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Neurological assessment in infants discharged from a neonatal intensive care unit

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ABSTRACT

Background: Longitudinal motor assessment in infants at different neurodevelopmental risk has not been previously evaluated using structured assessments.
Aim: To verify if the Hammersmith Infant Neurological Examination (HINE) is a good tool to predict the neuromotor outcome in infants discharged from a level II–III Neonatal Intensive Care Unit (NICU)
Methods: In this cohort analysis, 1541 infants discharged from our NICU between January of 2002 and the April 2006 were enrolled and assessed using the HINE at 3, 6, 9, 12 months. At two years, these infants were further assessed, and grouped into infants with normal outcome (1150), with mild disability (321) and with cerebral palsy (70),
Results: Correlation analysis of Spearman showed a significant ($p < 0.0001$) and moderate ($r^2 = -0.55$ to -0.73) negative correlation between HINE scores (3, 6, 9, 12 months) and neurological outcome at two years. Cut-off scores for each assessment' age were provided as predictive value for cerebral palsy.
Discussion: This study mainly showed that HINE, as soon as the first months of life, helps in the process of prediction of neurological outcome at two years of age in a heterogeneous population of infants discharged from an NICU.

1. Introduction

The possibility to differentiate a normal by an abnormal motor performance at early age is of interest for infants at risk for neurodevelopmental disabilities.[1] During the first year of age, special attention should be given to motor progresses of these infants, because of transitory neurological abnormalities (involving posture, fine and gross motor control, coordination and reflexes), detected in the 40–80% of cases but disappearing during the second year of life.[2,3] In order to follow up these infants, a specific evaluation tool can represent a good response to the parents requests for a correct valuation and

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prognosis. Several methods are used for the neurological assessment of the risk infants after the neonatal period.[1,3–6] In 1981, Dubowitz et al.[7,8] developed a neurological examination for the neonatal assessment of preterm and term infants to identify those at risk for neurological abnormalities. Later on, the same authors[9] developed the Hammersmith Infant Neurological Examination (HINE), based on the same principles, to be used during the first two years from birth. This tool is performed quickly and easily in a clinical setting and a high concordance with the severity of locomotor functioning has been demonstrated.[9–12]

Recently, we used the HINE in specific groups of high risk newborns,[13–16] providing detailed information on neurological assessment in these infants, but the experimental design did not allow us to give a significance of prediction to the results for children at different neurodevelopmental risk using specific cut-off scores. This topic could be worthy of interest since prediction of a neurodevelopmental abnormality could allow a precocious rehabilitation intervention resulting in promotion and acceleration of motor development.[17] Infants admitted to Neonatal Intensive Care Unit (NICU) are at different risk for neurodevelopmental disabilities due to possible brain damage related to prematurity, asphyxia, haemorrhage, etc.

Therefore, the aim of this study was to test the hypothesis that the HINE score within a specific range, from the age of 3 months, could be used to predict later neurodevelopmental outcomes at 2 year from birth in newborns discharged from an NICU.

2. Methods

All the infants described in this study were part of a follow-up research project carried out at the NICU of the Department of Paediatrics of the University of Catania. This is a level II (specialty care) and level III (subspecialty) neonatal intensive care center,[18] admitting patients affected by prematurity, twins, low birth-weight, asphyxia, cardiopathy, cerebral malformations as well as surgery newborns. All patients were enrolled routinely on a two-year follow-up research protocol. Between January 2002 and December 2006, 1853 consecutive patients were discharged from the NICU. A cranial ultrasound (US) was performed in all the infants within the 6th day from birth in both preterm and term born infants and at least another one at term age for preterm newborns. The US performed at term age 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[19]; (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[19]; (v) cystic periventricular leukomalacia with or without haemorrhage or unilateral intraparenchymal echodensity. For the purpose of the present study, we included those infants with a detailed clinical follow-up consisting of 5 evaluations (3, 6, 9, 12, 24 months). The exclusion criteria were the presence of congenital anomalies, transfer to another hospital, or an incomplete follow-up program. Then, 312 infants out of 1853 were excluded from the study: 20 infants due to the presence of congenital anomalies, other 34 infants because of transferring to II level hospitals in their own native towns, after stabilization of the clinical condition, and 258 infants because they did not complete the follow-up program.

The study protocol was previously approved by the Ethics Committee of our Institutions and informed consent was obtained from all the parents.

2.1. Neurological examination

The HINE[9] 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 function, posture, movements, tone and reflexes. An optimality score is obtained by calculating 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. The overall score ranges from a minimum of 0 to a maximum of 78. At 9 or 12 months, the scores equal or above 73 are regarded as optimal, if below 73 as suboptimal; while at 3 and 6 months healthy term infants scored equal or above 67 and 70 (median) respectively.[9,20] In this retrospective study, we analysed files of patients investigated by the HINE at 3, 6, 9 and 12 months (corrected for prematurity) with the score of single subsections of items and a global optimality score for each period, according to the clinical protocol routinely performed in our NICU. Global cut-off scores were used as previously reported.[11–13]

2.2. Outcome

At two years corrected age all infants were assessed with a structured neurologic examination[6,21] and using the Bayley Scales of Infant Development second edition (BSID-II).[22] Although BSID-II comprises three separate scales (Mental, Motor and Behaviour Scales), for the purpose of the present study, only the Motor Scale was administered. The BSID-II has been shown to be a comprehensive and appropriate instrument for assessing motor performance.[23] The motor scale of the BSID-II assesses gross and fine motor skills. Raw scores on this scale were converted to a psychomotor developmental index (PDI) with a mean of 100 and a standard deviation of 15.

Scores $\geq$115 are considered as accelerated performance, a score of 85–114 as within normal limits, a PDI of 70–84 as mildly delayed performance, whereas a score of not more than 69 is defined as significantly delayed motor performance.[22]

According to the motor outcome, infants were classified in: *normal* outcome (N) for those without neurological abnormalities and a PDI$\geq$85, with *mild disability* (MD) with a PDI $<$ 85 and/or mild neurological signs, but no cerebral palsy (CP), and in *cerebral palsy* (CP) according to the criteria proposed by Himmelmann et al.[24] The latter children were further followed until the age of 5 years, to confirm the diagnosis.

2.3. Statistical analysis

The anthropometric variables (weight and gestational age) were reported as mean $\pm$ SD. Values of HINE scores were reported as median and range at different ages, for each group of

Table 1 – Characteristics of the population and neurological outcome.

	Number	Gender		Gestational age		Weight	
		Male	Female	Median (weeks)	Range (weeks)	Median (GR)	Range (GR)
N	1150	601	549	36	25–42	2420	920–5350
MD	321	170	151	37+++	26–43	2450+++	630–4570
CP	70	45	25	33***	26–41	1880***	880–3900
TOT	1541	816	725	36	25–43	2500	630–5350

N, normal outcome; MD, minor neurological dysfunction; CP, cerebral palsy.
***$p < 0.0001$ Statistical difference between normal vs cerebral palsy.
+++$p < 0.0001$ Statistical difference between MD vs cerebral palsy.
No statistical difference between normal vs MD.

infants. Inter-group comparisons have been done by a non-parametric test (Kruskall-Wallis test followed by Dunn's post test). The Spearman Rank Correlation test was used to correlate the HINE scores obtained at 3–12 months and the US findings with the severity of the outcome at two years of age. Comparison between HINE scores of term born infants and preterm was done by using the non-parametric test of Mann–Witney *U*. The level of significance was set at $p < 0.05$. Sensitivity and specificity were further used to assess the predictive value of cut-off scores.

3. Results

3.1. Characteristics of population

A total of 1541 infants were included in the study: 149 were very preterm (gestational age (GA) 25–32 weeks); 754 were late-preterm (GA 33–36 weeks); 638 were born at term (GA 37–43 weeks). Table 1 shows the general characteristics of the population related to neurological outcome at 2 years. Of the 70 children with CP, 26 showed a diplegia, 20 a quadriplegia, 19 a hemiplegia and 5 a dyskinetic type. Infants with CP showed a significant lower mean gestational age than those with normal outcome ($p < 0.0001$) and children with MD ($p < 0.0001$). Similarly, infants with CP had a significant lower mean birthweight ($p < 0.0001$) than the other two groups of infants.

3.2. US scan findings

No abnormal signals or transient flares were present in 1185 infants (60 very preterm, 645 late-preterm, 480 term born infants); persistent flares in 226 infants (51 very preterm, 85 late-preterm, 90 term born infants); isolated ventricular dilatation in 95 infants (29 very preterm, 15 late-preterm, 51 term born infants); intraventricular haemorrhage grade II or III in 19 infants (6 very preterm, 3 late-preterm, 10 term born infants); cystic periventricular leukomalacia in 16 (6 very preterm, 6 late-preterm, 4 term born infants).

3.3. Infant neurologic examination

At 3 months of age (Table 2) all infants with normal outcome scored above 48 (median 64) and namely between 48 and 66

Table 2 – Global scores of the Hammersmith infant neurological examination and neurological outcome.

	Total number	Score median	Range of scores	Score ≥73	Score 67–72	Score 40–66	Score <40
N							
3 Months	1150	64*	48–71	0	135 (12%)	1017 (88%)	0
6 Months	1150	68*	54–76	28 (2%)	641 (56%)	483 (42%)	0
9 Months	1150	70*	59–78	429 (37%)	613 (53%)	110 (10%)	0
12 Months	1150	73*	63–78	581 (50%)	559 (49%)	12 (1%)	0
MD							
3 Months	321	58#	40–65	0	0	319 (100%)	0
6 Months	321	63#	43–70	0	37 (12%)	282 (88%)	0
9 Months	321	66#	46–74	8 (3%)	128 (40%)	183 (57%)	0
12 Months	321	67#	47–75	19 (6%)	155 (49%)	145 (45%)	0
CP							
3 Months	70	35.5+	14–62	0	0	32 (46%)	38 (54%)
6 Months	70	40+	16–65	0	0	37 (53%)	33 (47%)
9 Months	70	44+	22–69	0	4 (6%)	44 (63%)	22 (31%)
12 Months	70	45.5+	24–70	0	5 (7%)	47 (67%)	18 (26%)

N, normal outcome; MD, minor neurological dysfunction; CP, cerebral palsy.
*Normal vs MD ($p < 0.001$).
+Normal vs cerebral palsy ($p < 0.001$).
#MD vs cerebral palsy ($p < 0.001$).

(90%). A progressive increase of score was observed until 12 months. At this age the 50% of infants gained an optimality score ≥ 73. On the other hand, all infants with MD scored in the range of 40–66 at 3 months of age. In this group of infants, a progressive improvement of score from 3 months onward was observed, but with minimal changing from 9 months. Few infants only gained at 9 and 12 months scores ≥73 (3 and 6% respectively). The group of infants with CP showed the lowest scores with a median global score from 35.5 at 3 months to 45.5 at 12 months; no one of them gained the scores ≥73 at 9 or 12 months, considered as optimal. Global and subsection scores' details of infants with CP were previously reported.[13]

A statistical inter-group comparison showed that, at all ages, infants with *N* scored significantly ($p < 0.001$) higher than those with MD and CP.

Table 3 showed that at 3, 6, 9 and 12 months of age, infants with *N* scored significantly higher ($p < 0.01$) than infants with MD for all subsection but posture at 3 months. Infants with *N* scored significantly higher ($p < 0.001$) than those with CP in all subsections at every age; infants with MD scored significantly higher ($p < 0.001$) than those with CP except for cranial nerve at 3 and 6 months of age.

Fig. 1 showed the correlation analysis of Spearman with a moderate to strong and significant ($p < 0.0001$) negative correlation between HINE scores (3, 6, 9, 12 months) and outcome at two years; according to the GA, very preterm showed a better correlation (−0.72 to −0.76) than term born infants (0.58 to −0.72) at every ages. At 3 months, the cut-off score of 56 reported the higher prediction for CP with a sensitivity of 96% and a specificity of 85%; similar results were observed using a cut-off of 59 (se 90%; sp 89%), 62 (se 90%; sp 91%), and 65 (se 91%; sp 90%), respectively at 6, 9 and 12 months. Considering the type of CP, at 3 months the cut-off score of 39 showed the higher prediction for a severe CP (quadriplegia/diplegia/diskinetic) with a sensitivity of 100% and a specificity of 99%; the same power prediction was observed using a cut-off of 41, 45 and 47, respectively at 6, 9 and 12 months. For infants with hemiplegia at 3 months the cut-off score of 49 shows the higher prediction with a sensitivity <10% and a specificity of 99%; the same power prediction was observed using a cut-off of 55, 61 and 63, respectively at 6, 9 and 12 months.

When considering examinations longitudinally, the assessments showed to be not always consistent in classifying children results as suboptimal, according to the age specific cut-off value. In 61/256 infants with suboptimal scores at the first evaluation, the assessment was not consistent across the other three examinations, becoming optimal in at least one assessment; 46 of them were classified as normal at 2 years. In 13/1285 infants with optimal scores at the first evaluation, the assessment was not consistent across the other three examinations, becoming suboptimal in at least one assessment; four of them were classified as normal at 2 years.

All the children with CP and almost the 20% of those with MD were under a treatment in several services of rehabilitation (3–5 times/week) at 2 years. There were no significant differences of HINE scores for children with MD between those under treatment or not.

Irrespective of the neurological classification, very preterm infants (GA≤32 weeks) showed significantly lower global scores at all ages than term born ones.

Table 3 – Subsection's score of the Hammersmith infant neurological examination.

Age	Cranial nerve	Posture	Movements	Tone	Reflexes
	Median (range)	Median (range)	Median (range)	Median (range)	Median (range)
3 Months					
N	14 (11–15)***	14 (6–18)ns	6 (3–6)***	20 (13–24)***	9 (3–15)**
MD	13 (6–15)ns	14 (7–17)#	5 (0–6)#	18 (14–23)#	8 (3–13)#
CP	12 (7–15)+	10 (3–16)+	1 (0–5)+	12.5 (3–22)+	4 (1–9)+
6 Months					
N	15 (11–15)***	15 (6–18)***	6 (3–6)***	21 (13–24)***	11 (5–15)***
MD	14 (6–15)ns	14 (9–18)#	5 (1–6)#	20 (14–24)#	10 (4–13)#
CP	13 (7–15)+	11 (4.5–16)+	1 (0–5)+	13 (3.5–22)+	4 (1–9)+
9 Months					
N	15 (12–15)***	16 (7–18)***	6 (3–6)***	22 (15–24)***	12 (5–15)***
MD	15 (7–15)#	15 (10–18)#	5 (2–6)#	20 (15–24)#	11 (5–14)#
CP	13 (9–15)+	12 (6–17)+	1 (0–5)+	14 (6–23)+	5 (1–10)+
12 Months					
N	15 (13–15)***	17 (8–18)***	6 (3–6)***	23 (17–24)***	13 (6–16)***
MD	15 (7–15)#	16 (10–18)#	5 (2–6)#	21 (15–24)#	11 (5–14)#
CP	13.5 (9–15)+	13 (6–18)+	1 (0–5)+	15 (7–23)+	5 (1–11)+

N, normal outcome; MD, minor neurological dysfunction; CP, cerebral palsy.
*Normal vs MD (**$p < 0.01$; ***$p < 0.001$).
#MD vs cerebral palsy ($p < 0.001$).
+Normal vs cerebral palsy ($p < 0.001$).

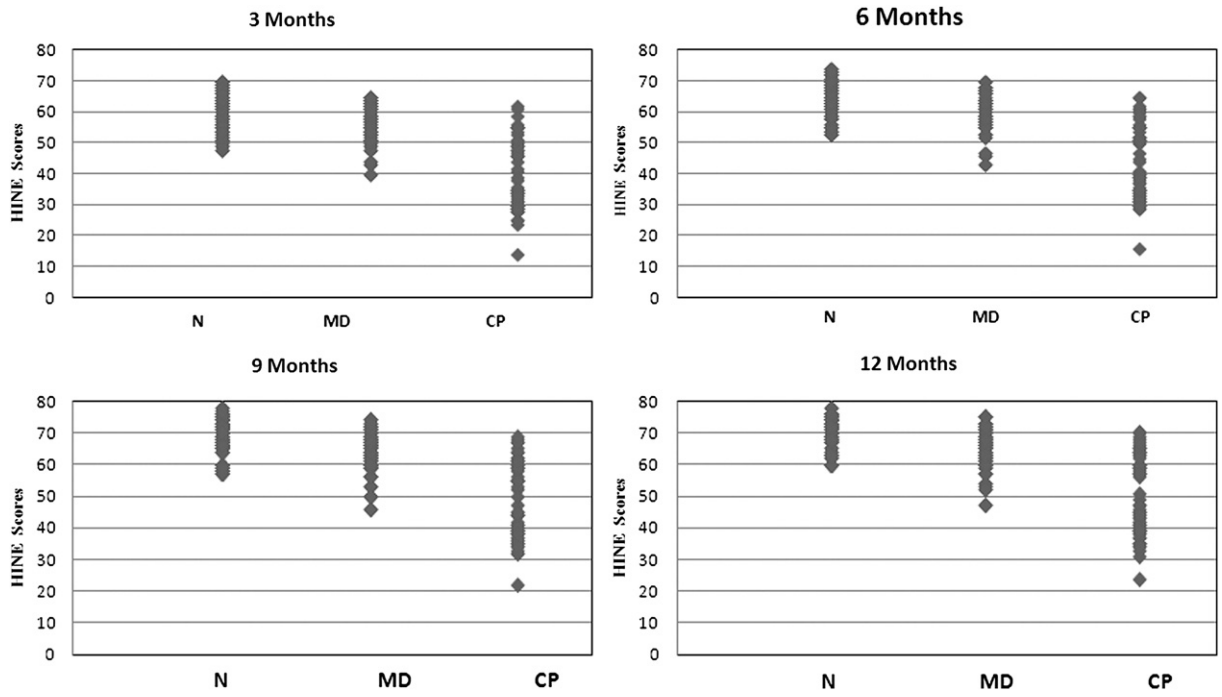

Fig. 1 – HINE, Hammersmith infant neurological examination; N, normal outcome; MD, minor neurological dysfunction; CP, cerebral palsy.

3.4. *Infant neurologic examination and cranial ultrasonography*

Of the 1188 infants with normal ultrasounds or transient flares only 25 had scores below the cut-off values at all age periods. All the infants with cystic periventricular leukomalacia had scores below the cut-off values at all age periods. Infants who had other ultrasonogram abnormalities had widely varying scores, both below and above the cut-off scores at all ages.

4. Discussion

The main results of this study showed that, as soon as the first months of life, the HINE helped to predict the neurological outcome at two years from birth in a heterogeneous and large population of infants discharged from an NICU.

In a previous study[13] we used the HINE to describe the neuromotor development of infants with CP during the first year of age and to differentiate infants with diplegia from those with quadriplegia by a lower scoring of the latter in the subsections tone and posture. In the present study, we extended these observations in term of prediction assessing a large population of infants discharged from NICU. As we expected, infants with N showed higher global and subsections scores at all ages than both those with MD, with the exception of posture at 3 months, and with CP. A progressive increase of motor development is observed during the first year of from birth. This last result is quite different from the findings reported by Haataja et al.,[9,20] who also showed, in low-risk term born infants, a progressive improvement before 7 months of age, but with little changes on the scores obtained at 9 and 12 months. Furthermore the median and range of scores obtained in the present study by those infants with normal outcome, were lower than the normative data,[9,20] mainly at earlier ages, whereas at 12 months more similar results were observed. Probably, these differences were related to the characteristics of our population. In fact, although they showed a normal outcome at two years of age, they were discharged from an NICU because of prematurity, sepsis, asphyxia etc; therefore they could not be considered a real low-risk population, with a possible different motor development at least during the first year of age.[10,25–27]

Very preterm infants showed lower scores than term born at each ages, as previously reported[10,12,14–16,24–26] and in the three sub-groups according to the outcome. Although normal scans or minor lesions tended to be associated with optimal scores and cystic periventricular leukomalacia with low scores, the HINE scores were not strictly associated with the pattern of US findings, consistent with previous reports.[10,15]

When we considered the subsection scores, other interesting information are observed. In fact, infants with N scored significantly better in all subsections than both those with CP and MD, even if the latter and N scored similarly for “posture” at 3 months; this data could reflect a similar early postural development in infants, with normal or quite normal motor outcome, who attended an NICU. Infants with MD showed higher scores than those with CP for all subsections except for “cranial nerve” at 3 and 6 months, making this subsection less sensitive than others in differentiating these two populations of infants.

The HINE global score was correlated with the outcome, with a better correlation for the results at 9 and 12 months and

for very preterm infants. It is not surprising that the findings of HINE performed at 3 months showed the lowest power of prediction. In fact, this tool was designed for and validated in older infants, and some of the items assessing sitting posture and defensive reactions could be considered less sensitive when assessing infants at 3 months.[14] However infants with a global score ≤56 and ≤ 65 had a high probability to develop a CP, at 3 months and 12 months respectively, with scores <40 were reported in CP only. Previous researches reported cut-off scores similar to those of the present study,[10–15] but for the first time we were able to provide a specific cut-off score for each age window, using a large cohort of infants at low and high neurological risk. Not surprisingly this correlation is more stronger in very preterm infants as they show a higher risk for neurological problems. Considering the different types of CP, the HINE scores could be used to identify only those infants with severe CP, whereas in infants with hemiplegia, due to an overlap of scores with those with N and MD, the sensitivity is very low.

Other neurological tools have been used to predict the neurological outcome in high risk infants; mainly, in the first months of life the use of general movements showed a higher sensitivity and specificity; the largest study so far, assessing 903 preterm infants at 3 months, reported a sensitivity of 98% and a specificity of 94% for the development of CP.[28] At older ages, the Alberta Infant Motor Scale showed at 4 and 8 months a good sensitivity and specificity (77% and 82% at 4 and 86% and 93% at 8 months respectively) to predict abnormal outcome at 18 months in risk newborns.[29] However, these tools showed a lower prediction when assessing infants at low risk.[30,31] Compared to these tools, the HINE showed the advantage to predict the motor outcome in low and high risk infants with a good power prediction at different ages.

A limitation of this study was the relatively short follow-up period (24 months), which was chosen to have a good compliance from parents, as previously reported by other authors.[32,33] It is possible that some infants with MD developed a normal neurological outcome after this age or, that some of them reported a slight type of CP; assessment at older ages could probably result in a more accurate measure of final neurological outcome.[34] On the other hand, infants with a diagnosis of CP were enrolled on a further clinical follow-up and then the diagnosis was confirmed for all of them at 5 years.

In conclusion, our study showed that the HINE is a helpful tool in the process of early diagnosis of infants at low and high neurological risk, with a good predictive value. The use of the cut-off scores at different ages allows to follow longitudinally high risk infants during the first age from birth to identify those infants needing specific rehabilitation programme.

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