Prognostic value of continuous electroencephalographic recording in full term infants with hypoxic ischaemic encephalopathy

D Wertheim, E Mercuri, JC Faundez, M Rutherford, D Acolet, L Dubowitz

Abstract

The prognostic value of early neonatal continuous electroencephalographic recordings in hypoxic ischaemic encephalopathy was evaluated. Thirty seven full term infants with hypoxic ischaemic encephalopathy were studied. The electroencephalogram (EEG) was recorded using four or eight channel Oxford Medilog recorders and was started as soon as possible after birth. The recordings were initially visually analysed and divided into four categories: three in relation to the grade of discontinuity of the background activity (continuous, discontinuous, and maximum depression) and an additional fourth category to include status epilepticus.

The EEGs with discontinuous activity were then analysed by computer to obtain a more objective assessment of discontinuity. The results were related to neurological outcome. Continuous background activity was associated with a normal outcome in all but the three infants who had continuous, but asymmetrical EEGs and who developed contralateral hemiplegia. In the eight infants with discontinuous activity, the outcome appeared to be related to the grade of continuity and the presence of clear convulsions on the EEG. The 10 infants with maximum depression and status epilepticus had severe impairment.

These preliminary results suggest that continuous recording of EEGs could be used routinely in term infants with hypoxic ischaemic encephalopathy. Computer analysis can improve the value of this technique, allowing the identification of infants who might benefit from early therapeutic intervention.

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gram (EEG) in the first week of life is a reliable indicator of a good prognosis in these infants.¹⁻⁴ Those whose EEG shows mild abnormalities in background activity that resolve within five to seven days after birth also have a good prognosis,¹⁻⁴ whereas marked or maximum depression are usually suggestive of later neurological handicap.⁴⁻⁶ There are no reports so far on the use of continuous EEG recordings in infants with hypoxic ischaemic encephalopathy. This method has been shown to be suitable for monitoring neonatal EEGs^{7,8} and has several advantages: it does not necessitate transport of the infant, the equipment does not interfere with the routine care of sick infants, and there are fewer technical problems. The long duration of the continuous recordings also enables spontaneous changes in activity on the EEG to be monitored and the effect of treatment evaluated.⁹⁻¹²

The aim of this study was to evaluate the prognostic value of continuous recording of EEGs in the early neonatal period in term infants with hypoxic ischaemic encephalopathy by comparing the results from visual or computer assessment of the EEGs with neurological outcome.

Subjects and methods

This study was approved by the research ethics committee of the Royal Postgraduate Medical School. Infants were recruited into the study if they met the following criteria: neurologically abnormal in the first 48 hours of life; evidence of fetal distress – that is, meconium stained liquor or type II dips or bradycardia on the cardiotocograph, or both; and Apgar score less than 5 at five minutes. Infants with congenital infection, congenital brain malformations, or proved metabolic disorders were excluded. The grade of encephalopathy was scored according to Sarnat and Sarnat.¹ The study consisted of 37 infants (19 boys, 18 girls) born at or referred to the Hammersmith or Queen Charlotte's Hospital between 1987 and 1993. The gestational age of the infants included in the study ranged from 37 to 42 weeks.

The EEG was continuously recorded on a four or eight channel Oxford Medilog recorder from F₄P₄ and F₃P₃ for the four channel recorders and F₄C₄, C₄P₄, F₃C₃, and C₃P₃ for the eight channel recorders. Silver/silver chloride electrodes were applied with collodion and the interelectrode impedances were less than 5 k Ohms. A time constant of 0.3 seconds was used. The four channel recorders were used as previously described.⁸ Recordings were

Department of Paediatrics and Neonatal Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 0NN
D Wertheim
E Mercuri
JC Faundez
M Rutherford
D Acolet
L Dubowitz

Correspondence to:
Dr Dubowitz.

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Hypoxic ischaemic encephalopathy is a major cause of non-progressive neurological handicaps in children. An improvement in perinatal care and diagnosis has increased the survival rate of newborn infants with hypoxic ischaemic encephalopathy, but the prediction of outcome remains difficult. The establishment of sensitive indicators of outcome in the first few hours after birth have become of major importance as a means for selecting patients for possible early therapeutic intervention.

Previous studies have shown that normal background activity on the electroencephalo-

Table 1 Classification of EEGs in relation to neonatal clinical data.

Patient No	EEG	Symmetry	Fetal distress	Delivery	GA (weeks)	Birth weight (g)	Apgar score	Intubation	Grade hypoxic ischaemic encephalopathy	pH	BP	Fits	Onset (hours)	Anticonvulsant drugs	Other drugs
1	Normal A	S	Bradycardia, CTG late dec	FOR	42	3090	0.1, 4	+	1	N	N				Pancuronium
2	Normal A	S	Bradycardia, meconium	E-LSCS	42	3174	3, 10	+	1	N					
3	Normal A	S	Bradycardia, CTG late dec	E-LSCS	38	3360	5, 9	–	1	N					
4	Normal A	S	Meconium	SVD	41	3870	8, 9	–	2	*	N				Morphine, pancuronium
5	Normal A	S	Bradycardia, meconium	E-LSCS	37	3650	3, 6	+	1	N	N				
6	Normal A	S	Meconium	SVD	40	2980	3, 7	+	1	*	N				Morphine, pancuronium
7	Normal A	S	Bradycardia, meconium	SVD	41	2470	4, 4	+	1	*	N				
8	Normal A	S	Tachycardia	SVD	37	3380	4, 4	+	1	*	N				
9	Normal B	S	CTG late dec	K1-FOR	42	3490	5, 5	–	1	*	N				
10	Normal B	S	Meconium, CTG dec	E-LSCS	40	4015	2, 8	+	2	*	N	Jerky movements			Morphine, pancuronium
11	Normal B	S	Meconium, CTG early dec	SVD	40	4255	3, 4	+	1	N	N				Dopamine
12	Normal B	S	CTG late dec	E-LSCS	41	3930	0, 0	+	2	N	N	Clonic	Day 2	Pb, Ph	
13	Normal B	S	Meconium	SVD	40	2810	5, 7	–	1	N	N				
14	Normal B	S	CTG early dec	FOR	41	3500	9, 10	–	2	N	N	Cycling, clonic	9	Pb, Ph	
15	Normal B	AS	Meconium, CTG late dec	VENT	38	1700	4, 8	–	2	N	N	Clonic	10	Ph	
16	Normal C	AS	Bradycardia	FOR	40	3304	9, 10	–	2	N	N	Jerky movements	6	Pb, Ph	
17	Normal C	AS	CTG early dec	FOR	41	3650	6, 10	–	2	N	N	Dusky episode	1.5	Pb	
18	Normal C	S	Meconium	FOR	40	3250	8, 10	–	2	N	N	Tonic-clonic	48	Pb	
19	Normal C	S	Bradycardia	SVD	40	3740	5, 10	–	2	N	N	Tonic-clonic	48	Pb	
20	Discontinuous A	S	CTG early dec	SVD	40	2285	7, 8	+	2	*	N	Not described	6	Pb	Dopamine
21	Discontinuous A	S	CTG early dec	E-LSCS	40	3150	4, 4	+	2	N	N	Jerky movements	Day 1	Pb, Ph	
22	Discontinuous A	S	Bradycardia	E-LSCS	40	3590	0, 5	+	2	*	N	Cycling	3–4	Ph, clon	
23	Discontinuous C	S	CTG early dec	SVD	40	3205	3, 9	–	2	N	N	Clonic	6	Pb, Ph	
24	Discontinuous C	AS	Meconium	K1-FOR	41	3400	4, 8	–	2	N	*	Tonic-clonic	7	Pb, Ph	Dopamine
25	Discontinuous C	S	Meconium, CTG dec	E-LSCS	38	2610	1, 4	+	2	*	N			Pb	
26	Discontinuous C	S	Bradycardia, CTG late dec	E-LSCS	41	4252	0, 2	+	2	*	N	Tonic-clonic	12	Pb, Ph	Dopamine
27	Discontinuous C	S	CTG early dec	E-LSCS	41	2650	1, 5	+	2	N	N	Jerky movements	24	Pb, diaz	
28	Max. depression C	S	Bradycardia	E-LSCS	39	3430	1, 5	+	2	*	*	Not described	Day 2	Pb, Ph	Dopamine
29	Max. depression C	S	Bradycardia	E-LSCS	40	2354	3, 5	+	3	*	N	Tonic-clonic	1	Pb, Ph	
30	Max. depression C	S	Bradycardia	E-LSCS	40	3460	2, 2	+	3	N	*				Dopamine
31	Max. depression C	S	Bradycardia	E-LSCS	38	3140	0, 2	+	3	N	N	Clonic	1	Pb, Ph	Pancuronium
32	Max. depression C	S	CTG late dec	E-LSCS	39	3800	2, 5	+	2	N	N	Clonic	8	Ph, clon	Pethidine
33	Max. depression S	S	Bradycardia, CTG dec	SVD	40	3050	0	+	3	N	N	Clonic	12	Pb, Ph	
34	Max. depression S	S	Meconium, bradycardia	E-LSCS	40	3190	0, 2	+	3	*	N	Tonic-clonic	1	Pb, Ph	
35	Status epilepticus	AS	Bradycardia	SVD	41	3240	3, 9	+	2	*	N	Clonic	32	Pb	
36	Status epilepticus	AS	Meconium	SVD	40	3920	0, 1	+	2	N	N	Jerky movements	Not stated	Pb	Dopamine
37	Status epilepticus	S	Bradycardia, meconium	E-LSCS	42	4125	1, 1	+	2	*	N	Clonic	28	Pb, Ph	

Abbreviations: A=no sharp waves or seizure activity; B=excessive sharp waves; C=electrical seizures; S=symmetrical; AS=asymmetrical; CTG=cardiotocographic; dec=decelerations; FOR=forceps; SVD=spontaneous vaginal delivery; E-LSCS=emergency low caesarean section; GA=gestational age; N=normal; BP=blood pressure; Pb=phenobarbitone; Ph=phenytoin; clon=clonazepam; diaz=diazepam; and *low values treated within three hours.

started as soon as possible and lasted for at least 12 hours. All EEGs were performed using fixed gain settings on the recorders and hence when assessing recordings the term 'no discernible cerebral activity' refers to the EEG recorded in this way.

The EEGs were initially visually assessed for background continuity, amplitude, symmetry, synchrony, range of frequencies, presence or absence of excessive frequency of sharp transients or spikes, and presence or absence of frank seizure activity. We have avoided using the term 'burst suppression' because of the wide range of meanings applied to the term in published work on neonatal EEGs.^{5 6}

The EEGs were divided into four main categories in relation to the continuity of the background activity: group 1, normal – normal continuity (appropriate for age), discontinuity observed only during quiet sleep state;

group 2, discontinuous – EEGs described as discontinuous if for at least one hour there were periods with bursts of cerebral activity separated by low voltage intervals with no discernible cerebral activity that could not be explained as 'tracé' alternant; and group 3, maximum depression – no discernible cerebral activity for at least one hour (infants whose EEG showed some seizure activity on a maximal depression background were classified in this group); and group 4, status epilepticus.

All recordings with status epilepticus were grouped in the last category as they could not be fitted in any of the previous categories. The EEG status epilepticus was defined as continuous EEG seizure type activity in one or more channels for at least four hours, or separated only for short periods by activity with frequent sharp waves or spikes.

The first three groups were subsequently

Figure 1 Computer analysis of an EEG with more than 50% of epochs of continuous background activity.

divided into three subgroups: (a) no excess of sharp transients and no seizures; (b) excessive number of sharp transients; and (c) clear EEG seizures.

COMPUTER ANALYSIS

Recordings that were at any time discontinuous were also subjected to computer analysis for the first six hours of the recording. The recordings were digitised and stored on a hard disk or optical disk. The digitised EEG was then analysed by computer for discontinuity and amplitude by an off line adaptation for EEG of term infants on an on line system described previously.¹⁴ The analysis of the right and left channels of the EEG were displayed as compressed graphs, with the background discontinuity changes on the vertical axis against time on the horizontal axis. The duration of the analysis takes less than 30 minutes.

The computer analysis was used to assess the discontinuity; three one minute epochs were averaged. A completely continuous EEG had 0% discontinuity and a completely discontinuous EEG had 100% discontinuity for each epoch. The values were plotted on a graph. The EEGs were subdivided into three groups on the basis of the percentage of epochs which showed continuous activity: (a) more than 50% continuous activity epochs; (b) less than 50% but greater than 0% continuous activity epochs; and (c) the EEG was always discontinuous.

Figure 2 Computer analysis of an EEG showing a marked asymmetry between the two sides with more marked discontinuity on the left side.

tinuous with no continuous activity epochs and no cycling of discontinuity.

The possible effect of clinical variables, such as anticonvulsants or other drugs, blood pressure, or pH, on the EEG were also evaluated.

ASSESSMENT OF OUTCOME

Follow up clinical assessment included neurological examination and the use of Griffith developmental scales. Infants were seen at three month intervals until 1 year, at 18 months, and then yearly. A detailed neurological examination and Griffith developmental scales were performed at each visit, where possible.

Results

Table 1 summarises the details of the clinical and EEG findings.

In inborn infants EEG recordings were started as soon as possible after birth; in outborn infants they were started soon after admission. In six patients recordings started within 12 hours, in 13 between 12 and 24 hours, in seven between 24 and 48 hours, in nine within 72 hours, and the remaining two within 80 hours.

EEG VISUAL ANALYSIS

Group 1

Nineteen patients had continuous background activity, including two infants whose EEG was initially considered to be of low amplitude but clearly continuous; the EEG amplitude returned to expected levels within 12 hours of the start of the recording. Eight of 19 infants were in group 1a and seven were in group 1b, showing frequent sharp waves, asymmetrical in one of them. The remaining four had clear EEG seizures, which were asymmetrical in two.

Group 2

Discontinuous recordings were present in eight infants, five of whom also had seizure activity. One of these five had marked asymmetry of background activity and seizure frequency.

Group 3

Maximal depression was observed in seven patients. In one of the seven no activity was detected during the whole duration of the recording. The other six showed seizure activity.

Group 4

Three patients had EEG status epilepticus; in two it was focal.

COMPUTER ANALYSIS

Seven of the eight recordings with discontinuous background activity were analysed by computer. The eighth recording was unsuitable because of a large number of artefacts. In

Table 2 Classification of EEGs in relation to outcome

	EEG	Motor impairment	Griffith mental developmental scales					Comments
			Locomotor	Personal/ social	Hearing/ speech	Eye-hand coordination	Performance Practical reasoning	
1	Normal A	Normal	106	112	100	100	108	
2	Normal A	Normal	125	133	150	108	108	150
3	Normal A	Normal	109	118	109	109	100	
4	Normal A	Normal	106	112	100	100	108	
5	Normal A	Normal						Not available
6	Normal A	Normal						Not available
7	Normal A	Normal	150	126	120	166	120	
8	Normal A	Normal	106	112	96	100	106	
9	Normal B	Normal	138	156	156	133	122	
10	Normal B	Normal	128	135	124	132	128	
11	Normal B							Died
12	Normal B	Normal	127	133	133	121	121	133
13	Normal B	Normal	98	106	98	90	98	
14	Normal B	Ocular apraxia developmental delay	105	111	105	94	88	116
15	Normal B	Mild hemiplegia	116	116	108	108	108	
16	Normal C	Hemiplegia	96	94	100	94	96	
17	Normal C	Hemiplegia	101	103	91	103	101	101
18	Normal C	Normal	122	116	94	108	98	
19	Normal C	Normal	116	101	110	101	120	
20	Discontinuous A	Normal	83	88	83	105	108	
21	Discontinuous A	Normal	87	81	70	70	70	
22	Discontinuous A	Quadriplegia	na	na	na	na	na	
23	Discontinuous C	Quadriplegia	na	na	na	na	na	
24	Discontinuous C	Hemiplegia	na	na	na	na	na	
25	Discontinuous C	Athetoid CP						Incomplete estimated quotient: 50
26	Discontinuous C	Increased tone, microcephaly	na	na	na	na	na	
27	Discontinuous C	Athetoid CP						Incomplete estimated quotient: 70–80
28	Max. depression C	Severe quadriplegia	na	na	na	na	na	
29	Max. depression C							Died
30	Max. depression C							Died
31	Max. depression C							Died
32	Max. depression C	Developmental delay	na	na	na	na	na	
33	Max. depression C							Died
34	Max. depression C	Severe developmental delay	na	na	na	na	na	
35	Status epilepticus	Quadriplegia epilepsy	na	na	na	na	na	
36	Status epilepticus	Severe developmental delay, hemiplegia						Incomplete estimated quotient: <50
37	Status epilepticus	Quadriplegia epilepsy	na	na	na	na	na	

Abbreviations: A=no sharp waves or seizure activity; B=excessive sharp waves; C=electrical seizures; CP=cerebral palsy; and na=not applicable.

four of these seven recordings more than 50% of the epochs were continuous (fig 1), in two less than 50% of epochs were continuous, and one of these was asymmetrical (fig 2). In one recording there was no continuous activity epoch.

CLINICAL VARIABLES

Phenobarbitone, alone or in association with phenytoin or other drugs, was used in seven patients in group 1, in six patients in group 2, in four of group 3, and in all three patients in group 4 (table 1).

Mild acidosis and hypotension, corrected

within one or two hours, occurred with variable frequency in all the groups (table 1).

OUTCOME

The duration of the follow up examination ranged from six months to six years. Table 2 gives the clinical details.

EEG group 1

One of the 19 infants with normal background activity on the EEG died from unrelated respiratory problems. Fourteen had a normal outcome. Seven of these 14 infants had

excessive sharp waves and three had electrical seizures. Four infants had an abnormal outcome. One of the four with an ocular motor apraxia had excessive sharp waves. Three children developed a hemiplegia and, although their background activity was continuous on both sides, they showed asymmetry either in amplitude or in the presence of abnormal transients and seizures, the more abnormal side being contralateral to the subsequent hemiplegia. On magnetic resonance imaging two of these children had an infarction in the territory of the middle cerebral artery; the third had a thalamic lesion with adjacent hemispheric infarction.

EEG group 2

In the group of eight infants with discontinuous activity seven recordings could be analysed by computer; four infants had completely continuous activity for more than 50% of the epochs analysed. Two of these had no motor impairment and the other two developed athetoid cerebral palsy.

In two infants the amount of continuity was less than 50% of the epochs; one of these is only 6 months old but he has abnormalities of tone and is microcephalic, whereas the other infant has a hemiplegia with mild global delay and specific perceptual difficulties. Seizures were present in four children with an abnormal outcome, but were absent in the two with normal outcome.

The seventh infant, who had no continuous epochs and no cycling of continuity, is quadriplegic and severely mentally retarded. Thus either the presence of EEG seizures or the absence of continuous epochs was associated with a less favourable outcome. The child whose EEG was not analysed by computer developed quadriplegia.

EEG group 3

Three of the seven infants in this group died in the first week of life. All four surviving infants have severe motor and mental impairment.

EEG group 4

All three infants with EEG status epilepticus have severe motor and mental impairment.

Discussion

Previous studies of neonatal EEGs in term infants with evidence of birth asphyxia have shown that background activity is an important prognostic indicator.¹⁻⁴ They showed that marked or maximal depression was associated with later handicaps, although mild EEG abnormalities which resolved in seven days were related to a good outcome. In these studies only standard multichannel EEG recordings were used and no systematic quantitative evaluation was applied. They also used the evolution of the EEG as a prognostic indicator. Our aim in this study was to use the earliest EEG available to evaluate recordings

which might be used for the selection of infants for intervention and also to apply a more quantitative evaluation of discontinuous recordings.

We were able to show that not only were our results equally reliable as published data, in spite of the small number of channels used, but that quantification, which is more easily performed by continuous analysis, was better at grading the continuity of the EEG than visual analysis alone. Our results confirmed previous findings of a normal outcome in infants with a good background activity, irrespective of the presence of convulsions. We were able to show, however, that asymmetry in the background activity was also a significant prognostic indicator. Three children had an asymmetrical though continuous background, and all developed hemiplegia.

In parallel with previous studies we have also confirmed a poor prognosis associated with maximal EEG depression but, in addition, we noted a similarly poor prognosis in infants with status epilepticus, in whom the background EEG activity could not be classified.

In the eight children with discontinuity, computer analysis allowed us to grade the severity of discontinuity in seven and relate it to outcome. Two children in this group had a normal outcome, one had increased tone, and four had severe motor deficits. It is of interest that the two normal children in this group were the only children without any seizure activity on the EEG. Although the group is small, it is possible that the absence of seizure activity in this group might be a good prognostic sign. Of the four children with motor impairment, in three there were some continuous epochs and these had a less severe intellectual impairment. The one infant in whom no continuous epoch was recorded was quadriplegic and severely mentally retarded. The number of patients is too small to reach definite conclusions about whether the amount of discontinuity relates to the severity of outcome, but the complete absence of any continuous epochs, which is not recognisable by visual analysis, suggests that it might be a poor prognostic sign equal to that of maximal depression.

There has been concern that anticonvulsant treatment could modify the EEG.¹⁵ The degree to which anticonvulsant drugs can modify EEG activity is not clear, however.¹⁶ In this study we did not have enough children in whom the EEG was recorded before the treatment to assess the possible effect of the drug. It is of interest, however, that from the prognostic point of view, treatment with phenobarbitone did not interfere with the EEG in those infants with normal background activity. This is illustrated by six patients who were receiving phenobarbitone and still showed full continuity. Five of the six had a loading dose of 20 mg, followed by a maintenance dose of 10 mg; one had a loading dose of 10 mg only. The EEG was started before or within 0-24 hour of the loading dose. As this study was not set up to evaluate prospectively the effect of anticonvulsant drugs, we have no

accurate timing of drug administration or concentrations of anticonvulsant drugs in relation to the EEG. Thus the acute effect cannot be evaluated. In the seven patients in group 2 the discontinuity remained invariable; it is possible that in these patients phenobarbitone could have affected the number of continuity epochs, but as all these children had an abnormal outcome, the interference is probably negligible.

Although this study has already shown the usefulness of continuous EEG and computer analysis, further prospective work will be needed to answer a number of additional questions, in particular to establish whether EEG recordings performed in the first 24 hours of life are equally prognostic to those performed later. It will also be necessary to evaluate prospectively the acute and prolonged effect of phenobarbitone and other drugs which can be monitored by on line analysis.

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