Early Human Development 85 (2009) 405–408

Contents lists available at ScienceDirect

Early Human Development

journal homepage: www.elsevier.com/locate/earlhumdev

Prognostic value of a scorable neurological examination from 3 to 12 months post-term age in very preterm infants: A longitudinal study

Domenico M.M. Romeo [a], Matteo Cioni [a,b], Mariacristina Scoto [a], Alessandra Pizzardi [a], Mario G. Romeo [c], Andrea Guzzetta [d,*]

[a] Division of Child Neurology and Psychiatry, Dept of Paediatrics, University of Catania, Italy
[b] Chair of Physical Medicine & Rehabilitation, School of Medicine, University of Catania, Italy
[c] Neonatal Intensive Care Unit, Dept of Paediatrics, University of Catania, Italy
[d] Dept of Developmental Neuroscience, Stella Maris Scientific Institute, Pisa, Italy

ARTICLE INFO

Article history:
Received 2 October 2008
Received in revised form 8 December 2008
Accepted 12 January 2009

Keywords:
Hammersmith Infant Neurological Examination
Prediction
Premature
Motor outcome

ABSTRACT

Aims and study design: The Hammersmith Infant Neurological Examination proved effective in predicting locomotor function in very preterm infants after 9 months of age. We performed the examination in a cohort of 103 very preterm infants (gestational age below 32 weeks) as early as 3 months' post-term age, and longitudinally at 6, 9 and 12 months. Our aim was to establish the frequency distribution of the optimality scores at each age period, to explore the predictive value of the examination from 3 months onwards as to developmental outcome and locomotor function at 2 years, and to explore its longitudinal consistency.
Results: The results showed that this standardized neurological examination can be performed in preterm infants as early as 3 months' post-term age to predict motor outcome at 2 years, and that its high predictive value is consistent across the first year of life due to an effective combination of different items for each age period.
Conclusions: We confirm the high predictive value of this neurological examination in very preterm infants after 9 months and extend it to the assessments performed as early as 3 months post-term. This is of great relevance as in very preterm infants early prediction of motor function is essential for a prompt planning of therapeutic interventions.

1. Introduction

In the last three decades, advances in perinatal care have led to better survival of preterm infants [1,2]. However, there is still a significant proportion of very preterm infants, ranging from 10 to 40%, who may show neurological and developmental disabilities [2]. In these infants, serial neurological examinations are generally performed during the first year of life in order to identify early indicators of abnormal neurological development.

About ten years ago, a simple and scorable neurological examination for infants between 2 and 24 months of age was developed in the Paediatric Department of the Hammersmith Hospital in London (the Infant Neurological Examination—HINE) [3]. It was standardized in a low-risk population of term infants assessed between 12 and 18 months of age and an optimality score was developed on the basis of the frequency distribution of the findings for each item [3]. The prognostic power of the HINE optimality score was recently explored in a population of very preterm infants between 9 and 18 months of age [4]. Using an optimality score with an adjusted cut-off value, a very high sensitivity and specificity to predict walking at 2 years were shown. In that study however, the age of test varied greatly from 6 to 16 months corrected age and subjects only had single examinations that were pooled together for statistical analysis. Thus, little is known as to prognostic value of HINE and possible use of different cut-offs at different time periods during the first year of life. In the present study we longitudinally performed the HINE at 3, 6, 9 and 12 months corrected age, in a large population of preterm infants below 32 weeks' gestation. Our specific aims were to evaluate (1) the range of optimality scores in these infants, (2) the correlation between the scores at the HINE and term US findings, and (3) the predictive value of the examination for each one of the four time-windows as to developmental outcome and locomotor function at two years.

2. Subjects and methods

All the infants included in the present study were part of a follow-up project carried out at the Neonatal Intensive Care Unit of the Department of Paediatrics of the University of Catania between January 2002 and December 2005. All subjects with a gestational age

Abbreviations: HINE, Hammersmith Infant Neurological Examination; US, ultrasounds; SD, standard deviation; ROC, receiver operating characteristic.

* Corresponding author. Department of Developmental Neuroscience, Stella Maris Scientific Institute, Via dei Giacinti, 2 I-56018 Calambrone, Pisa, Italy. Tel.: +39 050 886323; fax: +39 050 32214, +39 050 886247.
E-mail address: a.guzzetta@inpe.unipi.it (A. Guzzetta).

0378-3782/$ – see front matter © 2009 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.earlhumdev.2009.01.004

below 32 weeks were prospectively enrolled in the study. Exclusion criteria were the presence of congenital anomalies or the transfer to another hospital during the neonatal period. As part of the protocol, HINE evaluations were performed at 3, 6, 9 and 12 corrected months and a neurodevelopmental assessment was obtained at two years of corrected age. The study was approved by the Ethical Committee of our Institution, and informed written parental consent was obtained in all cases.

2.1. Cranial ultrasonography

A cranial ultrasonogram (US) was performed at least once within the first week of life, then every week until discharge and once around term age. Cranial US were classified as follows i) no abnormal signal or transient flare (periventricular echodensity lasting less than 14 days) or isolated intraventricular haemorrhage grade I according to Volpe [5]; ii) persistent flare (bilateral periventricular echodensity persisting more than 14 days) without haemorrhage; iii) isolated ventricular dilation; iv) intraventricular haemorrhage grade II or III according to Volpe [5]; v) cystic periventricular leukomalacia with or without haemorrhage or unilateral intraparenchymal echodensity.

2.2. Neurological examination

The HINE [3] was used for the assessment of all infants enrolled in this study. This is a simple and scorable method for assessing infants between 2 and 24 months of age, including items for cranial nerve, posture, movements, tone and reflexes (Table 1). It has been standardized in a low-risk population at 12 and 18 months and can be scored with the use of an optimality score, defining as optimal all the scores found in at least 90% of the normal population [3]. The overall score ranges from a minimum of 0 to a maximum of 78.

2.3. Outcome

Outcome was evaluated at 24 months.

Development was assessed using the Clinical Adaptive Test/Clinical, Linguistic and Auditory Milestone Scale (CAT–CLAMS) [6]. The CAT–CLAMS is used to assess development from 1 to 36 months; the CLAMS items measure receptive and expressive language development while the CAT items measure visual-motor problem-solving skills. This test was shown to highly correlate with the Bayley Scales of Infant Development [7,8]. As the test takes only 10 to 15 min to administer, it was preferred in this large follow-up program to other developmental scales.

Maximal locomotor function was graded according to a simplified version of the classification suggested by Palisano et al. [9] and already used in previous studies [4,10].

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

Table 1
Items included in the Hammersmith Infant Neurologic Examination.

Neurologic examination
Assessment of cranial nerve function
Facial appearance, eye appearance, auditory response and visual response, sucking/swallowing
Posture
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

2.4. Statistical analysis

Anthropometric variables (weight and gestational age) are reported as mean and standard deviation (SD). Optimality scores of HINE are reported as mean and SD for each time period. Changes of HINE scores across the four examinations were explored by means of repeated measures ANOVA and paired sample *t* test corrected for Bonferroni. Optimality scores were correlated to the CAT–CLAMS quotient and to the gestational age at birth using the Pearson's correlation coefficient. The level of significance was set at 0.05.

The receiver operating characteristic curve (ROC) analysis was used to measure the power of HINE at different age periods to predict locomotor outcome (independent walking) [11]. ROC curve analysis provides a powerful means of assessing a test's predictive power, with the advantage that the analysis does not depend on the threshold value selected as each point on the plot represents a sensitivity/specificity pair corresponding to a particular cut-off value. Sensitivity and specificity were also calculated at each time period using the best cut-off value.

3. Results

3.1. Characteristics of the population

A total of 189 preterm infants born before 32 weeks' gestation were enrolled in the study. Forty-two infants died, 24 missed one of the appointments or were lost at follow-up and 20 fulfilled our exclusion criteria because they had a diagnosis of genetic disorder (8) or were transferred during the neonatal period (12). The final cohort consisted of 103 infants (56 males, 47 females). Mean GA was 29.2 weeks (range 25–31; SD 2.0) and mean birth-weight 1333.5 grams (range 630–2260; SD 394).

3.2. Infant neurological examination

All the subjects had four examinations, at 3, 6, 9 and 12 months corrected age (+/−2 weeks). Mean optimality score was 56.1 at 3 months corrected age (SD 10.2), 59.5 at 6 months (SD 10.2), 63.1 at 9 months (SD 10.1) and 64.9 at 12 months (SD 10.4). The increase in HINE optimality scores with time was significant both globally (repeated measures ANOVA) and for paired consecutive assessments (paired sample *t* test corrected for Bonferroni).

According to normative data, at 12 months the global score was optimal ($\geq$73) in 38 infants and suboptimal ($<$73) in the remaining 65, but 19 of them scored $>$67.

3.3. Cranial ultrasonography

Twenty-nine infants had normal ultrasounds, transient flares or intraventricular haemorrhage grade 1; 46 infants had persistent flares without haemorrhage; 18 infants had isolated ventricular dilation; 8 infants had intraventricular haemorrhage grade II or III; 2 infants had cystic periventricular leukomalacia.

3.4. Outcome

At two years corrected age, 88 of the 103 children were able to walk independently, and 4 had a mild hemiplegia; 5 were able to sit but not to walk and the remaining 10 showed severely limited self-mobility and were unable to sit unsupported. Mean value at the CAT–CLAMS was 72.3 (SD = 19.9; range = 27.50–100). At the CAT subscale the mean

Table 2
Areas under ROC curve for each time period calculated in relation to locomotor outcome.

HINE	Independent walking	
	Area under ROC	Standard error
3 months	0.980	0.020
6 months	0.983	0.017
9 months	0.962	0.029
12 months	0.975	0.017

Table 3
Sensitivity and specificity for independent walking at two years.

	3 months (cut-off 50)	6 months (cut-off 52)	9 months (cut-off 59)	12 months (cut-off 60)
Sensitivity (%)	93	93	93	93
Specificity (%)	100	100	95	95

value was 72.6 (SD = 20.1; range = 25–100); at the CLAMS subscale the mean value was 72 (SD = 20.2; range = 30–100).

3.5. Correlation of the optimality scores with gestational age and age at test

There was no significant correlation between gestational age at birth and the neurological optimality score at any of the four assessments ($r = 0.035$, 0.053; 0.01 and 0.01 at 3, 6, 9 and 12 months respectively).

3.6. HINE and outcome

The correlation between CAT–CLAMS values at 24 months and HINE scores was significant at all age periods ($r = 0.75$ with $p < 0.001$ at 3 months; $r = 0.78$ with $p < 0.001$ at 6 months; $r = 0.76$ with $p < 0.001$ at 9 months; $r = 0.81$ with $p < 0.001$ at 12 months).

At all age periods HINE showed a very high predictive power, as expressed by the area under the ROC curve that was always above 0.96 as to locomotor outcome (Table 2). The high predictive power of the examination was also confirmed when directly calculating sensitivity and specificity. When using adjusted cut-off values, specific for each age period, a sensitivity of 93% and a specificity of 95% or above were found as to locomotor outcome (Table 3).

ROC curve analysis was also applied to the single items in order to identify those with the highest and the lowest prediction for each age period (Table 4). A few items were consistently present among the most predictive ones across the four examinations, such as movement quality and quantity and lateral tilting, while only one item, visual response, was consistently present among the least predictive. Three items changed category across the four examinations: popliteal angle and forward parachute were poorly predictive at 3 and 6 months and very predictive at 9 and 12 months; scarf sign was very predictive at 3 and 6 months and poorly predictive later on.

When considering examinations longitudinally, the assessment showed to be very consistent in classifying children results as optimal or suboptimal according to the age specific cut-off value. In all children but four the assessment was consistent across the four examinations, being either always optimal ($n = 85$) or always suboptimal ($n = 14$). In the four children with inconsistent results, score was optimal in the first two examinations and became suboptimal in the last two; all four were able to walk independently at two years of age, but showed soft signs of motor impairment (tremors, clumsiness, etc).

3.7. HINE and cranial ultrasonography

All 29 infants with normal ultrasounds, transient flares or intraventricular haemorrhage grade 1 had scores above the cut-off values at all age periods. Of the 18 infants with isolated ventricular dilatation, a proportion ranging from 68 to 95% had scores above the cut-off value and a proportion ranging from 5 to 32% had scores below the cut-off value, according to the different age periods. Of the 46 infants with persistent flares without haemorrhage, 80% had scores above and 20% below the cut-off values, at all age periods. Of the 8 infants with intraventricular haemorrhage grade II or III, 75% had scores above and 25% below the cut-off value, at all age periods. Both infants with cystic periventricular leukomalacia had scores below the cut-off values at all age periods.

4. Discussion

The Hammersmith Infant Neurological Examination was recently shown to be reliable in predicting motor outcome at 2 years of age in very preterm infants assessed between 9 and 18 months of age [4]. In the present study we expand former findings in at least three ways: we investigated the predictive value of the HINE from 3 months onwards, much earlier than previously done; we obtained reference cut-off values for the optimality scores at each age period; we assessed the longitudinal consistency of the data, as all our infants performed all four examinations.

The first important result of the present study is the demonstration in our cohort of very preterm infants of a high correlation, as early as at 3 months onwards, between the HINE and the developmental quotient at 24 months. This was true for both subscales of the developmental test used, the one assessing receptive and expressive language development and the one measuring visual–motor problem-solving skills. A similar finding was already reported by our group in a larger cohort of infants at neurological risk of different gestational ages, partially overlapping with the population of the present study

Table 4
Most and least predictive items according to ROC curve analysis.

	3 months	6 months	9 months	12 months
Most predictive	Movement quantity	Movement quantity	Movement quantity	Movement quantity
	Movement quality	Movement quality	Movement quality	Movement quality
	Feet posture	Lateral tilting	**Forward parachute**	**Forward parachute**
	Arm pronation/supination	Arm pronation/supination	Vertical suspension	Vertical suspension
	Ventral suspension	**Scarf sign**	Lateral tilting	**Popliteal angle**
	Scarf sign	Feet posture	Ventral suspension	Arm protection
	Lateral tilting	Ventral suspension	**Popliteal angle**	Lateral tilting
Least predictive	Arm protection	Head posture in sitting	Eye appearance	Arm traction
	Visual response	Visual response	**Scarf sign**	Visual response
	Popliteal angle	**Popliteal angle**	Passive shoulder elevation	Passive shoulder elevation
	Forward parachute	Leg posture	Visual response	Leg adductors
	Leg posture	Trunk posture in sitting	Head posture in sitting	**Scarf sign**
	Trunk posture in sitting	Facial appearance	Sucking/swallowing	Sucking/swallowing
	Ankle dorsiflexion	Ankle dorsiflexion	Facial appearance	Facial appearance

Items consistently found in the same category in all assessments are underlined. Items shifting category across the assessments are in bold.

[12]. A high predictive value was also found as to locomotor function assessed both in terms of sensitivity/specificity and of the area under the ROC curves. Predictive value was on the whole constant across the first year, slightly decreasing only from the 9-month assessment onwards, due to the presence of few false positives (especially infants with HINE sub-threshold values and good locomotor outcome).

Our findings suggest that the high predictive value of the HINE across the first year of life is granted by the effective combination of different groups of items for each age-period. Indeed, although a number of items were found to be consistently among the most predictive ones, namely movement quality, quantity and lateral tilting, the overall pattern of most and least predictive items changed across time. Tone items, such as ventral suspension, arm pronation/supination and scarf sign, tended to be more predictive at 3 and 6 months post-term, while maturational items, such as arm protection, vertical suspension and forward parachute, were highly predictive only after 9 months.

In our study we found that using the optimality score obtained in low-risk term infants, at 12 months only a limited number of preterm infants (38%) had optimal scores ($\geq$73). These data differ from the findings of Frisone and coworkers [4] who found optimal scores in about 52% of their premature infants. This inconsistency might be due, at least partially, to the heterogeneity of the two cohorts, with a larger number of more severe cases in our population, as shown by the higher incidence of abnormal outcomes. A comparison is however difficult as in the paper by Frisone, time of assessment was extremely variable, from 9 and 18 months of age. Similarly, it is not appropriate to compare the best cut-off values found in our study for each age period, with the one (score = 64) of their cohort.

In this study we were able to provide a specific cut-off score for each age window, based on the best predictive value as to locomotor outcome at two years. We cannot establish whether these values can be reliably applied to different populations at neurological risk, as to do so further longitudinal studies on large cohorts of low-risk infants would be needed. However, it is of interest that the longitudinal consistency of the assessments (optimal/suboptimal) was extremely high, as only four infants changed their score, from optimal in the first two assessments to suboptimal in the last two.

The HINE scores were not strictly associated with the pattern of US findings, consistent with previous reports [4].

In conclusion, our results confirm the high predictive value of neurological examination in very preterm infants from 9 to 12 months post-term age, and extend it to examinations performed as early as 3 months post-term. We provided cut-off values of optimality in very preterm infants for the examinations at 3, 6, 9 and 12 months post-term, which will however need confirmation in larger cohorts of low-risk infants. Further studies will be necessary to evaluate whether this examination can have such an early good predictive value in infants with different types of neurodevelopmental risk.

References

[1] de Kleine MJ, den Ouden AL, Kollee LA, Ilsen A, van Wassenaer AG, Brand R, et al. Lower mortality but higher neonatal morbidity over a decade in very preterm infants. Paediatr Perinat Epidemiol Jan 2007;21(1):15–25.

[2] Marlow N. Neurocognitive outcome after very preterm birth. Arch Dis Child Fetal Neonatal Ed May 2004;89(3):F224–8.

[3] 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 Aug 1999;135(2 Pt 1):153–61.

[4] Frisone MF, Mercuri E, Laroche S, Foglia C, Maalouf EF, Haataja L, et al. Prognostic value of the neurologic optimality score at 9 and 18 months in preterm infants born before 31 weeks' gestation. J Pediatr Jan 2002;140(1):57–60.

[5] Volpe JJ. Neurology of the newborn. 4th ed. 2001. USA: W.B. Saunders Company.

[6] Hoon Jr AH, Pulsifer MB, Gopalan R, Palmer FB, Capute AJ. Clinical Adaptive Test/Clinical Linguistic Auditory Milestone Scale in early cognitive assessment. J Pediatr Jul 1993;123(1):S1–8.

[7] Bayley N. Bayley Scales of Infant Development-II; 1993. San Antonio, TX: The Psychological Corporation.

[8] Kube DA, Wilson WM, Petersen MC, Palmer FB. CAT/CLAMS: its use in detecting early childhood cognitive impairment. Pediatr Neurol Sep 2000;23(3):208–15.

[9] 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 Apr 1997;39(4):214–23.

[10] Haataja L, Mercuri E, Guzzetta A, Rutherford M, Counsell S, Flavia Frisone M, et al. 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. J Pediatr Mar 2001;138(3):332–7.

[11] Metz CE. Basic principles of ROC analysis. Semin Nucl Med Oct 1978;8(4):283–98.

[12] Romeo DMM, Guzzetta A, Scoto M, Cioni M, Patusi P, Mazzone D, et al. Early neurologic assessment in preterm-infants: integration of traditional neurologic examination and observation of general movements. Eur J Paediatr Neurol May 2008;12(3):183–9.