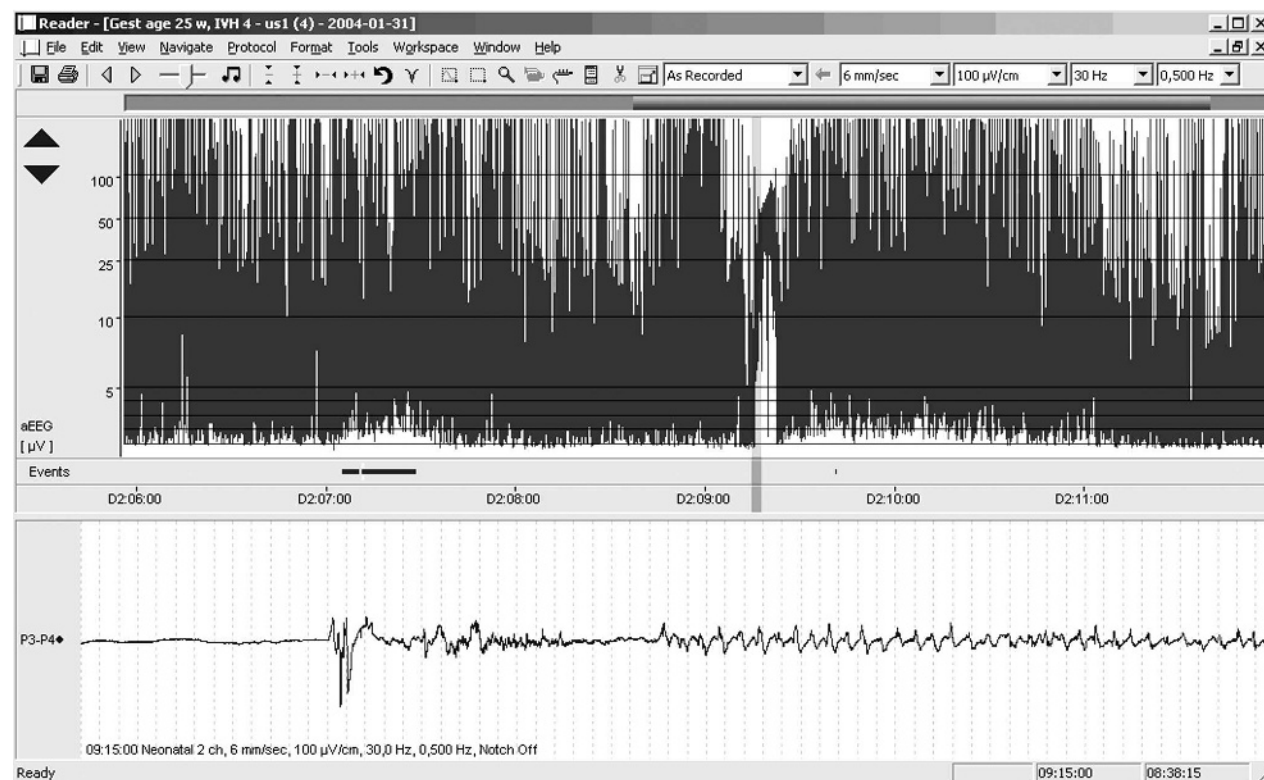
epileptic seizure activity. It is therefore very important that all care procedures are documented on the traces to facilitate correct interpretation. A status epilepticus usually looks like a “saw tooth” pattern, but a continuously raised background pattern can also sometimes be seen. Correct interpretation is only possible when a simultaneous raw EEG is available (fig 5).

It has been questioned whether a single channel aEEG is sufficiently reliable to detect seizure discharges. Owing to the nature of the single channel recording, it is not surprising that very brief seizure activity, as well as focal seizure activity,

may be missed.<sup>17–24</sup> The data in the study by Toet *et al*<sup>17</sup> did not identify focal seizures in two of 10 children who were noted to have electrical discharges during the simultaneous aEEG-EEG recording. The data in the study by Rennie *et al*<sup>24</sup> were less promising. They asked four neonatologists with rather limited experience (three to five hours) to analyse aEEG traces recorded at three different speeds. The infants were a mixture of preterm and full term infants. The seizures were poorly detected at the most commonly used speed (6 cm/h) with a sensitivity of only 38%. As the authors suggested themselves, these disappointing results may be attributed to



**Figure 5** Status epilepticus with a continuously raised voltage over a period exceeding one and a half hours. Raw electroencephalogram taken at the asterisk. Interruption is achieved after midazolam administration (Olympic 6000).



**Figure 6** Preterm infant, born at 25 weeks gestation with intraventricular haemorrhage grade 4 on ultrasound. The infant is mechanically ventilated and sedated with a continuous infusion of morphine. The amplitude integrated electroencephalographic (aEEG) recording has a duration of six hours and shows discontinuous background activity (burst suppression) without cyclical changes. A short seizure develops after 3.5 hours of recording, and can be seen in the aEEG as an abrupt and transient rise in the lower level of the trace. Below is 60 seconds of the raw EEG at the start of the seizure, corresponding to the shaded vertical line in the aEEG (NicoletOne; Vyasis).

the limited experience of the examiners. Furthermore, the group was inhomogeneous, with eight of the 19 infants having a gestational age <33 weeks, and five of the infants only showing focal seizures. This study stresses the fact that experience is required to be able to interpret aEEG traces. Ample examples can be studied in an aEEG atlas<sup>25</sup> and also at a website ([http://www.azzopardi.freeseerve.co.uk/CFM/olympic\\_cfm\\_manual.pdf](http://www.azzopardi.freeseerve.co.uk/CFM/olympic_cfm_manual.pdf)). The study of Rennie *et al*<sup>24</sup> also shows that one should be aware of the limitations of the technique. Focal seizures do, however, often generalise at a later stage and will then be identified by the aEEG. Some newer machines offer two channels, which may allow better detection of focal seizures, for instance in children with neonatal stroke. Newer systems also provide access to the raw EEG, which can often help to identify brief periods of seizure activity, which are not easily detected on the older aEEG equipment. Even though it is possible that some focal or very brief seizures will not be detected, the long duration of the aEEG registration outweighs the limitations of obtaining detailed information during a much shorter, 30 minute, standard EEG recording.

### ASSESSMENT OF SLEEP-WAKE CYCLING

The narrow trace in the aEEG represents more continuous activity during wakefulness or active sleep, and the periods of widening of the trace represent more discontinuous activity during quiet sleep (fig 1). It was recently shown that the presence, time of onset, and quality of sleep-wake cycling reflects the severity of the hypoxic-ischaemic insult to which newborns have been exposed.<sup>26</sup> The time of onset of sleep-wake cycling was shown to predict neurodevelopmental

outcome based on whether it returns before 36 hours (good outcome) or after 36 hours (bad outcome). With this method, an accurate prediction was made in 82% of the 171 newborn infants with different degrees of HIE.

These data are in agreement with two other recent reports. Ter Horst *et al*<sup>27</sup> studied 30 full term newborns with HIE. They found sleep-wake cycling in 10/13 newborns with a normal outcome, in 3/6 with a mildly abnormal outcome, and in none of 11 who had an abnormal outcome or died. Early sleep-wake cycling was also noted to correlate with a good outcome in a study by Thorngren-Jerneck *et al*,<sup>28</sup> who compared aEEG and positron emission tomography findings in 19 term newborns with HIE.

### THE PRETERM INFANT

aEEG is also feasible for monitoring cerebral activity in preterm infants during intensive care. In parallel with the EEG, aEEG background activity is more discontinuous in preterm infants. Normative values for aEEG background activity at different gestational ages have been published.<sup>29–30</sup> Sleep-wake cycling can be clearly identified in the aEEG from around 30 weeks gestation, but also at 25–26 weeks gestational age a cyclical pattern resembling sleep-wake cycling can be seen in stable infants. Effects from some common drugs—for example, surfactant, morphine, and diazepam—can be readily seen in the aEEG of preterm infants.<sup>31–32</sup>

### PREDICTION OF OUTCOME

Early prediction of outcome from aEEG is a more complicated issue in preterm infants than in full term infants. In the most immature infants, factors other than initial brain function

may influence long term neurodevelopmental outcome—for example, bronchopulmonary dysplasia and late onset sepsis—which makes prediction of outcome from early EEG less certain.<sup>33</sup> Nevertheless, several EEG and aEEG studies have shown early background depression to correlate with the severity of a periventricular-intraventricular haemorrhage.<sup>34–38</sup> A mainly discontinuous background pattern can be considered as normal in most infants below 30 weeks gestation. Consequently, a classification based on the type of background pattern is not feasible for preterm infants. By measuring, for example, percentage of activity above a predefined level, for example 3  $\mu$ V, or by counting burst activity, a quantitative measure of the degree of continuity or discontinuity can be obtained. In preterm infants with small periventricular-intraventricular haemorrhages, aEEG background is initially depressed but recovers within the first days of life, whereas the aEEG background remains depressed for longer periods in infants with larger haemorrhages. By counting the number of bursts/hour, early prediction of gross neurological outcome could already be made during the first 24–48 hours of life in preterm infants with large haemorrhages.<sup>39</sup>

### DETECTION OF EPILEPTIC SEIZURE ACTIVITY

Epileptic seizure activity in preterm infants can be identified in the same way as in full term infants. Epileptic seizure activity, often without clinical symptoms, is very common in the aEEG during development of intracerebral haemorrhages.<sup>37, 38</sup> Although not studied, it is our impression that epileptic seizure activity in preterm infants may be more difficult to assess, as it may be fragmentary, and status epilepticus with the typical saw tooth pattern is rarely seen. The new aEEG monitors, including display of the raw EEG, will contribute to more accurate diagnosis of seizure activity in preterm infants (fig 6).

### ASSESSMENT OF SLEEP-WAKE CYCLING

A cyclical pattern including periods with more continuous activity can be seen in aEEG of stable preterm infants. From around 32 weeks gestation, it is clear that this represents sleep-wake cycling.<sup>40</sup> Periods with discontinuous activity represent quiet sleep. Wakefulness and active sleep are represented by periods with continuous activity and cannot be distinguished in the aEEG without simultaneous observation of the infant. A recent study on aEEG scoring in infants from 24 to 39 weeks gestation showed that development of a cyclical pattern in preterm infants is closely related to increasing postconceptional age.<sup>14</sup> The aEEG has been used for quantifying quiet sleep in preterm infants when evaluating care procedures such as incubator covers and developmental care.<sup>41, 42</sup> Early presence of sleep-wake cycling in the aEEG was also associated with better outcome in infants with large haemorrhages.<sup>39</sup>

### aEEG: PAST, PRESENT, AND FUTURE DIRECTIONS

Experience with continuous aEEG is increasing, and many neonatal intensive care units would now find it hard to treat a full term infant with HIE without having access to this equipment. The use of this continuous monitoring device has also raised a number of questions. With longer recordings, it has become easier to see that neonatal seizures are difficult to control with commonly used anti-epileptic drugs.<sup>43</sup> Other drugs such as lidocaine and midazolam have been introduced and need to be assessed further.<sup>44–47</sup> The anti-epileptic effect of these drugs can only be seen with the use of continuous aEEG monitoring. Using a continuous monitor, we have become aware that subclinical seizures are very common. There are now some data to support the view that repeated seizures may have an adverse effect on the developing human

brain and even that the severity of seizures in newborns with perinatal asphyxia is independently associated with brain injury.<sup>4, 5, 48, 49</sup> Although the presence of brief rhythmic discharges was shown to be associated with an adverse outcome,<sup>49</sup> there is as yet no real evidence that subclinical seizures are harmful to the neonatal brain. Concerns have also been expressed about the apoptotic neurodegenerative effect of anti-epileptic drugs in the developing rat brain at plasma concentrations relevant for seizure control in humans.<sup>50</sup> The first randomised study of treatment of subclinical seizures (SuSeQue) has just started, with 10 neonatal units participating in the Netherlands and Belgium.

aEEG is also useful in the high risk preterm infant even though this has not yet been evaluated as extensively as in the full term infant. It is most likely that aEEG will soon be part of the routine care in the neonatal unit and some of the larger district general hospitals, and one would hope and expect that some of the questions raised by using this device will be answered in the not too distant future.

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