Neurologic examination in infants with hypoxic-ischemic encephalopathy at age 9 to 14 months: Use of optimality scores and correlation with magnetic resonance imaging findings

Leena Haataja, PhD, Eugenio Mercuri, MD, Andrea Guzzetta, MD, Mary Rutherford, MD, Serena Counsell, MSc, Maria Flavia Frisone, MD, Giovanni Cioni, MD, Frances Cowan, PhD, and Lilly Dubowitz, MD

Objectives: To evaluate whether a structured and scorable neurologic examination (The Hammersmith Infant Neurological Examination) correlates with early magnetic resonance imaging findings in a group of infants with hypoxic-ischemic encephalopathy (HIE) and whether the scores of this assessment can predict the locomotor function in these children.

Study design: A total of 53 term infants fulfilling the criteria for HIE underwent scanning within 4 weeks from delivery with a 1 Tesla HPQ magnet. The scores from the neurologic examination performed between 9 to 14 months were correlated to the neonatal magnetic resonance imaging findings and to the maximal locomotor function defined at the ages of 2 and 4 years.

Results: The scores were always optimal in the infants with normal or minor neonatal magnetic resonance imaging findings. The lowest scores were associated with severe basal ganglia and white matter lesions. All the infants who had a global score between 67 and 78 at 1 year were able to walk independently at 2 years and without restrictions at 4 years. Scores between 40 and 67 were associated with restricted mobility and scores <40 with severely limited self-mobility at 2 and 4 years.

Conclusions: The use of a standardized neurologic optimality scoring system gives additional prognostic information, easily available in the clinic, on the severity of the functional motor outcome in infants with HIE. (J Pediatr 2001;138:332-7)

From the Department of Paediatrics, Hammersmith Hospital and Robert Steiner MRI Unit, Imperial College, London, United Kingdom; Stella Maris Scientific Institute, Department of Reproduction and Developmental Medicine, University of Pisa, Pisa, Italy; the Division of Child Neurology, Catholic University, Rome, Italy; and the Department of Paediatric Neurology, Turku University Central Hospital, Turku, Finland.

Submitted for publication May 30, 2000; revision received Aug 22, 2000; accepted Aug 31, 2000.

Reprint requests: Eugenio Mercuri, MD, Department of Paediatrics, Hammersmith Hospital, Du Cane Rd, London W12 OHS, UK.

Copyright © 2001 by Mosby, Inc.

0022-3476/2001/$35.00 + 0 **9/21/111325**
doi:10.1067/mpd.2001.111325

Hypoxic-ischemic encephalopathy is the most frequent neurologic problem in term newborns and is a major cause of neurodevelopmental abnormalities.[1,2] Follow-up studies have demonstrated that the outcome cannot be always predicted by the severity of HIE. Although HIE stage 1 is usually associated with a normal outcome and HIE stage 3 with severe neurodevelopmental abnormalities, the outcome in infants with HIE stage 2 can be quite variable, ranging from normal to cerebral palsy and severe mental retardation. A few studies have reported that neurodevelopmental outcome is best predicted by the pattern of lesions observed on neonatal magnetic resonance imaging.[3,4]

HIE	Hypoxic-ischemic encephalopathy
MRI	Magnetic resonance imaging
PLIC	Posterior limb of the internal capsule

We recently developed a structured neurologic examination for infants that assesses cranial nerve function, posture, movements, tone, reflexes, and reactions. The examination was standardized at 12 and 18 months in a low-risk population, and we developed an optimality score based on the frequency distribution of the neurologic findings. The aim of this study was to use this scoring system in a group of infants with HIE at age 9 to 14 months. More specifically, we wished to evaluate (1) the range of optimality scores in

these infants, (2) the correlation between the scores at this age and early MRI findings, and (3) whether the scores can be used to predict locomotor function at 2 and 4 years.

SUBJECTS AND METHODS

Ethical permission for this study was obtained from the Hammersmith Hospital Research Ethics Committee. The infants described in this study are part of a large prospective cohort of term infants who were born with perinatal hypoxic-ischemic brain injury and who were born at or referred to the Hammersmith Hospital, London, for MRI. The diagnosis of HIE was made in infants who showed signs of fetal distress before delivery such as abnormal cardiotocograph recordings, that is, decreased variability, late decelerations, and a baseline bradycardia (<100/min) with or without meconium-stained liquor or abnormal Apgar scores (<5 at 1 minute and <7 at 5 minutes), and who had neurologic abnormalities during the first 24 hours after delivery. These included abnormal tone, poor feeding, convulsions, and altered level of consciousness.

HIE was classified during the first week of life as mild (stage 1), moderate (stage 2), or severe (stage 3) according to the criteria described by Sarnat and Sarnat.[5]

Term infants (>37 weeks' gestation) were included in the study (1) if they fulfilled our criteria for the diagnosis of HIE and they had (2) at least 1 brain MRI performed in the neonatal period within 4 weeks from delivery and (3) detailed neurodevelopmental follow-up performed in this hospital between 9 and 14 months and at 2 and 4 years of age.

Infants who subsequently were given the diagnosis of genetic or metabolic syndromes or who presented with other neonatal complications such as neonatal meningitis were excluded.

Infants with abnormalities on MRI suggesting an antenatal insult or congenital malformation were also excluded.

Magnetic Resonance Imaging

Infants underwent scanning with a 1-Tesla HPQ magnet. Images were obtained in the transverse plane with T_1-weighted spin echo (SE 860/20), T_2-weighted spin echo (SE 3000/120), and age-related inversion recovery (IR3800/30/950) sequences. Images obtained within 4 weeks of delivery, when the pattern of injury is easiest to define, were assessed for abnormal signal intensities by an experienced observer (M.A.R.) blinded to the neurodevelopmental data. If more than one image was available, the first image after the end of the first week was chosen. The pattern of abnormal signal intensities observed was documented as follows. (1) The posterior limb of the internal capsule was assessed as normal, equivocal, or abnormal according to our previously published criteria.[6] (2) The basal ganglia and thalami were assessed as normal, minimal, moderate, and severe: *minimal*, focal abnormalities but normal signal within the PLIC; *moderate*, focal abnormalities involving the posterior lentiform nuclei and ventrolateral nuclei of the thalami with equivocal or abnormal signal intensity within the PLIC; *severe*, widespread abnormalities in all regions of the basal ganglia and thalami with abnormal signal intensity within the PLIC. (3) White matter abnormalities were documented according to whether there was a hemorrhagic element to the lesions and whether they were subcortical, periventricular, or widespread. In some neonates mild changes of long T_1 and long T_2 in the periventricular white matter were difficult to differentiate from normal appearances, and for the purposes of this study, these were not classified as abnormal. Therefore abnormalities in the white matter were described as moderate or severe: *moderate*, small focal lesions with a short T_1 and short T_2 consistent with hemorrhage or areas with an exaggerated long T_1 and long T_2 but no loss of grey/white matter differentiation, and *severe*, more marked areas of abnormality consistent with larger hemorrhages or exaggerated long T_1 and long T_2 with loss of grey/white matter differentiation consistent with infarction. (4) Cortical abnormalities consisted of "highlighting" with an abnormally high signal on T_1-weighted images and were graded 1 to 3 according to how many cortical sites were involved.[7]

Cortical highlighting is usually associated with the development of abnormal signal intensity within the adjacent subcortical white matter during the second week. Apparent highlighting of the cortex around the central fissure may be seen in control groups. It is difficult to distinguish these mild changes from early myelination, the presence of a small amount of subarachnoid blood, or partial volume effects. Grade one highlighting in this region was called "normal" unless it was associated with abnormal signal intensity within the adjacent white matter.

The scans were classified according to the predominant pattern observed into 8 groups (a-h): (a) normal: normal basal ganglia and thalami, white matter, and cortex. This group included infants who may have mild periventricular white matter change of prolonged T_1 with or without grade 1 cortical involvement; (b) minimal basal ganglia and thalami: focal abnormalities in the basal ganglia and thalami, normal PLIC, and normal white matter with or without grade 1 cortical involvement; (c) moderate white matter: focal abnormalities in the white matter with or without cortical involvement but with normal basal ganglia and thalami and PLIC; (d) moderate basal ganglia and thalami: focal abnormalities in the basal ganglia and thalami and equivocal or abnormal PLIC; with or without cortical involvement; (e) moderate white matter and basal ganglia and thalami: focal abnormalities in the white matter and mild or moderate abnormalities in the basal ganglia and

Table I. The list of items included in the neurologic examination

Neurologic examination
Assessment of cranial nerve function
Facial appearance, eye appearance, auditory response and visual response, sucking/swallowing
Posture of
Head, trunk, arms, hands, legs, feet
Movements
Quantity/quality
Tone
Scarf sign, passive shoulder elevation, pronation/supination, adductors, popliteal angle, ankle dorsiflexion, pulled to sit, ventral suspension
Reflexes and reactions
Tendon reflexes, arm protection, vertical suspension, lateral tilting, forward parachute

Table II. The details of the optimality scores in the normal population at 12 months (range 11.5 to 13.5 months; mean 12.2 months)[8]

	Optimality scores
Cranial nerves (maximum score possible = 15)	15
Posture (maximum score possible = 18)	16 or above
Movements (maximum score possible = 6)	6
Tone (maximum score possible = 24)	22 or above
Reflexes and reactions (maximum score possible = 15)	13 or above
Global score (maximum score possible = 78)	73

Optimality scores are based on the distribution of the frequency of the scores in the normal population, defining as optimal all the scores found in at least 90%.

Table III. The median score of the neurologic examination according to the neonatal MRI findings

MRI finding	Median score	Range of the scores
Normal (n = 16)	78	74.5-78
Moderate WM (n = 6)	77.5	75-78
Minimal BG (n = 10)	77.5	70-78
Moderate BG (n = 5)	57	40.5-76
Moderate WM and BG (n = 3)	47.5	26-69
Severe WM (n = 4)	59	45.5-70
Severe WM hemorrhages (n = 2)	52	39-65
Severe BG and diffuse WM (n = 5)	25	15.5-34.5
Severe BG/subcortical WM (n = 2)	14.5	10.5-18.5

BG, Basal ganglia; *WM*, white matter.

thalami with or without cortical involvement; (f) severe white matter: multifocal abnormalities with or without white matter hemorrhage with cortical involvement but with normal basal ganglia and thalami and PLIC; (g) severe basal ganglia and thalami with subcortical white matter: widespread abnormalities in the basal ganglia and thalami always with abnormal PLIC with focal abnormalities in the subcortical white matter and in the cortex; (h) severe basal ganglia and thalami with diffuse white matter: widespread abnormalities in the basal ganglia and thalami with abnormal PLIC with widespread abnormalities in the white matter and cortex.

Neurologic Examination

The Hammersmith Infant Neurological Examination[8] was used to assess neurologic status. This includes 3 sections, the first assessing neurologic signs, the second the development of motor function, and the third assessing the state of behavior. The first section includes 26 items assessing cranial nerve function, posture, movements, tone, and reflexes. Table I shows a list of the items. This section has been standardized in a low-risk population at 12 and 18 months and can be scored with the use of an optimality score. This was based on the distribution of the frequency of the scores in the normal population, defining as optimal all the scores found in at least 90% of the cohort. Each item is scored separately, and the scores for the 26 items in this section can be added to achieve a global score.

In this study all the infants born before 1996 were scored on a previous version of the proforma, which included 25 items instead of 26, because assessment of pronation and supination was added at a later stage. For these children a prorated score based on the 25 items assessed was calculated. Table II shows the details of the optimality scores in the normal population at 12 months (range 11.5 to 13.5 months).[8]

Outcome

All the infants were assessed with a structured neurologic examination by one of the pediatric neurologists (F.C., L.D., L.H., E.M.). Cerebral palsy, if present, was classified according to the criteria proposed by Hagberg et al.[9] Maximal locomotor function was graded according to a simplified version of the classification suggested by Palisano et al.[10]

Table IV. Optimality scores and MRI findings: Correlation with outcome at 2 years

	Optimal score (73 or above)	Suboptimal (scores 67-73)	Suboptimal (scores 40-67)	Suboptimal (scores <40)
Normal MRI (n = 16)	❍❍❍❍❍❍❍❍ ❍❍❍❍❍❍❍❍			
Moderate WM (n = 6)	❍❍❍❍❍❍			
Minimal BG (n = 10)	❍❍❍❍❍❍❍❍	❍❍		
Moderate BG (n = 5)	❍		❍◗◗◗	
Moderate WM and BG (n = 3)	❍			●●
Severe WM (n = 4)		◗	◗◗◗	
Severe WM hemorrhages (n = 2)			◗	●
Severe BG and diffuse WM (n = 5)				●●●●●
Severe BG/subcortical WM (n = 2)				●●

BG, Basal ganglia; *WM*, white matter; ❍ = walks independently; ◗ = sits independently but does not walk; ● = cannot sit.

Table V. Optimality scores and MRI findings: correlation with outcome at 4 years

	Optimal score (73 or above)	Suboptimal (scores 67-73)	Suboptimal (scores 40-67)	Suboptimal (scores <40)
Normal MRI (n = 16)	❍❍❍❍❍❍❍❍ ❍❍❍❍❍❍❍❍			
Moderate WM (n = 6)	❍❍❍❍❍❍			
Minimal BG (n = 10)	❍❍❍❍❍❍❍❍	❍❍		
Moderate BG (n = 5)	❍		❍◗◗◗	
Moderate WM and BG (n = 3)	❍			●●
Severe WM (n = 4)		◗	◗◗◆	
Severe WM hemorrhages (n = 2)			❍	●
Severe BG and diffuse WM (n = 5)				●●●●●
Severe BG/subcortical WM (n = 2)				●●

BG, Basal ganglia; *WM*, white matter; ❍ = walks without restrictions; ◆, walks with assistive mobility and/or limitations walking outdoors; ◗ = limited self-mobility (rolling and/or crawling); ● = self mobility and unsupported sitting severely limited.

At 2 Years

- Walks independently without restrictions: can take more than 10 steps without any help.
- Sits independently: infants maintain floor sitting and may pull to stand and take steps holding onto furniture.
- Cannot sit: infants are unable to maintain antigravity head and trunk control in prone and sitting.

At 4 Years

- Walks without restrictions: no need for any assistive mobility device.
- Walks with assistive mobility devices or limitations walking outdoors and in the community.
- Self-mobility with limitations: self-mobility for short distances (within a room) is achieved through rolling or crawling.
- Self-mobility and unsupported sitting severely limited.

RESULTS

Between October 1991 and November 1997, 114 term infants fulfilling our criteria for HIE underwent scanning in our unit. Twenty-five of these infants died within the first year (15 had stage 2 HIE and 10 had stage 3). Thirty-five infants were referred from outside hospitals and either had their first scan outside the neonatal period (n = 8) or were not seen at the times designated for this study (n = 27). One infant had a postnatal infection and had new MRI findings at that time. There were no infants with preexisting antenatal lesions that excluded them from the study. Fifty-three infants (29 male, 24 female) fulfilled all our study criteria. Fifteen infants had stage 1 HIE and 38 infants had stage 2 HIE.

Magnetic Resonance Imaging

By the end of the first week, 16 of the 53 infants had normal scans, and 37 showed lesions. Table III shows details of the MRI findings.

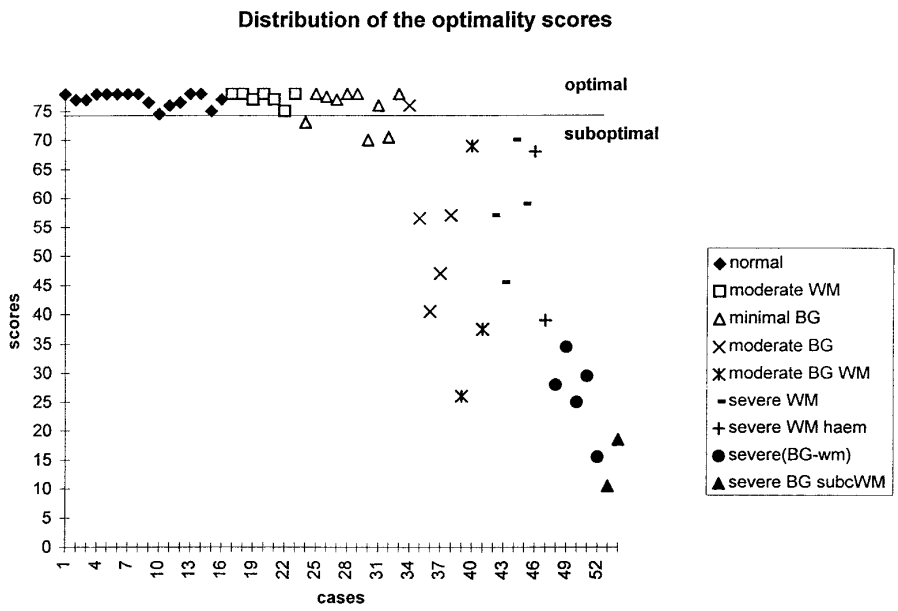

Figure. Distribution of neurological optimality scores in the cohort subdivided according to the MRI findings.

Infant Neurologic Examination

All the 53 infants had an examination between 9 and 14 months of age (mean 12.6 months; median 12 months). Thirty-one of the infants had an optimal total score, and 22 had a suboptimal score.

Outcome

Twenty-nine infants were neurologically normal, 1 had a hemiplegia, 1 diplegia, 3 movement disorders (1 had ataxia, 1 tremor, and 1 athetoid movements), 11 had quadriplegia, and 8 quadriplegia with dystonia.

Thirty-five of the 53 children were able to walk independently by the age of 2 and without any restrictions by the age of 4. Eight children were able to sit but not to walk at 2, and only 1 of them was able to walk without restrictions at 4 years. The remaining 10 children showed severely limited self-mobility and unsupported sitting at both 2 and 4 years.

Neonatal MRI Findings and Optimality Scores at 1 Year

The neurologic scores were optimal in all the children with normal MRI or moderate white matter lesions, in 8 (80%) out of 10 of the infants with minimal basal ganglia lesions, and in 1 (20%) of the 5 infants with moderate basal ganglia lesions. The scores were suboptimal in all the others.

The range of the suboptimal scores was different in the various MRI subgroups (Figure). The scores were very low in the infants with severe basal ganglia lesions associated with white matter lesions and intermediate in the ones with moderate basal ganglia lesions, moderate basal ganglia, and white matter lesions or severe white matter lesions. Table III shows the median score in the various subgroups.

Optimality Scores at 1 Year and Outcome

Tables IV and V show details of the optimality scores and locomotor function at 2 and 4 years. All of the 29 children with optimal scores walked independently by the age of 2 years and without restrictions by 4 years. Two of the 3 infants with suboptimal scores, which were above 67, were able to walk independently by the age of 2 years and without restrictions at 4 years. The other was able to sit at 2 years and had self-mobility with limitations (crawling) at 4 years. All of the 8 children with scores between 66 and 40 were able to sit by the age of 2 years, and 1 was also able to walk independently. At 4 years, 5 of the 8 had self-mobility with some limitations, 1 was able to walk with assistive motility, and 2 were able to walk without restrictions. All of the 10 children with scores <40 had severely limited self-mobility and could not sit unsupported at 2 and 4 years.

DISCUSSION

The results of this study showed that approximately 40% of the infants in our cohort had suboptimal scores on neurologic examination and that the magnitude of the suboptimal scores was related to the pattern of MRI lesion. The scores were always optimal in the infants with normal neonatal MRI findings or moderate white matter lesions. In contrast, very severe lesions such as severe basal ganglia and subcortical or diffuse white matter lesions were always associated with the lowest scores. Minimal and moderate basal ganglia lesions had intermediate scores. These findings are in agreement with the only 2 published studies that have previously correlated the patterns of lesions on MRI with the severity of neurologic impairment at follow-up. Both studies also reported that severe basal ganglia lesions, diffuse brain injuries, or both were associated with the most severe outcome.[3,11] Kuenzle et al[3] developed an optimality score that provided important additional information on the magnitude of the functional impairment. The main difference between their optimality score and ours is that whereas their definition of optimal or suboptimal was mainly based on empirical criteria, we based our criteria of optimality on the frequency distribution of the neurologic findings in a low-risk population. Barkovich et al[11] did not provide details of the neurologic examination.

The use of the optimality score gave additional prognostic information on

the severity of the functional motor outcome. This information is particularly valuable considering that at 1 year, it is often difficult to predict the severity of motor function in infants with mild or moderate neurologic problems. Neonatal electroencephalography, evoked potentials, and MRI can identify the infants who will have an abnormal outcome,[6,12-17] but the severity of the functional impairment cannot always be predicted. This is particularly true in infants with relatively less severe lesions. Although neonatal MRI can identify early the infants who will have cerebral palsy, the neurologic examination at 9 to 14 months can provide additional information on the severity of the functional motor impairment and distinguish the infants who will walk from those who will only sit or not even acquire the sitting posture. Scores <40 were always associated with severely limited self-mobility and unsupported sitting both at 2 and 4 years. Scores >40 but <67 were always associated with the ability to sit independently at 2 years and with some form of self-mobility by 4 years. In contrast, optimal scores or suboptimal scores that were >67 at 1 year were always associated with the ability to walk independently at 2 years and with walking without restrictions at 4 years. It is interesting, however, that 3 of the 36 children who were able to walk without restrictions in the community at 4 years had an abnormal gait, associated with a mild hemiplegia in 1 of the 3 and with mild movement disorders in the other 2, which suggested that mild neurologic abnormalities can also occur in the absence of widespread lesions or severe abnormalities in the first year of life. Further studies evaluating follow-up at school age are required to evaluate whether these minor neurologic abnormalities are related to any difficulty on the playground, in sports, or in everyday life.

In conclusion, our results suggest that the neurologic examination performed between 9 and 14 months can predict locomotor outcome in infants with HIE. Because the neurologic examination is easily performed and accessible to all clinicians, this could provide a valuable tool, especially in places where other techniques such as MRI or neurophysiology are not available. Further studies will be necessary to evaluate whether this examination will have similarly good predictive value in infants examined at an earlier age.

REFERENCES

1. Levene MI. The asphyxiated newborn infant. In: Levene MI, Lilford RJ, editors. Fetal and neonatal neurology and neurosurgery. Edinburgh: Churchill Livingstone; 1995. p. 405-25.
2. Volpe JJ. Hypoxic-ischaemic encephalopathy. In: Volpe JJ, editor. Neurology of the newborn. Philadelphia: WB Saunders; 1995. p. 314-69.
3. Kuenzle C, Baenziger O, Martin E, Thun-Hohenstein L, Steinlin M, Good M, et al. Prognostic value of early MR imaging in term infants with severe perinatal asphyxia. Neuropaediatrics 1994;4:191-200.
4. Rutherford MA, Pennock JM, Schwieso J, Cowan F, Dubowitz LMS. Hypoxic-ischaemic encephalopathy: early and late magnetic resonance imaging findings in relation to outcome. Arch Dis Child 1996;75:F145-51.
5. Samat HB, Samat MS. Neonatal encephalopathy following fetal distress: a clinical and electrophysical study. Arch Neurol 1976;33:696-705.
6. Rutherford MA, Pennock J, Counsell SJ, Mercuri E, Cowan FM, Dubowitz LMS, et al. Abnormal MRI signal in the internal capsule predicts poor neurodevelopmental outcome in infants with HIE. Pediatrics 1998;102:323-8.
7. Rutherford MA, Pennock JM, Schwieso YE, Cowan FM, Dubowitz LM. Hypoxic ischaemic encephalopathy: early magnetic resonance imaging findings and their evolution. Neuropediatrics 1995;26:183-91.
8. Haataja L, Mercuri E, Regev R, Cowan F, Rutherford M, Dubowitz V, et al. Optimality score for the neurologic examination of the infant at 12 and 18 months of age. J Pediatr 1999;135:153-61.
9. Hagberg B, Hagberg G, Olow I. The changing panorama of cerebral palsy in Sweden 1954-70. I. Analysis of general changes. Acta Paediatr 1975;64:187-92.
10. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. Dev Med Child Neurol 1997;39:214-23.
11. Barkovich AJ, Hajnal BL, Vigneron D, Sola A, Partridge JC, Allen F, et al. Prediction of neuromotor outcome in perinatal asphyxia: evaluation of MRI scoring systems. Am J Neuroradiol 1998;19:143-9.
12. De Vries LS, Pierrat V, Eken P, Minami T, Daniels H, Casaer P. Prognostic value of early somatosensory evoked potentials for adverse outcome in full-term infants with birth asphyxia. Brain Dev 1991;13:320-5.
13. Eken P, Toet MC, Groenendaal F, De Vries LS. Predictive value of early neuroimaging, pulsed Doppler and neurophysiology in full term infants with hypoxic-ischaemic encephalopathy. Arch Dis Child 1995;73:F73-80.
14. Hellström-Westas L, Rosén I, Svenningsen NW. Predictive value of early continuous amplitude integrated EEG recordings on outcome after severe birth asphyxia in full term infants. Arch Dis Child 1995;72:F34-38.
15. Shevell MI, Majnemer A, Miller SP. Neonatal neurologic prognostication: the asphyxiated term newborn. Pediatr Neurol 1999;21:776-84.
16. Taylor MJ, Murphy WJ, Whyte HE. Prognostic reliability of SEP and VEP of asphyxiated term infants. Dev Med Child Neurol 1992;34:507-15.
17. Wertheim D, Mercuri E, Faundez JC, Rutherford M, Acolet D, Dubowitz L. Prognostic value of continuous electroencephalographic recording in full term infants with hypoxic ischemic encephalopathy. Arch Dis Child 1994;71:F97-102.