Journal of Perinatology (2008) 28, 117–122

www.nature.com/jp

ORIGINAL ARTICLE

Should amplitude-integrated electroencephalography be used to identify infants suitable for hypothermic neuroprotection?

S Sarkar, JD Barks and SM Donn

Division of Neonatal-Perinatal Medicine, Department of Pediatrics, University of Michigan Health System, C.S. Mott Children's Hospital, Ann Arbor, MI, USA

Objective: Amplitude-integrated electroencephalography (aEEG) has been used adjunctively to identify infants suitable for hypothermic neuroprotection following severe intrapartum asphyxia. To determine whether an early aEEG predicts short-term adverse outcome in infants with significant hypoxic–ischemic encephalopathy (HIE) evaluated for hypothermic neuroprotection.

Study Design: The aEEG recordings were obtained within 6 h of birth in infants $\geqslant$36 weeks' gestational age during evaluation for possible selective head or whole-body cooling. Recordings were subsequently re-evaluated for both background pattern and voltage abnormalities by a certified reader masked to clinical history and brain-oriented interventions. All infants with moderate or severe HIE evaluated for hypothermic neuroprotection also underwent magnetic resonance imaging (MRI) of the brain at a median postnatal age of 7 days. The predictive value using the aEEG for determining short-term dichotomous outcomes, defined as early death related to HIE, or a characteristic pattern of abnormalities consistent with hypoxic–ischemic injury on the MRI brain scans was assessed.

Result: Fifty-four infants with moderate or severe HIE were evaluated with aEEG for hypothermic neuroprotection; 34 infants received selective head cooling, 12 infants underwent total body cooling and 8 infants were not cooled. Outcome data, available for 46 of the 54 infants, revealed a poor correlation between the early aEEG and short-term adverse outcomes, with a sensitivity of 54.8% and negative predictive value (NPV) of only 44%.

Conclusion: Because of the poor NPV of an early aEEG for a short-term adverse outcome, its use as an 'additional selection criterion' for hypothermic neuroprotection may not be appropriate.
Journal of Perinatology (2008) **28,** 117–122; doi:10.1038/sj.jp.7211882; published online 15 November 2007

Correspondence: Dr S Sarkar, Division of Neonatal-Perinatal Medicine, Department of Pediatrics, University of Michigan Health System, C.S. Mott Children's Hospital, Ann Arbor, MI 48109, USA.
E-mail: subratas@med.umich.edu
Received 16 July 2007; revised 15 October 2007; accepted 17 October 2007; published online 15 November 2007

Keywords: hypoxic–ischemic encephalopathy; hypothermic neuroprotection; amplitude-integrated EEG; MRI brain scans

Introduction

The management of newly born term and late pre-term infants at risk for hypoxic–ischemic brain injury is complicated by the difficulty in predicting which infants are likely to develop adverse neurodevelopmental sequelae.[1] An early and accurate method for predicting the maximal severity of cerebral injury and the subsequent neurodevelopmental outcome is important because these injuries might be amenable to hypothermic neuroprotection. Clinical signs in infants at risk for hypoxic–ischemic encephalopathy (HIE), as indicated by profound fetal acidemia or the need for prolonged resuscitation after acute hypoxic events, may take hours to develop fully.[1] Indeed, a majority of the infants with HIE show recovery from primary energy failure related to hypoxic–ischemic insult, but in some this recovery of cerebral oxidative metabolism may be transient, and soon after secondary cerebral energy failure ensues. A narrow therapeutic window exists, and hypothermic neuroprotection is effective only if it is started before the onset of secondary cerebral energy failure.[2]

To objectively control for this 'clinical and pathophysiological heterogeneity' of HIE, an early electrophysiological assessment by amplitude-integrated electroencephalography (aEEG) was utilized to help identify infants suitable for the Cool Cap (selective head cooling) trial.[3] Another method for predicting which infants are likely to develop adverse neurodevelopmental outcome is to look for brain lesions characteristic of hypoxic–ischemic injury by magnetic resonance imaging (MRI), but these abnormalities are more evident if imaging is done after the first week of life when brain swelling has subsided. The brain lesions on MRI scans in infants with HIE show characteristic patterns of involvement in the basal ganglia and thalamus, posterior limb of the internal capsule, subcortical white matter and cortical gray matter and can be considered as a surrogate marker for long-term neurodevelopmental sequelae.[4,5] Although aEEG was

recommended by the Cool Cap study group to identify infants eligible for hypothermic neuroprotection,[3] it is not known if this 'additional selection criterion' improves the specificity of selection of cases at risk for significant hypoxic–ischemic brain injury and who might benefit from hypothermic neuroprotection.

The University of Michigan was one of the participating centers in the Cool Cap trial[3] and subsequently has been using hypothermic neuroprotection in infants at risk for significant hypoxic–ischemic brain injury under a continued access protocol since January 2004. Since then, there have been a few infants with significant fetal acidemia and severe clinical encephalopathy following an acute intrapartum event, who were not eligible for selective head cooling because of a non-qualifying aEEG recording. Some of these infants were later noted to have clinical findings and MRI brain lesions characteristic of significant hypoxic–ischemic injury. This prompted a change in practice in July 2006, whereupon infants at risk for significant intrapartum hypoxic–ischemic injury and with moderate or severe encephalopathy underwent whole-body cooling if they fulfilled the clinical and laboratory eligibility criteria of the continued access protocol but had a normal (non-qualifying) aEEG. It also prompted a review of the data collected prospectively under the continued access protocol to ascertain whether the MRI brain scan abnormalities correlated with the early aEEG findings in infants evaluated for hypothermic neuroprotection. Thus, the objective of this study was to determine whether an early aEEG finding in infants with moderate or severe hypoxic–ischemic encephalopathy evaluated for hypothermic neuroprotection could predict a short-term abnormal outcome, defined as early death related to HIE or a characteristic pattern of abnormalities consistent with hypoxic–ischemic injury on the MRI brain scan.

Methods

The infants in the continued access protocol were evaluated using the same criteria of the Cool Cap trial, which included an Apgar score of $\leqslant 5$ at 10 min; a continued need for resuscitation (including endotracheal or mask ventilation) at 10 min after birth; or umbilical cord pH or a postnatal blood pH $\leqslant 7.0$, or a base deficit $>16\,\mathrm{mEq\,l^{-1}}$ at birth or in the first hour. These infants, in addition, had a history of an acute intrapartum event (such as abruptio placenta, uterine rupture, cord prolapse and so on). The infants were then assessed on admission for evidence of moderate (stage 2) or severe (stage 3) encephalopathy using criteria modified from Sarnat and Sarnat,[6] including lethargy, stupor or coma with either hypotonia, abnormal reflexes (including oculomotor or pupillary abnormalities), absent or weak suck, or clinical evidence of seizures. Infants older than 5.5 h of age at the time of evaluation and infants with major congenital anomalies, severe growth restriction or microcephaly were not considered eligible for hypothermic neuroprotection. Infants meeting the aforementioned criteria underwent $\geqslant 20$ min of aEEG recording. Eligible infants underwent 72 h of selective head cooling if they fulfilled all the three criteria (clinical evidence of intrapartum hypoxic–ischemic event, an abnormal neurological examination and an abnormal aEEG recording). From July 2006 onwards, infants meeting clinical and laboratory criteria, but with a normal aEEG, were given whole-body cooling. Clinical monitoring and treatment during cooling, whether head or whole body, were done as previously reported.[3,7] Infants with significant hypoxic–ischemic encephalopathy evaluated for hypothermic neuroprotection also had neuroimaging studies, usually an MRI of the brain, after the first week of life.

Data collection for the present study was concurrent with the continued access protocol and included the details of the perinatal events, presence of moderate or severe encephalopathy on clinical examination before 6 h of age, time of aEEG; receipt and dose of phenobarbital prior to aEEG; type of hypothermic neuroprotection; any postnatal hypoxic–ischemic insult; any persistent, uncontrollable metabolic abnormality; postnatal age when the MRI was done and the result; and other short-term outcomes, including death.

The aEEG recordings (CFM 6000, Olympic Medical, Seattle, WA, USA) obtained during evaluation of possible selective head or whole-body cooling were subsequently re-evaluated for abnormalities by one of the investigators (SMD) certified to read aEEG recordings[3] and masked to MRI brain results and brain-oriented interventions. Both the background pattern and voltage criteria were evaluated, and care was taken to recognize interference, which can cause significant upward drift of the baseline.[8] The aEEG traces were classified as having moderately abnormal amplitude, with the lower margin of the trace $<5\,\mu$V and upper margin $>10\,\mu$V, or severely depressed amplitude, with the upper margin of the trace $<10\,\mu$V. In addition, each aEEG was classified according to the presence or absence of seizures. Use of voltage criteria for classifying the EEG has been shown in previous reports to have excellent agreement on tests of interobserver variability ($\kappa = 0.85$).[9]

MRI of the brain was performed using a 1.5 T magnet with T1- and T2-weighted imaging sequences in both the transverse and sagittal planes. The MRI brain scans were reviewed by neuroradiologists unaware of aEEG findings or details of the clinical course and also by pediatric neurologists unaware of aEEG findings. The images were assessed for normal anatomic development and for the presence or absence of abnormal signal intensities within the basal ganglia, thalamus, internal capsule, subcortical white matter or cortex.

Written informed consent was obtained from a parent before the start of cooling in the study infants, and the study protocol for secondary data analysis, including re-evaluation of aEEG recordings, was approved by the Institutional Review Board.

Statistical analysis

The primary outcome was dichotomous. The predictive values for determining short-term dichotomous outcomes using the aEEG recording were assessed by calculation of positive and negative predictive values and likelihood ratios.

Results

Sixty-four infants $\geqslant 36$ weeks' gestational age admitted to our NICU between January 2004 to June 2007 were identified to be at risk for significant hypoxic–ischemic brain injury, but only 54 infants were noted to have evidence of moderate (stage 2) or severe (stage 3) encephalopathy. Fifty (92%) of these 54 infants were transferred to our unit from the birth hospital for possible hypothermia treatment because of the presence of moderate to severe encephalopathy following a significant intrapartum event. All 54 infants with moderate or severe HIE were evaluated by aEEG within 6 h of birth; 34 infants received selective head cooling, 12 infants underwent total body cooling and eight infants were not cooled because of non-qualifying aEEG recordings. These 8 infants were not offered total body cooling because they were born before the change in practice in July 2006, prior to which infants either underwent selective head cooling under the FDA-approved continued access protocol if they fulfilled all the three eligibility criteria (clinical, laboratory and aEEG) or were not cooled if they had a non-qualifying aEEG recording.

The selective head or whole-body hypothermia in the 46 cooled infants was started at a median age of 4.8 h (mean 4.6, s.d. 0.9). The primary outcome data (death related to HIE during the first week of life or abnormal MRI brain scan among survivors beyond the first week) were available in 46 of the 54 infants. This constitutes the final study population. Eight infants from the head-cooled group surviving beyond the first week of life were excluded, as they had only CT but not MRI scanning of the brain following cooling. Early aEEG recordings were abnormal in four of these eight infants, but all eight had abnormal CT scans showing changes consistent with hypoxic–ischemic injury.

The maternal and neonatal characteristics of the study infants are shown in Tables 1 and 2. Twelve (26%) of the 46 infants had clinical seizures, but only half received phenobarbital at doses $\leqslant 20\,\mathrm{mg\,kg^{-1}}$ before aEEG evaluation (Table 2). The aEEG recordings had moderate to severe background suppression in 21 (45%) infants, and 10 of these infants in addition had electrographic seizures (Table 2). Only 1 of the 25 infants with a normal aEEG received phenobarbital before evaluation.

Four of the 46 study infants died before MRI evaluation. Three infants had an abnormal aEEG and were started on head cooling; the other early death was not cooled because of a normal aEEG. All of the four deaths were related to hypoxic–ischemic encephalopathy with multi-organ system dysfunction. The remaining 42 infants had MRI of the brain done at a median age of 7 days (range 6–22 (mean 8.4, s.d. 4.3)). The correlation between aEEG and MRI brain lesions is shown separately for the 7 non-cooled (Table 3) and 35 cooled (Table 4) infants surviving

Table 1 Obstetrical characteristics of the 46 study infants evaluated for hypothermic neuroprotection

Maternal characteristics	*Number* (%)
Emergency cesarean section	31 (67)
Antepartum hemorrhage, including abruptio placentae	17 (37)
Prolonged rupture of membrane (>18 h)	4 (9)
Maternal fever	4 (9)
Pregnancy-induced hypertension	3 (7)
Gestational diabetes	3 (7)
Multiple gestation	2 (4)
Cord prolapse	2 (4)
Uterine rupture	2 (4)
Home birth	1 (2)

Table 2 Baseline characteristics of the 46 study infants evaluated for hypothermic neuroprotection

Neonatal characteristics	
Birth weight (g)	3181 ± 807
Gestational age (weeks)	38.7 ± 1.7
Male	24 (52)
Transferred from birth hospital	43 (94)
5 min Apgar score	
0–3	32 (70)
4–5	9 (20)
⩾6	5 (10)
10 min Apgar score ($n = 41$)	
0–3	15 (37)
4–5	16 (38)
⩾6	10 (24)
Blood gas within 60 min of birth ($n = 39$)	
pH ($n = 39$)	6.9 (6.5–7.2)
Base deficit ($\mathrm{mmol\,l^{-1}}$, $n = 32$)	20.3 ± 7.1
HCO_3 ($\mathrm{mmol\,l^{-1}}$, $n = 7$)	10.8 ± 5.2
Intubation in delivery room	42 (91)
Continued resuscitation at 10 min	44 (96)
Clinical seizure before admission	12 (26)
Phenobarbital before aEEG	6 (13)
Abnormal aEEG within 6 h after birth	21 (45)
Moderately abnormal	7 (15)
Severely abnormal	14 (30)
Seizures present	10 (22)

Data are mean ± s.d., number of patients (%) or median (range).

Table 3 Correlation between aEEG and MRI brain lesions in seven infants evaluated for hypothermic neuroprotection, but not cooled

	MRI normal	*MRI abnormal*
aEEG normal	3	4[a]
aEEG abnormal	0	0

Abbreviations: aEEG, amplitude-integrated electroencephalography; MRI, magnetic resonance imaging.
[a]All four infants had cortical lesions and three had basal ganglia and/or thalamic lesions in addition.

Table 4 Correlation between aEEG and MRI brain lesions in 35 infants evaluated for hypothermic neuroprotection and cooled

	MRI normal	*MRI abnormal*
aEEG normal	8	9[a]
aEEG abnormal	4	14[b]

Abbreviations: aEEG, amplitude-integrated electroencephalography; MRI, magnetic resonance imaging.
[a]Five infants had basal ganglia/thalamic lesions (two also had internal capsule involvement), one had isolated internal capsule lesions and three had cortical and/or subcortical white matter lesions without basal ganglia/thalamic involvement.
[b]Seven infants had only diffuse cortical lesion, two had both cortical and basal ganglia/thalamic lesions, three had both basal ganglia/thalamic and white matter lesions and two had both cortical and subcortical white matter lesions.

Table 5 Correlation between aEEG and adverse short-term outcomes (abnormal MRI or early death) in infants evaluated for hypothermic neuroprotection

	Adverse outcomes in both cooled and non-cooled infants (n = *46*)	
	No adverse outcome	*Adverse outcome*
aEEG normal	11	14[a]
aEEG abnormal	4	17[b]

Abbreviations: aEEG, amplitude-integrated electroencephalography; MRI, magnetic resonance imaging.
[a]Includes one non-cooled infant with early death.
[b]Includes three infants with early death in whom selective head cooling was prematurely terminated.

Table 6 Predictive values of aEEG evaluation for the adverse short-term outcomes

Adverse outcome measures	*Sensitivity*	*Specificity*	*PPV*	*NPV*	*LR+*	*LR−*
Abnormal MRI ($n = 42$)	51.8%	73.3%	77.7%	45.8%	1.9	0.65
Abnormal MRI+death ($n = 46$)	54.8%	73.3%	81%	44%	2.0	0.61

Abbreviations: aEEG, amplitude-integrated electroencephalography; MRI, magnetic resonance imaging; NPV, negative predictive value; PPV, positive predictive value.

beyond the first week of life. Abnormal MRI brain scans were evident in 27 of the 42 (64%) study infants surviving beyond the first week of life. The most frequently observed lesions included abnormalities in the basal ganglia and/or thalamus in isolation or in association with cortical or subcortical white matter lesions in 13 infants; isolated diffuse cortical lesions in 8 infants; and combined cortical and subcortical white matter lesions with or without internal capsule involvement in 6 infants. Four of the surviving infants with moderate or severe encephalopathy and an abnormal early aEEG were noted to have a normal MRI of the brain following cooling (Table 4). Table 5 shows the correlation between the aEEG and the primary outcome of death related to HIE during the first week of life or abnormal MRI brain scans among the survivors beyond the first week. Outcome data revealed a poor correlation between the early aEEG and short-term adverse outcome with a sensitivity of 54.8% and an NPV of only 44% (Table 6).

Discussion

This study demonstrates that an aEEG recording before 6 h of age in infants with moderate or severe clinical hypoxic–ischemic encephalopathy following an acute perinatal event does not always correlate with early death or abnormal MRI brain scan. Of greater practical importance is the NPV of a normal or non-qualifying aEEG for short-term adverse outcome, which was noted to be low in the study infants. Therefore, aEEG as an 'additional selection criterion' may not be appropriate, as many infants who might otherwise benefit from hypothermic neuroprotection will be missed if an abnormal aEEG is required for this novel treatment.

A number of factors are likely to influence whether an aEEG in the first 6 h of life may be abnormal, including the timing of the hypoxic–ischemic insult and the timing of the aEEG. Spontaneous recovery of severely abnormal EEG patterns within 24 h in asphyxiated term infants is not uncommon.[10,11] Both positive and negative predictive values of an abnormal aEEG background pattern for subsequent poor neurodevelopmental outcome change significantly, even when assessed at different times (3 and 6 h) during the first 6 h of life.[12]

Since the period from birth to the initial aEEG varied little in the study infants, the stage of evolution of damage would mainly be influenced by the timing of intrauterine hypoxia. Westgate *et al*.[13] previously reported that only a quarter of infants with evidence of post-asphyxial encephalopathy were exposed to a sentinel, catastrophic event, such as uterine rupture or prolapsed cord, whereas an additional quarter had evidence of antepartum hypoxia.[13] In most of the remainder, the timing of injury was unclear but was likely to have evolved during labor. Thus, in some infants in the present study, by the time of assessment by aEEG, primary cerebral energy failure from hypoxic–ischemia might already be improving, or damage from delayed ('secondary') energy failure might already be occurring.[14] It was also suggested

by Wyatt *et al*.[15] that some infants with severe encephalopathy may have 'slowly evolving injuries (as reported in some experimental paradigms),'[16] and it is plausible that these infants may have a normal early aEEG. This might explain why few infants in our study had adverse short-term outcomes despite a normal aEEG. As the infants with slowly evolving injuries retain the potential to respond to hypothermia treatment initiated within 6 h,[15] these infants will miss the potential benefit if aEEG is used to decide whom to cool.

The low sensitivity and NPV of an early aEEG for short-term adverse outcome noted in the study infants is at variance with previous reports by al Naqeeb *et al*.[9] and Shalak *et al*.[17] In both the previous studies, the high sensitivity, specificity and predictive values of aEEG may be reflections of study patient populations skewed toward more severely injured newborns. In the study by al Naqeeb *et al*.[9] no data were presented regarding fetal acidemia or any intrapartum hypoxic–ischemic events. That 27 of the 35 (77%) infants with abnormal aEEG either died or had neurodevelopmental sequelae at 18–24 months suggests that the study group was skewed toward the more severely injured. In the study by Shalak *et al*.,[17] the aEEGs were abnormal in 15 (30%) of the 50 infants 'at risk' for hypoxic–ischemic encephalopathy, with 11 (73%) having persistent encephalopathy or death at 5 days of life. Seven (50%) of the 14 infants with or without an abnormal EEG, but with persistent encephalopathy beyond 5 days, died. Hence, an early abnormal aEEG, particularly in combination with an early neurological examination, demonstrated a sensitivity of 78%, specificity of 94%, positive predictive value of 85% and NPV of 92% for short-term adverse outcome. Again, the study patients appear skewed toward the moderately severe to severely injured as in the case of the al Naqeeb *et al*.[9] study. Such a skewed population would increase the sensitivity, specificity and the predictive values of the measurement tool. Perhaps a reason for the less significant outcome findings of the Cool Cap trial[3] resulted from a selection process biased toward more severely injured patients as based on their aEEG inclusion criteria.

This investigation is the first to evaluate how the MRI brain scan abnormalities relate to both a normal and an abnormal initial aEEG in infants evaluated for hypothermic neuroprotection. Rutherford *et al*.[18] reported the severity and distribution of cerebral MRI lesions in infants evaluated for hypothermic neuroprotection, but all infants in that study had an abnormal initial aEEG irrespective of whether they were cooled or not. It is also interesting to note that 4 of our 46 study infants with clinical evidence of an intrapartum hypoxic–ischemic event and moderate or severe encephalopathy had an abnormal early aEEG but normal MRI, following cooling. Conversely, 23 of the 35 infants had lesions on the MRI scan despite 72 h of selective head or whole-body cooling, and 9 of these 23 infants had a normal aEEG. Both selective head cooling and total body cooling are associated with decreased extent and severity of lesions in the basal ganglia, thalamus and cortex,[18] but it is not known if hypothermic neuroprotection can lead to a normal appearance of the MRI brain scans in infants who had moderate or severe encephalopathy following an acute intrapartum event and an abnormal aEEG in the first 6 h of life. The infants in our study, like those reported by Rutherford *et al*, had brain MRI only after cooling. Thus, it is difficult to interpret whether a normal MRI represents either an improvement of the hypoxic–ischemic injury or a lack of initial injury. The adverse short-term outcomes (death or abnormal MRI) might have been higher if the decision to cool in all of the study infants required an abnormal aEEG as the final selection criterion. Furthermore, it is not yet clear whether residual MRI abnormalities after therapeutic hypothermia always represent the final neuropathology or injury that in some cases may still be evolving.

Clinical signs of HIE in at-risk infants evolve over time, and the stage of encephalopathy determined by clinical assessment at $\geqslant$24 h of age has been shown to correlate with long-term outcomes.[6,19,20] A recent secondary analysis of the Cool Cap study strongly supports the value of this clinical assessment, even in the first few hours of life.[15] It showed that the outcomes after hypothermic treatment were strongly influenced by the severity of neonatal encephalopathy during the first 6 h. In the whole-body cooling trial by Shankaran *et al*.[7] as well, the classification of moderate or severe encephalopathy during 'the first few hours of life' was as predictive of the long-term neurodevelopmental outcome as those made later in the first week.[7,19,21] Conversely, almost all of the infants with milder early encephalopathy evaluated for hypothermic neuroprotection had normal long-term neurodevelopmental outcomes.[14] In light of this, and because of the poor correlation between aEEG and short-term outcomes, it seems appropriate to offer cooling to all infants with significant fetal or immediate neonatal acidemia and clinical signs of moderate or severe encephalopathy following an acute intrapartum event, even if the aEEG recording is normal or non-qualifying.

References

1 Volpe JJ. Hypoxic–ischemic encephalopathy: clinical aspects In: Volpe JJ (ed). *Neurology of the Newborn*. W.B. Saunders: Philadelphia, 1994, pp 314–369.
2 Gunn AJ, Gunn TR, Gunning MI, Williams CE, Gluckman PD. Neuroprotection with prolonged head cooling started before postischemic seizures in fetal sheep. *Pediatrics* 1998; **102**: 1098–1106.
3 Gluckman PD, Wyatt JS, Azzopardi D, Ballard R, Edwards AD, Ferriero DM *et al*. Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentre randomised trial. *Lancet* 2005; **365**: 663–670.
4 Rutherford M, Pennock J, Schwieso J, Cowan F, Dubowitz L. Hypoxic–ischaemic encephalopathy: early and late magnetic resonance imaging findings in relation to outcome. *Arch Dis Child Fetal Neonatal Ed* 1996; **75**: F145–F151.
5 Rutherford MA, Pennock JM, Counsell SJ, Mercuri E, Cowan FM, Dubowitz LM *et al*. Abnormal magnetic resonance signal in the internal capsule predicts poor neurodevelopmental outcome in infants with hypoxic–ischemic encephalopathy. *Pediatrics* 1998; **102**: 323–328.

6 Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress: a clinical and electroencephalographic study. *Arch Neurol* 1976; **33**: 696–705.
7 Shankaran S, Laptook AR, Ehrenkranz RA, Tyson JE, McDonald SA, Donovan EF *et al.* Whole-body hypothermia for neonates with hypoxic–ischemic encephalopathy. *N Engl J Med* 2005; **353**: 1574–1584.
8 de Vries LS, Hellstrom-Westas L. Role of cerebral function monitoring in the newborn. *Arch Dis Child Fetal Neonatal Ed* 2005; **90**(3): F201–F207.
9 al Naqeeb N, Edwards AD, Cowan FM, Azzopardi D. Assessment of neonatal encephalopathy by amplitude-integrated electroencephalography. *Pediatrics* 1999; **103**: 1263–1271.
10 Ter Horst HJ, Sommer C, Bergman KA, Fock JM, van Weerden TW, Bos AF *et al.* Prognostic significance of amplitude-integrated EEG during the first 72 h after birth in severely asphyxiated neonates. *Pediatr Res* 2004; **55**: 1026–1033.
11 van Rooij LG, Toet MC, Osredkar D, van Huffelen AC, Groenendaal F, de Vries LS. Recovery of amplitude integrated electroencephalographic background patterns within 24 h of perinatal asphyxia. *Arch Dis Child Fetal Neonatal Ed* 2005; **90**(3): F245–F251.
12 Toet MC, Hellström-Westas L, Groenendaal F, Eken P, de Vries LS. Amplitude integrated EEG 3 and 6 h after birth in full term neonates with hypoxic–ischaemic encephalopathy. *Arch Dis Child Fetal Neonatal Ed* 1999; **81**: F19–F23.
13 Westgate JA, Gunn AJ, Gunn TR. Antecedents of neonatal encephalopathy with fetal acidaemia at term. *Br J Obstet Gynaecol* 1999; **106**: 774–782.
14 Battin MR, Dezoete JA, Gunn TR, Gluckman PD, Gunn AJ. Neurodevelopmental outcome of infants treated with head cooling and mild hypothermia after perinatal asphyxia. *Pediatrics* 2001; **107**: 480–484.
15 Wyatt JS, Gluckman PD, Liu PY, Azzopardi D, Ballard R, Edwards AD *et al.* Determinants of outcomes after head cooling for neonatal encephalopathy. *Pediatrics* 2007; **119**(5): 912–921.
16 Geddes R, Vannucci RC, Vannucci SJ. Delayed cerebral atrophy following moderate hypoxia-ischemia in the immature rat. *Dev Neurosci* 2001; **23**: 180–185.
17 Shalak LF, Laptook AR, Velaphi SC, Perlman JM. Amplitude-integrated electroencephalography coupled with an early neurologic examination enhances prediction of term infants at risk for persistent encephalopathy. *Pediatrics* 2003; **111**: 351–357.
18 Rutherford MA, Azzopardi D, Whitelaw A, Cowan F, Renowden S, Edwards AD *et al.* Mild hypothermia and the distribution of cerebral lesions in neonates with hypoxic–ischemic encephalopathy. *Pediatrics* 2005; **116**(4): 1001–1006.
19 Robertson CM, Finer NN, Grace MG. School performance of survivors of neonatal encephalopathy associated with birth asphyxia at term. *J Pediatr* 1989; **114**: 753–760.
20 Miller SP, Latal B, Clark H, Clark H, Barnwell A, Glidden D *et al.* Clinical signs predict 30-month neurodevelopmental outcome after neonatal encephalopathy. *Am J Obstet Gynecol* 2004; **190**: 93–99.
21 Shankaran S, Woldt E, Koepke T, Bedard MP, Nandayal R. Acute neonatal morbidity and long-term central nervous system sequelae of perinatal asphyxia in term infants. *Early Hum Dev* 1991; **25**: 135–148.