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REGULAR ARTICLE

Early prediction of neurological outcome by term neurological examination and cranial ultrasound in very preterm infants

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Abstract

Aim: To assess the value of term neurological examination and cranial ultrasound in the early prediction of neurological outcome at 12 months corrected age in a cohort of very preterm infants.
Methods: A cohort of 102 preterm infants born at <32 weeks gestation or with a birth weight of <1500 g were assessed using the Hammersmith Term Neurological Examination. They underwent cranial ultrasound examinations according to local guidelines. The Hammersmith Infant Neurological Examination was performed at 12 months corrected age. Scores for the term examinations were compared with scores derived from healthy infants born at term and with scores from low-risk preterm infants at term equivalent age. Term neurological scores and cranial ultrasound findings were compared in the prediction of 12-month neurological outcome.
Results: Seventy-eight (76.5%) preterm infants had suboptimal total neurological scores at term when compared to healthy infants born at term. However, most went on to have optimal neurological scores at 12 months corrected age. When our cohort was compared with low-risk preterm infants at term equivalent age only 14 (13.7%) scored outside the normal range. Neither system of scoring predicted neurological outcome at 12 months corrected age as reliably as cranial ultrasound (sensitivity 0.83, specificity 0.87).

Conclusion: Neurological examination of preterm babies at term may be unreliable in the prediction of neurological outcome at 12 months corrected age. For early prediction of neurological outcome cranial ultrasound examination was found to be more reliable.

INTRODUCTION

At follow-up approximately 8–10% of very low birth weight babies will have cerebral palsy (1). In this study we aimed to show how early neurological and cranial ultrasound examinations might be used to predict neurological outcome at 12 months corrected age. Such information would be useful in targeting interventional therapies.

The Hammersmith Term Neurological Examination was originally developed by Dubowitz and Dubowitz in 1981. The assessment tool has been updated and standardized in healthy newborn infants and optimal scores have been assigned to each part of the neurological examination (2). However, when applying the assessment tool to preterm infants with normal cranial ultrasounds, the range of scores for each test item was found to be far wider than for healthy term infants (3). Recently scores for the Hammersmith Term Neurological Examination have been published for a cohort of low-risk preterm infants at term equivalent age (4). Infants with major ultrasound abnormalities were found to have more test items scoring outside the normal range.

Abbreviations
PPV, positive predictive value; NPV, negative predictive value.

This study aimed to test the use of the Hammersmith Term Neurological Examination in assessing a cohort of unselected preterm babies and in predicting their neurological outcome at 12 months corrected age. As cranial ultrasound is known to be a good predictor of motor outcome in preterm infants (5) we also aimed to compare the predictive value of cranial ultrasound with term neurological examination.

PATIENTS AND METHODS

The study cohort included preterm infants born at <32 weeks gestation or with a birth weight of <1500 g and receiving care within the first 24 h after birth in a tertiary neonatal intensive care unit in Brighton, UK between October 2002 and September 2004. The infants were enrolled to a neurodevelopmental follow-up programme including neurological and cranial ultrasound examinations according to local guidelines.

Hammersmith term neurological examination

We examined infants as close as possible to 40 weeks postmenstrual age. The examination was undertaken by either PA or CM according to a standard proforma (6). Each item of the examination (tone and posture, tone patterns,

movements, reflexes, abnormal signs and orientation and behaviour) was scored separately and then added together to give a total score. Scores were compared with those derived from a cohort of 224 healthy, term newborns with suboptimal scores defined as those lying below the fifth centile (6). We also compared term neurological scores from our cohort with the range of scores derived from 157 low-risk preterm infants described in the study by Ricci et al. (4). We recorded scores lying outside the 90th centile for the cohort as suboptimal.

Our standard of newborn examination was confirmed by assessing 12 healthy, newborn term infants and comparing our scores with those obtained by Mercuri and Dubowitz (6). Intra- and inter-observer reliability for the examination have been published (6).

Hammersmith infant neurological examination

Infants were assessed using the Hammersmith Infant Neurological Examination by either PA or YK at 12 months corrected age. Each item of the examination (function of cranial nerves, tone, posture, movements, reflexes, motor milestones and behaviour) was scored separately and then added together to give a total score. Scores were compared with optimal scores derived from a cohort of 249 healthy 12 and 18-month-old infants born at term (7). Suboptimal scores were defined as those lying below the fifth centile for the study cohort.

Cranial ultrasound examination

Infants underwent cranial ultrasound examination according to recommended standards (8) at <3 days and again at 1, 2 and 3 weeks and again at term or discharge. Scans were reviewed by HR who was blinded to the neurological examination scores. Ultrasound scans were classified as low, intermediate or high risk according to degree of abnormality.

Low risk

No abnormality or single lesions such as germinal layer haemorrhage, intraventricular haemorrhage (with no ventricular dilatation), parenchymal echodensity or flare not proceeding to cyst formation, ventricular dilatation.

Intermediate risk

Two or more of the above, or hydrocephalus without atrophy.

High risk

Loss of brain tissue including porencephalic cysts following a haemorrhagic parenchymal infarction, cystic periventricular leukomalacia, hydrocephalus with porencephalic cysts or general atrophy.

Data analysis

The Microsoft Excel macro DAGStat by Kraemer (1992) was used to calculate predictive values for the Hammersmith Term Neurological Examination and cranial ultrasound examinations. Guidelines for reporting observational studies (STROBE) were used to aid manuscript preparation (9).

Table 1 Details of study cohort

	Gestational age (weeks) range (mean)	Birth weight (g) range (mean)
Cohort at birth (n = 130)	23–34 (28.3)	435–2000 (1153)
Deaths before term (n = 17)	23–30 (24.7)	435–1505 (769)
Total eligible for study at term (n = 113)	23–34 (28.8)	585–2000 (1210)
Infants assessed at term (n = 102)	24–34 (28.9)	585–2000 (1212)
Infants not assessed at term (n = 11)	27–31 (29.3)	630–1900 (1264)
Infants assessed at 12 months (n = 91)	23–34 (29.0)	585–2000 (1215)
Infants not assessed at 12 months (n = 22)	24–31 (28.7)	620–1855 (1191)
Infants assessed at term and 12 months (n = 82)	23–34 (28.9)	585–2000 (1210)
Infants not assessed at either term or 12 months (n = 31)	23–31 (28.8)	620–1900 (1210)

RESULTS

Our cohort included 130 preterm babies born between October 2002 and September 2004 at <32 weeks gestation or with a birth weight of <1500 g. Seventeen babies did not survive to term, leaving a study cohort of 113. Eleven infants at term and 22 infants at 12 months were lost to follow-up as they had either moved out of the area or failed to attend for assessments. Those not assessed did not differ in gestational age or birth weight when compared with those that were assessed (Table 1). The ratio of low and intermediate risk cranial ultrasound examinations were similar in the follow-up and lost to follow-up groups. There were no high-risk cranial ultrasounds in those lost to follow-up (Table 2).

Hammersmith term neurological examination

One hundred and two preterm infants were examined at 37–46 (mean 40.3) weeks postmenstrual age. All 11 babies that missed their term examination have had normal one or two year neurodevelopmental assessments. Approximately

Table 2 Details of study cohort

	Cranial ultrasound findings		
	Low risk	Intermediate	High risk
Infants assessed at term (n = 102)	79	18	5
Infants not assessed at term (n = 11)	9	2	0
Infants assessed at 12 months (n = 91)	69	17	5
Infants not assessed at 12 months (n = 22)	19	3	0

Table 3 Scores for term neurology examination

Test item and range of scores	Comparison with scores from healthy term infants: Number of babies (total = 102) n	Comparison with scores from healthy term infants: Babies with suboptimal scores n (%)	Comparison with scores from low-risk preterm infants at term equivalent: Number of babies (total = 102) n	Comparison with scores from low-risk preterm infants at term equivalent: Babies with suboptimal scores n (%)
Posture and tone score (8 or below = suboptimal)				
10–9	42	60 (59)	88	14 (13.7)
8–5	45		14	
<5	15		0	
Tone pattern score (4 or below = suboptimal)				
5	57	45 (44)	97	5 (4.9)
4	34		5	
<4	11		0	
Movement score (2 or below = suboptimal)				
3	54	48 (47)	96	6 (5.8)
<3	48		6	
Orientation and behaviour score (5 or below = suboptimal)				
6–7	79	23 (22.5)	94	8 (7.8)
5	9		7	
<5	14		1	
Total score (30 or below = suboptimal)				
34–30.5	24	78 (76.5)	88	14 (13.7)
30–25	54		14	
<25	24		0	

half of the cohort at term scored below the optimal scores for posture, tone and movements when compared to healthy term infants (Table 3). The orientation and behaviour score, which includes assessment of visual function scored rather better, being suboptimal in 23% of infants. We recognized a common pattern of neurological findings in our preterm cohort at term. They tended to be visually alert but their posture was less flexed than infants born at term. Flexion was less on traction and recoil tests especially in the upper limbs. The balance of neck flexor and extensor muscles seen in normal term babies was not achieved in preterm babies at term as contraction of neck flexor muscles seemed to be weaker. Axial tone was also reduced on ventral suspension. When we compared our cohort with scores from low-risk preterm infants at term only 13.7% or less scored outside the normal range (as defined by Ricci et al.) for all sections of the neurological examination (Table 3).

Our assessment of 12 normal term infants on day one or two after birth and at 39 to 40 (mean 40) weeks post-menstrual age using the Hammersmith Term Neurological Examination showed scores in keeping with optimal scores derived by Dubowitz and Mercuri (6).

Hammersmith infant neurological examination

Ninety-one of the original 113 infants were examined at one year. The age of examination was between 45 and 71 (mean 54.2) weeks corrected age. Thirteen of the 22 infants not assessed at one year went on to have normal two-year assessments. Nine of the 22 were lost to follow-up and no information on outcome was obtained. Suboptimal scores in tone, posture and movement were found in 8 to 10% of infants at one year (Table 4). Visual and auditory deficits accounted for the higher percentage of infants with suboptimal total scores in the cranial nerve test item.

Table 4 Scores for 12 month neurology examination

Test item and range of scores	Number of infants (total = 91) n	Infants with suboptimal scores n (%)
Posture score (15 or below = suboptimal)		
18–16	83	8 (8.8)
15–10	7	
<10	1	
Tone Score (21 or below = suboptimal)		
24–22	82	9 (9.8)
21–15	6	
<15	3	
Movement Score (5 or below = suboptimal)		
6	84	7 (7.6)
<6	7	
Cranial nerve scores (14 or below = suboptimal)		
15	73	18 (19.7)
14–12	15	
<12	3	
Total score (72 or below = suboptimal)		
78–73	77	14 (15.3)
72–70	4	
<70	10	

Table 5 Prediction of 12 month neurology scores by term neurology scores (study cohort compared at term with scores derived from healthy term infants)

Term scores versus one year scores	Sensitivity	Specificity	PPV	NPV
Term total score versus 12 month total score	0.19	0.89	0.86	0.24
Term posture and tone score versus 12 month tone score	0.14	0.94	0.78	0.42
Term posture and tone score versus 12 month posture score	0.18	1.0	0.82	0.45
Term posture and tone score versus 12 month total score	0.24	0.85	0.71	0.43
Term tone pattern score versus 12 month tone score	0.11	0.89	0.44	0.55
Term tone pattern score versus 12 month total score	0.16	0.80	0.40	0.54
Term movement score versus 12 month movement score	0.11	0.95	0.71	0.47

Table 6 Prediction of 12 month neurology scores by term neurology scores (study cohort compared at term with scores derived from low-risk preterm infants at term equivalent age)

Term scores versus one year scores	Sensitivity	Specificity	PPV	NPV
Term total score versus 12 month total score	0.50	0.89	0.43	0.91
Term posture and tone score versus 12 month tone score	0.17	0.90	0.22	0.86
Term posture and tone score versus 12 month posture score	0.15	0.9	0.22	0.85
Term posture and tone score versus 12 month total score	0.25	0.83	0.20	0.87
Term tone pattern score versus 12 month tone score	0.20	0.88	0.10	0.95
Term tone pattern score versus 12 month total score	0.25	0.82	0.07	0.96
Term movement score versus 12 month movement score	0.17	0.92	0.14	0.93

Prediction of outcome by term examination

Eighty-two preterm infants underwent both term and 12-month neurological examinations. When our cohort was compared at term with healthy, term infants 64 from 82 were found to have suboptimal total neurological scores. However, 52 of the 64 went on to have optimal total scores by 12 months (Figure S1a). It was not possible to identify those infants most likely to normalize. We found that some of those with the most suboptimal scores at term were capable of neurological recovery by the 12-month assessment. Suboptimal term scores were poorly predictive of suboptimal scores at 12 months (sensitivity 0.11–0.24, NPV 0.35–0.55) (Table 5). Eighteen infants scored optimally at term with all but two having optimal scores at 12 months. For all items of neurological examination, an optimal score at term was predictive of an optimal score at one year (specificity 0.8–1.0, PPV 0.40–0.86).

Seventy of our 82 babies scored within the normal range at term when compared with low-risk preterm infants at term equivalent age. Sixty-three went on to have optimal scores and seven suboptimal scores at 12 months corrected age (Figure S1b). Of the 12 infants with suboptimal scores at term, six had optimal and six had suboptimal scores at 12 months. Table 6, shows values for sensitivity, specificity, PPV and NPV for prediction of 12 month neurological outcome using term scores from Ricci's low-risk preterm cohort.

Cranial ultrasound examination

All infants underwent cranial ultrasound examinations within the first three days of life and near to term age. Table 7, shows the distribution of low, intermediate and high risk cranial ultrasounds amongst the cohort. For the infants that underwent term and 12 month assessments Table 8 shows neurology scores according to ultrasound category. There is a trend for lower neurology scores in infants with high-risk ultrasound scans.

Prediction of outcome by cranial ultrasound examination

Cranial ultrasound was evaluated as a predictor of 12-month neurological outcome in the 82 infants that had undergone both term and 12-month neurological assessments. Low risk cranial ultrasound was predictive of optimal neurological scores at 12 months (specificity 0.87, NPV 0.98). Nevertheless, eight out of 62 infants with low risk cranial ultrasounds went on to have suboptimal total neurology scores at 12 months. Although numbers were low, high risk cranial ultrasound seemed to be predictive of suboptimal 12 month neurology scores (sensitivity 0.83). For the 5 infants with high risk scans, total neurology scores were 68, 63, 59, 53 and 29, well below the optimal score of $\geq$ 73. Figures S2a and S2b show the neurological progression from term to 12 months for infants with low, intermediate and high-risk cranial ultrasound examinations.

DISCUSSION

Standardized newborn neurological examinations have been used to predict outcome in term babies following perinatal hypoxic-ischaemic brain injury (10) and to predict motor function in preterm babies when undertaken at 12 months of age (11). However, in this study neurological examination at term has proven unreliable in the prediction of neurological outcome at 12 months in a cohort of preterm babies.

When our cohort was compared at term with healthy, term infants, approximately half had suboptimal neurological scores. These suboptimal scores rarely equated to poor neurological outcome at 12 months although it is still possible that they might herald future neurodevelopmental problems that we have not yet identified in this study. Neurodevelopmental follow-up of our cohort to school age is on-going.

The high frequency of suboptimal neurology scores described above may have resulted from poor examination technique. However, our assessment of 12 normal term

babies gave us confidence that our basic examination techniques were at least adequate. For both term and 12-month examinations, we kept examiner numbers to two in an attempt to reduce inter-observer variability. Our infants were examined at similar corrected ages to the cohorts with which they were compared.

We believe that physiological rather than pathological reasons explain the majority of suboptimal term neurology scores we recorded. As for the cohort described by Mercuri et al. we found that preterm infants examined at term equivalent age have a wider range of neurology scores than term infants examined in the first days after birth (3). This may be the result of lying relatively flat and having had splints for drips all of which might interfere with the normal flexed posture that would have been maintained in-utero. Even infants born at term show a physiological reduction in limb flexor tone when examined six weeks after birth (12). Delayed maturation of subcorticospinal pathways in the preterm infant by term age may also be an important factor in determining neurological scores. From 28 to 40 weeks gestation, passive tone and flexion of the limbs increases progressively in a caudocephalic direction as medial subcorticospinal pathways myelinate (13). The lower limbs assume flexion first, then the upper limbs later at approximately 36 weeks gestation. Neck flexor muscles only become active after 36 weeks as the lateral subcorticospinal pathways begin to mature. It is possible that the normal process of maturation is delayed in the preterm infant by a combination of environmental factors, poor nutrition and neonatal illness such as sepsis.

Many of the infants in this study have been reported as having 'suboptimal' neurology at term equivalent age. In reality, we have probably described a typical pattern of neurology for the preterm baby at term that results from a combination of postural disturbance and maturational delay.

We did not see the extended postures, arm flexion and leg extension described in some preterm infants (6,13). This might be due to improved postnatal positional care, reduction in use of mechanical ventilation or less white matter brain damage related to improving neonatal care and use of antenatal steroids. All infants in this study were included into the neonatal individualized developmental care and assessment programme.

We hoped that scoring our cohort against the preterm cohort described by Ricci et al. would prove more useful in the prediction of 12-month neurological outcome. However, the normal ranges derived by Ricci et al. for each neurological item within the Hammersmith Term Examination were very wide. This resulted in many of our cohort scoring within the normal range including some that went on to have abnormal neurological outcomes. For the same reason we did not demonstrate that infants with high-risk cranial ultrasounds necessarily had term neurological scores out of the normal range.

Table 7 Cranial ultrasound findings according to risk category

Cranial ultrasound category	Number of babies (n = 113)
Low risk	88 (78%)
Intermediate risk	20 (18%)
High risk	5 (4%)

Table 8 Term and 12 month neurology scores according to cranial ultrasound

Cranial ultrasound category (n = 82)	Term score when compared with healthy term infants (mean)	Term score when compared with low-risk preterm infants (mean)	12 month neurology score (mean)
Low risk	17–33 (27.4)	29–34 (32.5)	51–78 (75.4)
Intermediate risk	15–32 (26.5)	30–34 (32.2)	70–78 (76.5)
High risk	20–33 (24.6)	28–34 (30.4)	29–68 (54.4)

Within this study an optimal, term neurological examination in preterm infants has proven reassuringly predictive of normal neurological outcome at 12 months. However, use of term neurological assessments to identify preterm babies at risk of poor neurological outcome has proven unreliable in our hands. We found that a basic system of cranial ultrasound examination is more useful as an early predictor of motor deficit. However, we recommend a degree of caution as we recognized that some infants with low risk cranial ultrasounds went on to develop suboptimal neurology at 12 months.

This study has demonstrated limitations of early neurological examination of preterm babies at term. Sequential examinations or a single examination at 3 months corrected age may be more meaningful. By three months, corrected age effects of postural disruption and maturational delay should have passed and development of genuinely abnormal signs should be more obvious. To help improve early prediction of outcome we have added movement studies according to Prechtl to our early follow-up schedule (14).

CONFLICT OF INTEREST AND FUNDING

The named authors have no financial disclosures or conflicts of interest that might bias this study.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1a Progression of total neurological scores from term to 12 months (study cohort compared at term with scores derived from healthy term infants).
Figure S1b Progression of total neurological scores from term to 12 months (study cohort compared at term with scores derived from low-risk preterm infants at term equivalent age).
Figure S2a Neurological outcome according to cranial ultrasound risk category (study cohort compared at term with scores derived from healthy term infants).
Figure S2b Neurological outcome according to cranial ultrasound risk category (study cohort compared at term with scores derived from low-risk preterm infants at term equivalent age).

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