Predictive value of early neuroimaging, pulsed Doppler and neurophysiology in full term infants with hypoxic-ischaemic encephalopathy

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Abstract

To evaluate their prognostic value, five different non-invasive techniques were used on 34 full term infants with hypoxic-ischaemic encephalopathy (HIE) within six hours of delivery. Cranial ultrasonography, the resistance index (RI) of the middle cerebral artery obtained with Doppler ultrasonography, somatosensory evoked potentials (SEPs), visual evoked potentials (VEPs) and the cerebral function monitor (CFM) were used. According to the criteria of Sarnat, 11 infants developed mild, seven moderate, and 16 severe encephalopathy. The CFM had the highest positive (PPV 84.2%) and negative predictive value (NPV 91.7%). All but one of the infants with a continuous pattern had a good outcome. The CFM of 11 cases with a suppression-burst pattern changed to a continuous pattern over 24 to 48 hours in four infants, and was associated with a normal outcome in three. All five cases with an isoelectric CFM died. The SEPs also provided useful information (PPV 81.8%; NPV 91.7%). VEPs were often delayed during the first hours of life and did not carry a poor prognosis in five of 14 cases (PPV 77.3%). Both ultrasonography and Doppler RI were of little value, as they were almost always normal at this early stage.

In 34 full term infants with HIE, studied within 6 hours of life, the CFM and SEPs provided the most useful information about the expected course of encephalopathy and subsequent neurodevelopmental outcome.

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Keywords: hypoxic-ischaemic encephalopathy, Doppler ultrasonography, evoked potentials, cerebral function monitor.

The incidence of hypoxic-ischaemic encephalopathy (HIE) in full term infants is 2-9/1000. This has remained constant for the past four decades.¹ Using the criteria of Sarnat and Sarnat² to classify the degree of encephalopathy, 25-40% of the infants with a moderate encephalopathy and 90-100% of those with severe encephalopathy either die or develop major neurological sequelae.²⁻⁵ It often takes 12-24 hours for the clinical picture to evolve, and several studies have shown that early markers, such as Apgar scores, cord blood pH, and delay in establishing regular respiration, have a limited role in predicting which infants

will go on to develop moderate or severe encephalopathy.⁶⁻⁸

Trials with neuroprotective agents have already begun in adults⁹ with cerebral hypoxia-ischaemia and it is expected that they will also be started in the near future in newborn infants.¹⁰ Early identification of those infants most at risk of dying or developing severe neurological impairment is therefore of great importance.

The aim of this study was to perform cranial ultrasound, pulsed Doppler measurements, visual and somatosensory evoked potentials and cerebral function monitor recordings during the first six hours of life, to determine which test, or which combination of tests, would enable us to select, at a very early stage, those infants at risk of developing a major handicap.

Methods

Between January 1993 to January 1995 68 infants with a gestational age of between 37 and 42 weeks were admitted to the level III neonatal intensive care unit of the Wilhelmina Children's Hospital. HIE was defined according to the criteria of Sarnat.² Although all patients in our hospital are outborn, 34 of these 68 infants were admitted immediately after delivery and were therefore studied within 6 hours of age.

The infants were diagnosed as having HIE when they developed the requisite clinical picture within 24 hours of delivery and when at least three of the following criteria were met:

- (a) signs of intrauterine asphyxia, as indicated by late decelerations on fetal monitoring or by meconium staining of the amniotic fluid;
- (b) arterial cord blood pH of <7.10;
- (c) delayed onset of spontaneous respiration;
- (d) Apgar score of <5 at 5 minutes;
- (e) multi-organ failure.

The infants were classified as having mild, moderate, or severe encephalopathy.²

CRANIAL ULTRASOUND

Ultrasonography was performed within six hours of delivery and subsequently daily during the first week and twice weekly thereafter until discharge, using an Ultramark-4 mechanical sector scanner with a rotating transducer (5-7.5-10 MHz crystals). The 7.5 and 10 MHz transducer was used routinely. The findings were classified at 6 hours of age as normal or as abnormal when (i) areas of increased echogenicity were seen in the periventricular or subcortical white matter,

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(ii) in the cortical grey matter, or (iii) in the thalami and/or basal ganglia.

RESISTANCE INDEX (RI) OBTAINED WITH DOPPLER ULTRASOUND

Doppler signals were obtained with a 5 MHz pulsed wave ATL duplex Doppler system. The transducer was placed between the eye socket and the ear, just above the zygoma, to obtain signals from the middle cerebral artery. The back-scattered Doppler signals were subjected to real-time spectral analysis and then displayed visually as a sonogram on a variable persistence monitor, and as an auditory signal. This method allowed the optimal signal to be obtained as maintained during the recording. When the image was stored the RI was calculated by analysing the maximum frequency envelope from at least five consecutive cardiac cycles to give peak or systolic frequency (S) and trough or diastolic frequency (D). This was repeated two to three times to ensure reproducibility. The RI was then derived from the equation: $RI = (S - D) / S$.

An RI above 0.55 was considered normal. An RI of less than 0.55, a reversed diastolic flow, or an absent diastolic flow associated with a $PaCO_2$ above 30 mm Hg were considered abnormal.

SOMATOSENSORY EVOKED POTENTIALS (SEPs)

SEPs were recorded with a Nihon Kohden Neuropack IV machine. Ag/AgCl disc electrodes were used: the negative electrode on C3', the positive one on Fz, and the neutral one on the lower arm. The impedance was less than 2 kOhms. Electrical stimuli of 0.1 millisecond in duration were delivered at a rate of one every

2 seconds. A hand-held device, placed on the ventral wrist overlying the median nerve, was used. The stimulation intensity was that required to produce a minimal thumb twitch. Recordings were obtained from the left somatosensory cortex, following stimulation of the right median nerve. Recordings were obtained from both hemispheres when a unilateral lesion was found on cranial ultrasound examination. A total of 50 responses was averaged through a bandpass of 2–100 Hz. Each trial was repeated two to three times to ensure reproducibility. The analysis time took 200 milliseconds. The latency to peak of the first negative wave (N1) was measured according to the criteria of Desmedt *et al.*¹¹ The normal data of Klimach and Cooke¹² were used, as the same filter settings and stimulation time were used.

The SEPs were graded as abnormal when the latency fell outside the normal range, when the waveform was abnormal, which in all cases coincided with a delay in latency, or when a response could not be elicited.

VISUAL EVOKED POTENTIALS (VEPs)

VEPs were recorded with the same machine. The negative electrode was placed on Fz, the positive one on Oz, and the neutral one on the lower arm. The impedance was less than 5 kOhms. Red-light flash stimuli were delivered by an Amplaid LED-stimulator placed at a distance of 10–20 cm in front of the infant's eyes. Flashes of 10 milliseconds in duration were delivered at a rate of one every 2 seconds. A total of 50 responses was averaged through a bandpass of 2–100 Hz. Each trial was repeated two to three times to ensure reproducibility. Analysis time took 1000 milliseconds. The latency to peak of the first positive wave (P200)

Table 1 Results of 34 infants studied within six hours of life

Case No	Sex	Grade	Ultrasound	RI	SEP	VEP	CFM	Outcome	Necropsy
1	M	I	Normal	0.7	Normal	Delayed	Continuous activity	Normal	-
2	F	I	Normal	AD/CO2	Normal	Normal	-		
3	F	I	PVE	0.6	Normal	Normal	Continuous activity		
4	F	I	PVE	0.7	Normal	Delayed	Continuous activity		
5	F	I	Normal	0.8	Delayed	Normal	Continuous activity		
6	M	I	PVE	0.7	Normal	Normal	Continuous activity		
7	F	I	Normal	0.7	Delayed	Normal	Continuous activity		
8	M	I	Normal	0.8	Normal	Normal	Continuous activity		
9	M	I	Normal	0.7	Normal	Delayed	Continuous activity		
10	F	I	Normal	AD/CO2	Normal	Normal	Continuous activity		
11	M	I	Normal	0.7	Delayed	Normal	Continuous activity		
12	M	II	IHF	0.7	Normal	Delayed	Continuous activity		
13	F	II	PVE	0.7	Normal	Normal	BS		
14	M	II	PVE	0.7	Delayed	Normal	BS		
15	M	II	PVE	0.9	Delayed	Normal	Continuous activity	Major handicap Minor handicap	-
16	M	II	PVE	0.7	Delayed	Normal	BS		
17	M	II	Normal	0.8	Normal	Delayed	BS/C	Normal	-
18	M	II	TENT TEAR	0.7	Delayed	Delayed	CLV		
19	F	III	Normal	AD	Absent	Delayed	BS/IE	Died	+
20	F	III	Normal	0.6		Delayed	BS		
21	F	III	PVE	0.7		Delayed	BS		
22	M	III	Normal	0.6		Absent	CLV		
23	F	III	Normal	-		Absent	-		
24	F	III	Normal	0.7		Absent	BS/IE		
25	M	III	Normal	Reversed flow		Absent	-		
26	M	III	PVE	0.6		Absent	IE		
27	F	III	Normal	0.7		Delayed	BS		
28	M	III	PVE+THAL	0.7		Delayed	IE		
29	F	III	Normal	-		Absent	BS		
30	M	III	Normal	AD/CO2		Absent	BS/IE		
31	M	III	PVE+THAL	0.8		Delayed	IE		
32	F	III	Normal	AD/CO2		Absent	CLV		
33	F	III	PVE+THAL	0.5		Absent	IE		
34	M	III	Normal	0.5		Absent	IE		

PVE=periventricular echodensities; IHF=increased echogenicity around the interhemispheric fissure; TENT TEAR=tentorial tear; PVE+THAL=PVE+thalamic densities; AD/CO2=AD associated with $CO_2 < 30$; - = not done; BS=burst-suppression; CLV=continuous low voltage; IE=isoelectric.

Table 2 Predictive value of different tests at less than 6 hours of age

	Ultrasonography (n=34)	RI (n=32)	SEP (n=34)	VEP (n=34)	CFM (n=31)
Sensitivity	42.1	23.5	94.7	89.5	94.1
Specificity	60	100	73.3	66.7	78.6
PPV	57.1	100	81.8	77.3	84.2
NPV	45	53.6	91.7	83.3	91.7

and the subsequent negative wave (N300) was measured according to the criteria of McCulloch and Taylor.¹³ The normal data of Taylor *et al*¹⁴ were used, as the same filter settings and stimulation rate were used.

The VEP was graded as abnormal when the P200 latency fell outside the normal range, when the waveform was abnormal, which in all cases coincided with a prolonged latency, or when no response could be elicited.

CEREBRAL FUNCTION MONITOR (CFM)

An amplitude integrated continuous electroencephalogram (EEG) recording, the cerebral function monitor (CFM 4640, Lectromed Devices Ltd), was applied. The CFM records a single channel EEG from two biparietal electrodes. The filtered signal is rectified, smoothed, and amplitude integrated before it is written out at slow speed (6 cm/hour) at the cot-side.¹⁵ Both the background activity and the presence of seizure activity were taken into account when analysing the data. The CFM was graded as normal when background activity was continuous and of normal voltage and when no seizure patterns were present. The CFM was graded as abnormal when background activity showed burst-suppression, continuous extremely low voltage (main activity below 5 μ V), was flat (mainly isoelectric), or when seizure patterns were present.¹⁵

ASSESSMENT OF NEURODEVELOPMENTAL OUTCOME

The survivors were seen in the follow up clinic at 3, 9, 18, and 24 months of age. Assessment of outcome was made using the Griffith's mental developmental scale¹⁶ and items from the Amiel-Tison and Grenier evaluation¹⁷ and Touwen's findings.¹⁸ A DQ below 85 on the Griffiths scale was considered abnormal and cerebral palsy was classified according to the criteria of Haberg *et al*.¹⁹

Figure 1 Normal N1 latency (49 milliseconds) at 3 hours of age in case 4.

Results

Table 1 summarises the ultrasound findings, the resistance indices and the electrophysiological findings (SEPs, VEPs, CFM) obtained within the first six hours of life, and the neurodevelopmental progress at the age of 6–24 months (median age 12 months) in the 34 subjects studied.

The predictive value of the different tests is summarised in table 2.

CRANIAL ULTRASONOGRAPHY

No ultrasound abnormalities were noted in 20 cases. Only nine of these infants had a good outcome; the other 11 infants had severe encephalopathy and died.

Areas of increased echogenicity in the periventricular and/or subcortical white matter were present in nine cases. Two infants died, one had a major, one a minor handicap (DQ 84), and five had a good outcome.

Five cases had a different type of ultrasound abnormality. One showed an increase in echogenicity in the grey matter around the interhemispheric fissure, which subsequently evolved into a few small cysts. This child was normal at follow up. One child had blood above the cerebellum, suggestive of a tentorial tear, which was subsequently confirmed by computed tomography. This child died. The other three children had areas of increased echogenicity in the thalami and in the periventricular white matter and also died.

RI

RIs were available in 32 of the 34 cases. An RI of >0.55 was found in 28 cases. An absent diastolic flow, associated with a PaCO_2 of <30 mm Hg was found in four of these 28 infants. Fifteen infants had a normal outcome, one a major, one a minor handicap, and the remaining 11 died.

Only four infants with severe encephalopathy had an abnormal RI. One child had no diastolic flow while the PaCO_2 was 31 mm Hg at the time; one child had a reverse diastolic flow and the other two children had an RI of <0.55 . All four died.

SEPS

Twelve infants had a normal waveform and normal N1 latency. All but one of the infants had a good outcome (Fig 1). In the one infant who died no response could be elicited at 36 hours of age at which stage the CFM showed a status epilepticus. Eight of these 12 infants had mild, three moderate, and the child who died severe encephalopathy.

Eight infants had a delayed N1 latency. Two infants died, one developed a major, one a minor handicap, and four infants were normal at follow up. Three of these eight had mild, four moderate, and one severe encephalopathy.

In 14 infants no response could be obtained (fig 2). All had severe encephalopathy and all died.

Figure 2 At 3 hours of age no cortical response could be elicited following stimulation of the median nerve (top), while the P200 (274 milliseconds) was present but delayed (bottom) in case 19.

VEPS

Twelve infants had a reproducible response with a normal waveform and latency of the P200. All but two of the infants had a good outcome. One had a major and one a minor handicap. The infants with a good outcome all had mild encephalopathy, while the two with an abnormal outcome had moderate encephalopathy.

Fourteen infants had a delayed response. Nine infants died, one with moderate and eight with severe encephalopathy (fig 2). Five were normal at follow up, three had mild, and two moderate encephalopathy.

No response could be obtained in eight infants who all had severe encephalopathy; all died.

CFM

CFM was recorded in only 31 of the 34 infants, as the machine was not yet available when the first three infants were studied. Twelve infants had a continuous background activity of normal voltage. One infant could only be recorded between 4 and 6 hours of age as he had to be transferred to another neonatal intensive care unit for treatment with extracorporeal membrane oxygenation (ECMO). All infants except the infant treated with ECMO had a good outcome. Ten of the 12 infants had mild and two moderate encephalopathy. Nineteen infants had abnormal CFM patterns.

Three infants with a continuous but extremely low voltage pattern died. Eleven infants had a suppression-burst pattern. Seven died and in three of them the suppression-burst pattern changed into a mainly isoelectric

pattern by 6 hours of age. One infant had a minor handicap and three were normal at follow up. In one of the three with a normal outcome, the CFM pattern had changed to a continuous pattern by 6 hours of age (fig 3). The other five infants had a mainly isoelectric pattern and all died (fig 4).

SEIZURES

Repetitive subclinical seizures were found on the CFM in nine infants, three with moderate and six with severe encephalopathy. One of the three with moderate encephalopathy died, the other two were normal at follow up. All six with severe encephalopathy died.

In eight infants a loading dose of intravenous phenobarbitone (20 mg/kg) was administered while the CFM had been recording for at least 20 minutes. In four of the five infants with a mild encephalopathy the CFM pattern remained continuous, but a lower voltage was noted for 60–120 minutes (fig 5). In one of the five infants with mild and one with moderate encephalopathy a suppression-burst pattern occurred following administration of the drug (fig 5). In two infants with severe encephalopathy the suppression-burst pattern remained unchanged.

CAUSE OF DEATH

Seventeen infants died during the neonatal period, one with moderate and 16 with severe encephalopathy. In nine infants intensive care was withdrawn because of an isoelectric CFM and an isoelectric 16 channel EEG obtained after the first 24 hours of age. Post mortem histology was available for two of these nine infants; they showed extensive hypoxic-ischaemic damage. Two infants died due to multi-organ failure and both had a post mortem examination.

In the remaining six cases intensive care was withdrawn as the results of all the different tests described above remained severely abnormal on two or more occasions. Four of these six infants had a post mortem examination and extensive hypoxic-ischaemic changes were found on histology in all cases.

Discussion

During a two year period, 34 full term infants who met the criteria for HIE, were studied within six hours of birth. In all cases transfer to our neonatal intensive care unit had been requested. Most of the infants either developed mild ($n=11$) or severe ($n=16$) encephalopathy. Only seven infants developed moderate encephalopathy. This intermediate group is the most interesting one, as it is especially difficult to predict neurodevelopmental outcome in these infants using clinical examination alone, but referral is often delayed as spontaneous respiration is commonly established after resuscitation and referral is postponed until seizures, sometimes associated with apnoeic spells, develop between 12–24 hours of age. The neurodevelopmental out-

Figure 3 CFM recorded in case 17 between 3 and 6 hours of age, showing a change from a suppression-burst pattern to a continuous pattern.

Figure 4 CFM recorded in case 19, showing a severe suppression-burst pattern, changing into an isoelectric pattern.

come of all 11 infants with mild encephalopathy was good. All 16 cases with severe encephalopathy died and two of the seven with moderate encephalopathy had an unfavourable neurological outcome. These findings agree with previous follow up studies.²⁻⁵

Five different tests were performed as soon as possible following admission and stabilisation of the infants. All tests had been shown to be good predictors of neurodevelopmental outcome, when performed during the first week, but only the CFM was recently used during the first 6 hours of life.^{15 20-30} As expected, very little information was obtained from both cranial ultrasound as well as pulsed Doppler studies. Cranial ultrasound has been considered to be of little value in the full term infant with HIE³¹⁻³⁴ and the use of neonatal magnetic resonance imaging (MRI) has been advocated instead.³⁵⁻³⁷ Some groups, using the 10 MHz for visualisation of the cortex, have shown good agreement with computed tomography and MRI data.³⁸⁻⁴⁰ Most of the infants with severe encephalopathy developed severe changes on ultrasonography in the cortex and/or basal ganglia between 24-72 hours of age, and a good correlation was found of the ultrasound abnormalities and histological findings.⁴⁰ As these ultrasound changes took several days to develop, ultrasonography is not useful for early identification of infants at risk of severe neurological sequelae.

The pulsed Doppler data were also of little predictive value. An absent diastolic flow was noted in a few cases, but was in all but one associated with a low PaCO₂ at the time. In only one of the infants was a reverse flow seen during the diastole, which is an ominous sign

in the absence of a patent ductus arteriosus.⁴¹ The high diastolic flow associated with an RI of <0.55, which usually develops between 12-24 hours of age, was only present before 6 hours of age in two of our severe cases. A further nine out of 12 infants with severe encephalopathy, who survived beyond the first day of life, developed an RI of <0.55 after the 6 hours of age. As all five different examinations usually had to be performed within one to two hours, only RI measurements were performed because there was no time to study the effect of changing the PaCO₂ on the diastolic flow.

Neurophysiology was very useful for predicting neurodevelopmental outcome during the first six postnatal hours. The sensitivity was more than 90% for both the CFM as well as the SEP and slightly lower for the VEP. The specificity was also best for the CFM and the SEP, being 78.6 and 73.3, respectively.

The CFM data agree with those of Hellström-Westas *et al*,¹⁵ although their specificity was slightly higher. This can partly be explained by the fact that we scored the CFM as early as possible. One of the infants improved from a suppression-burst pattern to a continuous pattern before 6 hours of age, which would change the specificity to 80%. A continuous normal voltage pattern at 6 hours of age was a good prognostic indicator in 11 of 12 infants. In the one infant who did develop a major handicap the CFM was only recorded for a period of two hours, before he had to be referred for ECMO treatment. At 3 weeks of age small subcortical cysts were identified on ultrasonography and MRI. As in the study of Hellström-Westas *et al*,¹⁵ three of the 11 infants with a suppression-burst pattern were normal at 18-24 months of age. The remaining 16 infants with an abnormal background activity at 6 hours of age either died or had an abnormal neurodevelopmental outcome.

We were able to study the effect of a loading dose of phenobarbitone on the CFM in eight infants. In only one of the five children with mild encephalopathy was a suppression-burst pattern possibly induced by the drug, while a definite change in the CFM with a significantly lower minimum voltage was noted in the other infants, lasting between 60-120 minutes. In one child with moderate encephalopathy seizures were discontinued and a suppression-burst pattern was subsequently noted, and in the two infants with severe encephalopathy the suppression-burst pattern remained unchanged. So, although a change from a normal continuous background pattern into a suppression-burst pattern can occur, this seems to be rare in the infants with mild encephalopathy and it lasts only for a short period. Repetitive seizure activity was present in nine cases and was associated with a poor outcome in seven. Seizure activity was often noted not to develop till 6-24 hours of age.

A normal SEP or VEP obtained within 6 hours of age was also a good prognostic indicator. Only in one case was the SEP initially normal but could no longer be obtained at the age of 36 hours, at which stage the infant had a status epilepticus, resistant to extensive

Figure 5 Effect of phenobarbitone (Ph, L) on the CFM is shown in an infant with mild (case 4) and an infant with moderate (case 14) encephalopathy. In the mild case a decrease of the minimum voltage is seen, while in the moderate case seizure activity changes to a suppression-burst pattern.

anticonvulsive treatment. It was more common for the SEP or VEP to normalise over the next 24–48 hours from a delayed to a normal latency, and this was associated with a good outcome in most of the infants. When the specificity was calculated at 72 hours of age, it had increased to 93.3% and 86.6% for the SEP and VEP, respectively. These findings agree with earlier data.^{23–27} The evoked responses are more time consuming to perform and provide little additional information compared with the CFM, which is now increasingly being used and which is easy to apply and interpret.^{15–21–28}

Except for the Apgar score, cord blood pH, and time of onset of spontaneous respiration, few data available within the first few hours of life have been evaluated as possible predictors of neurodevelopmental outcome. Wayenbergh *et al.*⁴² found that a clinical score performed at 30 minutes of age and an arterial base excess measurement taken at this time were also good prognostic indicators of neurodevelopmental outcome. Data taken in the neonatal period in our infants were often incomplete, Apgar scores were not always recorded, and the first blood gas was often a capillary sample. We were therefore unable to compare our findings with those of Wayenbergh *et al.*⁴²

In conclusion, the present data indicate that neurophysiology performed within the first six hours of life can reliably predict which infants will go on to develop moderate or severe encephalopathy and are subsequently likely either to die or develop adverse neurological sequelae. These tests may be of help in selecting infants who might benefit from neuroprotective agents.

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