Early Serial EEG

in Hypoxic Ischaemic Encephalopathy

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Abstract

Objective: To perform early serial EEGs in infants with hypoxic ischaemic encephalopathy (HIE) and compare the findings with neurodevelopmental outcome.

Methods: Nine full-term neonates with HIE had simultaneous Video-EEG polygraphic studies within 8 hours of birth. The EEG was repeated at 12-24 hourly intervals. All surviving infants had a neurodevelopmental assessment at 1 year.

Results: Two infants had a normal or mildly abnormal EEG within 8 hours of birth and neurodevelopmental outcome was normal. Seven infants had severely depressed background activity in the first 8 hours of life. In three infants the EEG activity recovered within 12 to 24 hours showing continuous activity with no or only minor abnormalities. All these infants had a normal outcome. The remaining four infants, who also had an initially inactive recording, subsequently developed severe background abnormalities. At follow up, two infants had died and the remainder developed major neurological sequelae.

Conclusion: Early EEG is an excellent prognostic indicator for a favourable outcome if normal within the first eight hours of life and for a poor outcome if the background activity continues to be inactive or grossly abnormal beyond eight to twelve hours of life. However, an inactive or very depressed EEG within the first eight hours of life can be associated with good outcome if the EEG activity recovers within twelve hours.
1. Introduction

Hypoxic ischaemic encephalopathy (HIE) is a common and serious neonatal illness and a major cause of lifelong disability. Reliable early prediction of neurological outcome in these infants not only allows appropriate advice for parents, but also may identify infants who benefit from immediate neuroprotective treatment (Vannucci and Perlman, 1997). Fetal heart monitoring, cord pH and Apgar score have not been proven useful. The clinical grade of HIE according to Levene’s modification of the Sarnat criteria (Sarnat and Sarnat, 1976; Evans and Levene, 1999) is easy to assess and reliably predicts outcome. However, the worst clinical grade cannot be determined until 48 hours after birth and sedation or high dose antiepileptic medication may falsify the clinical grade. The prognostic value of electroencephalography (EEG) in full-term infants with HIE has been well documented from recordings obtained between the second and seventh day of life (Monod et al., 1972; Watanabe et al., 1980; Holmes et al., 1982; Selton and Andre, 1997). A good outcome is seen in those infants with normal background activity following a hypoxic event. Severely abnormal background recordings (inactive or isoelectric) are generally associated with major sequelae or death. There is still uncertainty about the significance of moderately abnormal EEGs and the predictive value of EEGs recorded within the first 12 to 24 hours of life. There are a few reports of EEG recordings during the first 12 hours of life in infants (Pezzani et al., 1986; Wertheim et al., 1994) and no studies on the evolution of the EEG in HIE. Furthermore, there are no reports on very early EEG recordings in normal neonates. Recently, early single channel amplitude integrated EEG (Cerebral Function Monitor, CFM) has been shown to be useful, but has limitations (Hellstrom-Westas et al., 1995).
The aim of this study was to perform very early EEG recordings in full-term infants with HIE, to examine the early evolution of the EEG over the first few days after birth and compare it to neuro-developmental outcome.
2. Materials and Methods

2.1. Subjects

From a prospective research study of infants at risk of seizures we included in this study all full-term infants with HIE who had an initial EEG recording within the first 8 hours of life. The study was approved by the ethics committee of King’s College Hospital, London. Written informed parental consent was obtained in all cases.

The diagnosis of HIE was made on the following clinical criteria: evidence of fetal distress (including meconium stained liquor, abnormal or suspicious cardiotocography (CTG), Apgar score < 3 at 1 minute and/or < 5 at 5 minutes, umbilical cord pH < 7.1), delayed onset of spontaneous respiration and abnormal neurological examination in the first 48 hours of life. The clinical grade of HIE was staged according to Levene’s modification of the Sarnat criteria (Evans and Levene, 1999).

2.2 Methods

A 16 channel Telefactor (Modac) Video-EEG system was used to record 12 bipolar channels of EEG using the 10-20 system of electrode placement modified for neonates (F4, C4, T4, P4, O2, Cz, F3, C3, T3, P3, O1). A single channel electro-oculogram (EOG) was recorded from above the outer canthus of the right eye to below the outer canthus of the left eye and the sub-mentalis electromyogram was also recorded on one channel. The remaining two channels were configured to display electrocardiogram (ECG) and respiration via an output from the infant’s clinical monitor. A video recording was made of each baby for the entire duration of the recording. The EEG-polygraphy waveforms were embedded on to the video picture and recorded by a Panasonic video recorder on to conventional videotape.
Depending on the clinical status and the first EEG findings, the EEG was repeated at 12-24 hourly intervals. All EEGs were interpreted by the same electroencephalographer (RMP). Careful review was made of each videotape and analysis was made for periods of (i) background activity, (ii) abnormal features and (iii) seizure patterns. Background activity was classified according to the criteria defined in Table 1. The main features of this classification have been defined previously (Watanabe et al., 1980; Wertheim et al., 1994; Selton and Andre, 1997).

If the EEG recording lasted longer than 60 minutes, a background activity grade was assigned to the initial 60 min. The diagnosis of an electrographic seizure required the evolution of sudden, repetitive, evolving stereotyped forms with a definite beginning, middle, and end (Shewmon, 1990). Neonatal status epilepticus was defined as continuous seizure activity for at least 30 minutes or recurrent seizures for more than 50% of the entire recording duration (Scher et al., 1993).

All infants had a neurodevelopmental assessment at 1 year using the Amiel-Tison Test, the Griffiths developmental scale for infants and a neurological examination. Neurodevelopmental outcome of infants was classified as normal (Amiel-Tison score: 0; Griffiths quotient ≥85%) or abnormal (Amiel-Tison score of 1 or 2; Griffiths quotient of < 85%) with minor or major sequelae (cerebral palsy, motor or sensory deficits, and/or epilepsy).
3. Results

3.1 Clinical findings

Nine full-term infants with gestational ages (GA) ranging from 38 to 41 weeks were studied (4 female and 5 male infants). The mean birth weight was 3472 g (2624 - 4670g). Four infants were delivered by caesarean section, two by forceps and one by ventouse delivery. A placental abruption occurred in two cases, in one of them combined with cord prolapse (Case 9). All infants, except case 8, required active resuscitation; seven were on assisted ventilation at the time of the first EEG recording. Table 2 summarises the clinical data of the infants. Clinical seizures were diagnosed in eight infants during the first or second day of life. These were confirmed on EEG in all but three patients (cases 2, 4 and 5). Phenobarbitone was used as the first line antiepileptic drug in all infants using a loading dose of 20 – 30 mg/kg and a second loading dose was given if required. The maintenance dose used was 5 mg/kg/day (Table 3). Five infants received antiepileptic medication before the initial EEG was performed. Clonazepam or phenytoin was used as the second line antiepileptic drug in 3 infants. Phenobarbitone drug levels were done on the second or third day of life in four infants; they were in the upper normal range in case 3, 6 and 8 (30 – 40 mg/l) and high in case 9 (53.3 mg/l). The phenytoin level in case 6 was low at 3.3 mg/l (normal range 10-20mg/l). As most infants were ventilated they were given morphine for analgesia and midazolam for sedation when necessary (Table 3).

3.2. EEG findings
The average time of the first EEG recording was 5.6 hours (range 2 - 8 hours) after birth. In three infants the recording was repeated once, in four infants twice and in the remaining two infants three times (Table 4).

**Initial EEG moderately abnormal**

Two infants had a moderate background abnormality in the first recording. The EEG of case 1 showed interburst intervals (IBI) up to 8 seconds and the EEG of case 2 a mildly decreased voltage for GA and IBI up to 6 seconds despite being on morphine, phenobarbitone and high dose midazolam (Table 4). The second EEG of case 1 was still discontinuous, but the IBI lasted only 1 - 3 seconds. The second recording of case 2 improved, showing continuous activity with only slightly suppressed voltage. Both infants were clinically doing well, so the EEG was not repeated.

**Initial EEG inactive**

Seven infants initially had an inactive EEG (Figure 1 and 2). Three of these infants had occasional bursts of activity lasting up to two seconds with a frequency of less than 1 per 3 minutes (cases 4, 7 and 9). In three cases, the subsequent recording showed a dramatic improvement with only mild (case 5) to moderate (cases 3 and 4, Figure 3) abnormalities (Table 4). One of these infants (case 3) developed occasional electro-clinical seizures over the right posterior region during the first day of life, which responded well to a combination of phenobarbitone and clonazepam. She had a final EEG recording after 15 days, which was normal.

(Figure 1 - 4 around here)
The remaining four infants continued to show very suppressed EEG activity, with IBI up to 60 seconds in subsequent EEGs during the first two days of life (Figure 4). On day three the EEG was more continuous with IBIs up to 8 seconds in three cases, but a suppressed and discontinuous pattern continued to be seen in one (case 9).

3.3 Neurodevelopmental outcome
The outcome was normal in both infants with moderate background abnormalities in the initial EEG. The three infants who had an initial inactive recording but recovered within 12 to 24 hours had a favourable outcome without neurological sequelae. However, the outcome of the remaining four infants who continued to show major background abnormalities was poor with the development of major sequelae: one died after five days despite full intensive care and three developed spastic quadriplegic cerebral palsy and severe developmental delay during the first year of life. One of these died during the second year of life from an aspiration pneumonia.

Table 4 summarises the EEG results and the correlation to the clinical outcome.
4. Discussion

We have shown that EEG recorded in the first hours of life is a good prognostic indicator. In our study two infants had moderately abnormal activity in the first eight hours of life. The activity improved and both infants had a normal outcome. Seven infants initially had an inactive recording. In three infants the EEG activity recovered after eight to twelve hours of life and despite one developing electro-clinical seizures all subsequently had a good outcome. In four, the EEG activity was persistently very abnormal over the next 48 hours and all of these infants had a poor outcome.

A moderately abnormal EEG recorded within eight hours is a favourable sign; but an inactive EEG recorded within eight hours of birth can recover spontaneously with a normal clinical outcome. An EEG that remains very abnormal for more than eight to twelve hours after birth is a poor prognostic sign.

We have avoided using the term ‘burst suppression’ because of the wide range of meanings applied to the term in the literature (Holmes et al., 1982; Grigg-Damberger et al., 1989; Wertheim et al., 1994).

The prognostic value of the EEG in HIE has been studied since 1972 (Monod et al., 1972; Sarnat and Sarnat, 1976; Watanabe et al., 1980; Holmes et al., 1982). Watanabe and colleagues recorded 13-17 channel EEG polygraphic studies in 132 asphyxiated infants and followed them up for 2 - 9 years (Watanabe et al., 1980). A markedly abnormal background (very discontinuous; burst suppression; very low voltage or inactive) predicted a poor outcome. In these earlier studies however, the first EEG was usually recorded after the second or third day of life. EEG background activity which was initially abnormal can improve progressively with recovery of acute brain damage. The cause of this recovery is unknown and is seen even when permanent neuronal
damage has occurred (Takeuchi and Watanabe, 1989). If the initial EEG is performed as close as possible to the peak of symptomatic neurological impairment, an accurate prognostic statement can usually be made (Tharp, 1987). Therefore, a normal EEG recorded two to three weeks after a severe hypoxia could lead to a falsely optimistic prognosis.

More recently studies have concentrated on the early EEG (within three days of birth) and a strong correlation between early EEG and outcome has been demonstrated even for minor sequelae (Takeuchi and Watanabe, 1989; van Lieshout et al., 1995). There is only one study of EEG recordings within 24 hours of birth (Pezzani et al., 1986) and few in which some of the infants were recorded within 24 hours of life (Wertheim et al., 1994; Selton and Andre, 1997). Pezzani recorded 8 to 16 channel EEGs within the first 24 hours of birth in 80 full term infants admitted to neonatal intensive care for different reasons (Pezzani et al., 1986). They found the EEG to be a reliable predictor of outcome, but did not differentiate for underlying diagnosis. An inactive EEG was recorded at an early stage in two infants, which subsequently recovered; one child had a normal outcome and the other had only minor sequelae. They concluded that if the EEG was obtained within the first 10 hours after birth it might be misleading. Selton and Andre reported one infant with normal neurodevelopmental outcome in their series who had a severely abnormal recording (permanent discontinuous activity) 8 hours after life which recovered within 24 hours. Seizure burden was not a predictor of outcome (Selton and Andre, 1997). Our data confirm these single observations in a larger sample of patients with a defined diagnosis of HIE.

In an animal model the time of recovery of the EEG depended on the duration of the ischaemia. Gunn and colleagues monitored the EEG of fetal lambs during and following
ischaemia and found that during the ischaemic event the EEG trace became isoelectric (Gunn et al., 1992). Depending on the length of the ischaemic event, the amplitude and frequency could recover rapidly. However if the ischaemia lasted 30 minutes or longer a stereotypic sequence of depressed EEG activity followed by low frequency epileptiform activity was always seen.

There is no established effective treatment for HIE, though several new treatments are on trial at present, including oxygen radical inhibitors, excitatory amino acid antagonist and potential neuroprotective effects of selective brain cooling (Vannucci and Perlman, 1997). Animal studies have shown that cooling the brain by as little as $3^\circ$-$6^\circ$ reduces the extent of tissue injury following cerebral insults, but the therapeutic window is thought to be short. Encouraging results from a pilot study of brain cooling in infants have been published (Gunn et al., 1998). One of the problems is to identify infants at high risk of subsequent brain damage who would benefit from experimental treatment, which may have serious side effects (Vannucci and Perlman, 1997). A few specialised centres in the UK are now running pilot trials of brain cooling. Infants are enrolled into a cooling trial based on findings obtained using CFM. CFM has recently been shown to predict outcome within the first 3 to 6 hours after birth asphyxia (Hellstrom-Westas et al., 1995; Eken et al., 1995; Toet et al., 1999). The CFM displays the amplitude integrated EEG from one or two compressed and highly filtered EEG channels. The disadvantages of CFM are the inability to detect focal seizures and seizures of less than 30 seconds, the limitation to one channel and risk of recording over oedematous areas. As CFM only records one EEG channel from biparietal electrodes, seizures lasting less than 30 seconds were always missed as it was impossible to distinguish them from artefacts (Hellstrom-Westas et al., 1995). Furthermore, it can be difficult to differentiate
between a flat tracing and continuous low voltage background activity, or between burst suppression pattern and discontinuous activity. Although no infants with flat CFM tracing and normal outcome have been reported so far, our and other reports demonstrate that children can not be included in experimental studies on the basis of CFM studies within the first eight hours of life.

Anticonvulsive drugs and other drugs routinely used in neonatal intensive care are believed to have some effect on the neonatal EEG. There is evidence that phenobarbitone can prolong discontinuity and/or suppress EEG activity in sick preterm and term neonates (Radvanyi-Bouvet et al., 1985; Ashwal and Schneider, 1989; Bell et al., 1993).

Ashwal and Schneider (1989) reported that phenobarbitone levels greater than 25 mg/l in sick preterm & term neonates suppressed EEG activity. Bell et al (1993) compared the effects of phenobarbitone and morphine on the EEG activity of preterm infants in a retrospective study. Mean maximum IBI was significantly longer following the administration of phenobarbitone or morphine for a period of 5-6 hours compared to a control group without medication. However, these studies were retrospective, contained a mixed population or a small sample size. It is still unclear whether phenobarbitone suppresses background EEG activity more in very sick infants. Background suppression was also seen after administration of morphine, pethidine and midazolam (Bell et al., 1993; Bye et al., 1997). This might explain the discontinuous EEG pattern in the first EEG of case 2 as ten hours later the IBI was much shorter after phenobarbitone and morphine were stopped. It might also account for the discontinuous pattern of the third EEG of case 3. In case 6 to 9 medication may be partially responsible for the EEG abnormality. However, case 9 was only on phenobarbitone compared to cases 2, 3, 6, 7.
and 8 who were on a combination of drugs. It is therefore impossible to differentiate between the effects of the medication and the effects of the brain injury in these children. Furthermore, case 2 had only a moderately abnormal initial EEG despite being on morphine, phenobarbitone and midazolam. Case 3 was also on a combination of drugs and nevertheless there was an obvious improvement in the EEG which was not seen in case 9. Therefore, antiepileptic medication does effect the EEG but should not be regarded as the sole cause for the abnormalities. More prospective controlled studies are required.

In conclusion, early EEG is an excellent prognostic indicator if normal or continues to be inactive after eight hours of life. However, an inactive or very depressed EEG only within the first eight hours of life can be associated with good outcome and may therefore be misleading. Such an EEG must therefore be repeated after 12 - 24 hours. Larger prospective studies on early EEG in full-term infants with and without HIE are necessary before the early EEG can be used to identify those infants at highest risk of permanent brain damage. We are aware that the time frame of eight hours is somehow artificial as the number of EEG recordings is too small. We are currently performing a study on continuous EEG monitoring in infants with HIE to establish a more exact time frame of changes in background activity during the first day of life.

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References


### Table 1

Classification of EEG background activity\(^a\)

<table>
<thead>
<tr>
<th>Normal/mild abnormalities</th>
<th>normal pattern for GA, including slightly abnormal activity, e.g. mild asymmetries, mild voltage depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate abnormalities</td>
<td>discontinuous activity with IBI $\leq$ 10 sec, other types of continuous activity, clear asymmetry or asynchrony</td>
</tr>
<tr>
<td>Major abnormalities</td>
<td>IBI 10-60 sec, severe depression, no wake-sleep cycles</td>
</tr>
<tr>
<td>Inactive EEG</td>
<td>background activity $&lt; 10 \mu$V, IBI $&gt; 60$ sec</td>
</tr>
</tbody>
</table>

\(^a\) GA: gestational age, IBI: interburst intervals.
<table>
<thead>
<tr>
<th>Case</th>
<th>CTG</th>
<th>Complications in labour</th>
<th>pH*</th>
<th>Apgar†</th>
<th>HIE‡</th>
<th>Seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ominous</td>
<td>meconium stained liquor</td>
<td>7.2</td>
<td>2/7/8</td>
<td>II</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>ominous</td>
<td>eclampsia, meconium stained liquor</td>
<td>6.98</td>
<td>2/5/5</td>
<td>II</td>
<td>clinical</td>
</tr>
<tr>
<td>3</td>
<td>ominous</td>
<td>Abruption</td>
<td>6.6</td>
<td>0/0/4</td>
<td>III</td>
<td>clinical, electrical</td>
</tr>
<tr>
<td>4</td>
<td>normal</td>
<td>shoulder dystocia</td>
<td>7.26</td>
<td>1/5/5</td>
<td>II</td>
<td>clinical</td>
</tr>
<tr>
<td>5</td>
<td>suspicious</td>
<td>failed forceps</td>
<td>7.15</td>
<td>1/5/7</td>
<td>II</td>
<td>clinical</td>
</tr>
<tr>
<td>6</td>
<td>not done</td>
<td>2nd twin</td>
<td>6.9</td>
<td>0/3/3</td>
<td>III</td>
<td>clinical, electrical</td>
</tr>
<tr>
<td>7</td>
<td>not done</td>
<td>meconium stained liquor</td>
<td>7.06</td>
<td>0/0/2</td>
<td>III</td>
<td>clinical, electrical</td>
</tr>
<tr>
<td>8</td>
<td>suspicious</td>
<td>reduced fetal movements in last 24 h</td>
<td>6.89</td>
<td>6/7/?</td>
<td>II</td>
<td>clinical, electrical</td>
</tr>
<tr>
<td>9</td>
<td>ominous</td>
<td>abruption / cord prolapse</td>
<td>6.75</td>
<td>2/6/7</td>
<td>II</td>
<td>clinical, electrical</td>
</tr>
</tbody>
</table>

*a* cord or scalp pH. †1 min/5 min/10 min. ‡HIE grading according to Levene’s modification of the Sarnat criteria (Evans and Levene, 1999).
<table>
<thead>
<tr>
<th>Case</th>
<th>EEG at</th>
<th>≤ 8 h</th>
<th>8 - 24 h</th>
<th>24 - 48 h</th>
<th>48-72 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mo⁴</td>
<td>Mo²</td>
<td>Mo²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Mo¹, PB⁵, Md⁴</td>
<td>Md⁴</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>PB⁵</td>
<td>-</td>
<td>PB⁵, Cz¹</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>none</td>
<td>PB⁵</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>PB⁵</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>none</td>
<td>PB⁵</td>
<td>PB⁷, Ph⁵</td>
<td>PB⁷, Ph⁸</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Mo²</td>
<td>Mo², PB⁶</td>
<td>Mo²</td>
<td>Mo²</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>PB⁵</td>
<td></td>
<td>Mo², PB⁷, Cz³</td>
<td>Mo², PB⁷, Cz³</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>PB⁵</td>
<td>PB⁷</td>
<td>PB⁷</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mo: morphine, PB: phenobarbitone; Md: midazolam; Cz: clonazepam; Ph: phenytoin.

¹10 μg/kg/hr; ²20 μg/kg/hr; ³30 μg/kg/hr; ⁴60 μg/kg/hr; ⁵20 mg/kg; ⁶30 mg/kg; ⁷PB maintenance 5 mg/kg/day; ⁸Ph maintenance: 5 mg/kg/day.
Table 4

EEG results and clinical outcome

<table>
<thead>
<tr>
<th>Case</th>
<th>EEG background</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤ 8 h</td>
<td>8 - 24 h</td>
</tr>
<tr>
<td>1</td>
<td>moderate</td>
<td>moderate</td>
</tr>
<tr>
<td>2</td>
<td>moderate</td>
<td>mild</td>
</tr>
<tr>
<td>3</td>
<td>inactive</td>
<td>moderate, sz</td>
</tr>
<tr>
<td>4</td>
<td>inactive</td>
<td>moderate</td>
</tr>
<tr>
<td>5</td>
<td>inactive</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>inactive</td>
<td>major, sz</td>
</tr>
<tr>
<td>7</td>
<td>inactive</td>
<td>major, sz</td>
</tr>
<tr>
<td>8</td>
<td>inactive</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>inactive</td>
<td>-</td>
</tr>
</tbody>
</table>

sz, electrical or electro-clinical seizures.
**Figure Legends**

Fig. 1: Case 4: The initial EEG was recorded at 4 hours of life and shows an inactive recording.

Fig. 2: Case 8: The initial EEG recorded at 6 hours of life shows background activity of \(<5 \mu V\).

Fig. 3: Case 4: The EEG after 24 hours was moderately abnormal showing continuous activity with voltage depression.

Fig. 4: Case 8: The EEG was repeated on the second day of life and shows major abnormalities: the background activity is asymmetric and discontinuous with IBI up to 30 seconds.