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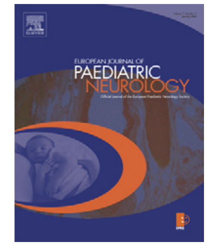

Original article

Neuromotor development in infants with cerebral palsy investigated by the Hammersmith Infant Neurological Examination during the first year of age

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ABSTRACT

Background: The Hammersmith Infant Neurological Examination (HINE) is a simple and scorable method for assessing infants between 2 and 24 months of age.
Aims: The purpose of this retrospective study was firstly, to evaluate the neuromotor development of infants with cerebral palsy (CP) by the HINE, during the first year of age; secondly, to correlate the scoring of this neurological tool with levels of the Gross Motor Function Classification System (GMFCS).
Methods: A cohort of 70 infants with a diagnosis of CP at 2 years of age was evaluated by the HINE at 3, 6, 9 and 12 months of corrected age and by GMFCS at 2 years of age.
Results: The main results indicate that at 3–6 months, infants with quadriplegia (IV and V levels of GMFCS) and those with severe diplegia (III level) scored below 40, whereas those with mild or moderate diplegia (I–II level) and hemiplegia (I–II level) mainly scored between 40–60. Interestingly, the 26% of infants with hemiplegia scored $\geqslant 67$ at 12 months. We observed a strong ($r = -0.82$) and significant ($p < 0.0001$) negative correlation between the scores of the neurological examination and the levels of GMFCS.
Conclusions: Our results point out that the HINE can give additional information about neuromotor development of infants with CP from 3–6 months of age, strictly related to the gross motor functional abilities at 2 years of age.

1. Introduction

In the last 15 years, intensive medical care performed in Neonatal Intensive Care Units (NICU) has allowed an increase in the survival of very low birth-weight and extremely premature newborns.[1] New risk factors have appeared among infants who previously would have died[2,3] and the incidence of neurodevelopment impairments in survivors of NICU is higher than in normal birth-weight newborns.[4,5] In particular, due to the high risk of intraventricular haemorrhage (IVH) or periventricular leukomalacia (PVL), an increasing prevalence of cerebral palsy (CP) has occurred in

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premature, low birth-weight newborns and children born with asphyxia[6–9].

In 1981, Dubowitz et al.[10] developed a neurological examination, recently updated,[11] for the neonatal assessment of preterm and term infants to identify those at risk for neurological abnormalities. The Hammersmith Infant Neurological Examination[12] (HINE) was developed by them with the same principles for use as a standard neurological examination after the neonatal period. The HINE 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. This examination and the obtained optimality scores, based on the frequency distribution of neurological findings, were standardized at 12 and 18 months in a low-risk population[12] and in healthy term infants between 12 and 32 weeks of age.[13] The HINE was recently used in a cohort of term infants with hypoxic-ischemic encephalopathy at birth and in those born prematurely, at 9 and 12 months of age.[14,15] These studies showed that global optimality scores can help in the prediction of locomotor outcomes at 2 and 4 years of age.[14,15]

The primary objective of this retrospective study was to evaluate the neuromotor development during the first year of age in a population of infants discharged from a NICU and with a diagnosis of CP at 2 years of age. It was hypothesized that (i) children with CP should show some specific abnormalities of their development when tested by HINE at 3, 6, 9 and 12 months and consequently they should get a sub-optimal global score, possibly different for each clinical form of CP, (ii) in addition, there would be a correlation between global optimality scores collected during the first year of age and levels of Gross Motor Function Classification System (GMFCS)[16] at 2 years of age.

2. Materials and methods

In the NICU of the Department of Paediatrics of the University of Catania, we admit out-born patients affected by prematurity, twins, low birth-weight, asphyxia, cardiopathy, cerebral malformations as well as surgery newborns. A standard protocol is performed for each patient including: physical and neurological examination, cranial ultrasonograms (US), magnetic resonance imaging (MRI), ophthalmologic and auditory examinations and electrophysiological assessments. All patients are enrolled routinely on a two-year follow-up. In this study, that was approved by the Ethical Committee of our Institution, 1541 patients' files were selected from a review of 1853 charts of consecutive patients discharged from the NICU between January 2000 and December 2004. The criteria of inclusion were a detailed clinical follow-up consisting of five evaluations (3, 6, 9, 12, 24 months) and parental written permission. A cranial US was performed within the 6th day of life and at least another one at term age. The term 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[17]; (ii) persistent flare (bilateral periventricular echodensity persisting more than 14 days) without haemorrhage; (iii) isolated ventricular dilation; (iv) intraventricular haemorrhage grade II or III[17]; (v) cystic periventricular leukomalacia with or without haemorrhage or unilateral intraparenchymal echodensity. The criteria of exclusion were the presence of congenital anomalies, the transfer to another hospital, or an incomplete follow-up program. Therefore, 312 infants out of 1853 were excluded from the study. Namely, 20 infants with congenital anomalies were excluded because their neuromotor development could not be compared with that of other infants; other 34 infants, were transferred to II level hospitals in their own native towns, after stabilization of the clinical condition. The remaining 258 infants were excluded because they did not complete the follow-up program, even if they showed peri-postnatal clinical characteristics (Apgar scores, ultrasonagram findings, gestational age, birth-weight and HINE scoring at three months) as well as socio-cultural background similar to those of not-developing CP infants.

2.1. *Neurological examination*

The HINE[12] was used for the assessment of all infants enrolled in this study. It includes three sections, the Neurological Examination, the Development of Motor Functions and the State of Behaviour. The first section evaluates cranial nerve, posture, movements, tone and reflexes. These items are not age-dependent. An optimality score is obtained by calculating the distribution of the frequency of the scores of the first section in the normal population, defining as optimal all the scores found in at least 90% of the cohort. The second section valuates head control, sitting, voluntary grasping, rolling, crawling and walking. The third section valuates state of consciousness, emotional state and social orientation. The data obtained in the second and third sections are not included in the calculation of global optimality scores. They give additional information on the interpretation of neurological findings, but a frequency distribution for these two age-dependent sections was not calculated.[12] 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 sub-optimal; while at 3 and 6 months healthy term infants scored equal or above 67 and 70 (median) respectively.[12,13] In this retrospective study, we analysed files of patients investigated by the HINE at 3, 6, 9 and 12 months (corrected for prematurity) with a single item and global optimality score for each period, according to the clinical protocol routinely performed in our NICU.

2.2. *Outcome*

The neurological outcome was performed at a corrected age of 2 years by two of the authors (D.M.M.R., M.S.). All infants were grouped: those without a pathological diagnosis, those with mild disability and those with CP, according to Touwen's criteria,[18] and to a motor developmental quotient.[19] In this study we report the data of 70 infants with CP, whereas those infants without a pathological diagnosis and with mild disability will be discussed in a further paper. CP was defined as a non-progressive central nervous system disorder characterized by abnormal muscle tone in at least one extremity with abnormal control of movement and posture, and was classified according to the criteria proposed by Hagberg et al.[20] Infants were also classified according to the GMFCS with skill levels of 0–5 developed by Palisano and colleagues.[16] At the moment of diagnosis of CP, infants were all under a treatment in several services of physical therapy (3–5 times/week).

2.3. Statistical analysis

The anthropometric variables (weight and gestational age) are reported as mean±SD (standard deviation). Due to the small sample of infants ($n = 5$) with a dyskinetic form of CP, they were included only in the descriptive statistical analysis. Values of HINE scoring are reported as median and range at different ages, for each group of infants. Inter-group comparisons has been done by a non-parametric test (Kruskall–Wallis test followed by Dunn's post test). Intra-group comparison at 3, 6, 9, and 12 months of age was performed by the Friedmann test followed by Dunn's post test. Correlations between HINE scoring and levels of GMFCS were calculated by the Spearman Rank Correlation test. The level of significance was set at $p < 0.05$.

3. Results

3.1. Characteristics of population

Table 1 shows that, at the age of 2 years, infants with a diagnosis of CP were classified in the following types: diplegia (37.2%) quadriplegia (28.6%) and hemiplegia (27.2%). Another five infants showed a dyskinetic type of CP (7%). The percent of prematurity was 84%, and most of them were males (ratio male/female = 1.8). Infants with diplegia and quadriplegia were more frequently of a gestational age lower than 32 weeks (respectively, 61% and 59%), whereas those with hemiplegia were of a gestational age above 36 weeks in 58% of cases. Infants with diplegia and quadriplegia showed the lowest weight at birth (<1500 g, respectively 54% and 59%) whereas those with hemiplegia showed the highest weight (>2500 g, 58%). However, no statistical differences were observed among the different types of CP for gestational age or birth-weight (Table 1). Cranial US performed at term age, showed some abnormalities in 69 infants: persistent flare ($n = 34$), cystic periventricular leukomalacia ($n = 18$), intraventricular haemorrhage grade II or III according to Volpe[17] ($n = 8$), isolated ventricular dilation ($n = 9$). Only in one case no abnormal signal was observed.

3.2. HINE testing

All infants showed sub-optimal scores in each evaluation. Table 2 indicates that, at the age of 3 months, all infants with quadriplegia ($n = 20$) scored <40, whereas those with diplegia scored both <40 ($n = 14$) and between 40–60 ($n = 12$). Infants with hemiplegia ($n = 19$) scored in the range of 40–60. A statistical inter-group comparison shows that, at this age, infants with quadriplegia scored significantly ($p < 0.05$) lower than those with diplegia, whereas infants with hemiplegia scored significantly ($p < 0.001$) higher than those with diplegia and quadriplegia. At the age of 6, 9 and 12 months, infants with quadriplegia scored mainly <40 (respectively, $n = 14$, $n = 11$) and the others of this group scored between 40–60, namely <48. At 6 months of age, infants with diplegia scored similarly to the evaluation of 3 months, whereas at 9 and 12 months they mainly scored between 40–60 ($n = 16$) or <40 ($n = 8$); only a few infants with diplegia scored >60 at 9 and 12 months (respectively, 2 and 3 infants). Infants with hemiplegia scored between 40–66 ($n = 19$), but few infants scored between 67–72 at the age of 9 and 12 months (respectively, $n = 4$ and 5). At 3 months of age, infants with dyskinetic CP scored both <40 ($n = 2$) and 40–60 ($n = 3$). At 12 months of age, all of them scored between 40–60 ($n = 5$). Fig. 1 shows the modifications of HINE scoring throughout the evaluation periods at 3, 6, 9 and 12 months of corrected age. All three groups of infants showed a similar trend with a percentage increase scoring of 7.2±3.0–12.3±5.8%, between 3–6 and 6–9 months, with very small changes (<3.8%) in the period between 9–12 months. The intra-group comparison every three months (3 vs 6, 6 vs 9 months) showed that infants with diplegia only scored significantly higher ($p < 0.01$), whereas between 9 and 12 month of age we did not observe any significant difference for the three groups of infants. On the other hand, the intra-group statistical comparison every 6 months (3 vs 9 months and 6 vs 12 months) was significantly ($p < 0.001$) different for all groups.

Table 3 shows that at 3, 6, 9 and 12 months of age, infants with quadriplegia and diplegia scored similarly for the subsections cranial nerve, movements and reflexes ($p > 0.05$). On the other hand, at 3, 6, 9, and 12 months, the scoring for the subsection tone and posture in infants with diplegia improved significantly ($p < 0.001$) more than in infants with

Table 1 – Clinical characteristics of infant population

	Population (no.)	Gender		Gestational age		Weight	
		Male (no.)	Female (no.)	Mean±SD (weeks)	Range (weeks)	Mean+SD (grams)	Range (grams)
Diplegia	26	17	9	33.3±2.9 ns	28–39	1997±609 ns	1000–3200
Quadriplegia	20	16	4	32.9±4.3 ns	26–40	1807±687 ns	880–3300
Hemiplegia	19	10	9	36.0±4.0 ns	27–41	2383±787 ns	1000–3900
Dyskinetic	5	2	3	34.6±2.9 ns	31–37	2115±533 ns	1280–2550

ns = no statistical significance on difference between groups.

Table 2 – Hammersmith Infant Neurological Examination in different types of cerebral palsy

	Total number	Score median	Range of score	Score 60–70	Score 40–60	Score <40
Diplegia						
3 months	26	36.5[a]	24–56	–	10 (38%)	16 (62%)
6 months	26	40.0[a]	29–58	–	12 (46%)	14 (54%)
9 months	26	43.0[a]	35–62	2 (8%)	16 (61%)	8 (31%)
12 months	26	44.5[a]	35–66	3 (12%)	16 (61%)	7 (27%)
Quadriplegia						
3 months	20	29.5[b]	14–39	–	–	20 (100.0%)
6 months	20	32.0[b]	16–44	–	2 (10.0%)	18 (90.0%)
9 months	20	37.5[b]	22–45	–	6 (30.0%)	14 (70.0%)
12 months	20	39.0[b]	24–47	–	9 (45.0%)	11 (55.0%)
Hemiplegia						
3 months	19	55.0[c]	46–62	-	19 (100.0%)	–
6 months	19	56.0[c]	51–65	2 (10%)	17 (89.5%)	–
9 months	19	61.0[c]	55–69	11 (58%)	8 (42.1%)	–
12 months	19	64.0[c]	57–70	13 (68%)	6 (31.6%)	–

[a] Diplegia vs quadriplegia ($p<0.05$).
[b] Diplegia vs hemiplegia ($p<0.001$).
[c] Quadriplegia vs hemiplegia ($p<0.001$).

quadriplegia. Namely, at 3 months of age infants with quadriplegia scored less than those with diplegia in the items "scarf sign", "popliteal angle", "adductors" "pull to sit" and "ventral suspension". At 9 and 12 months of age, they scored worse than infants with diplegia for "passive shoulder elevation" and "adductors". Regarding the item of posture, infants with quadriplegia scored less in the "trunk in sitting" and in "legs in sitting" than infants with diplegia.

The comparison between infants with diplegia and those with hemiplegia, shows that the former, at all ages, scored significantly lower for every subsection ($p<0.001$) than the latter. The same trend was observed for infants with quadriplegia vs those with hemiplegia ($p<0.0001$).

We have not identified a clear relation between the neurological optimaliy score and the US data. In fact, infants with severely abnormal cranial US scored at 12 months between 24 and 68 and infants with other findings (normal or persistent flares) between 33 and 70.

3.3. *HINE and GMFCS*

Infants with diplegia were in the functional level I (14% of cases) II (45%) and III (41%) and those with quadriplegia were in the functional level III (5%) IV (40%) and V (55%). In contrast, infants with hemiplegia were in the functional level I (72%) and II (28%) and those with dyskinetic CP were in the level II (40%) and III (60%). Fig. 2 shows a correlation analysis of Spearman for non parametric data with a strong and significant ($p<0.0001$) negative correlation between scoring by HINE and levels of GMFCS.

4. Discussion

In this study, we have confirmed and extended previous observations[14,15,20] by describing the HINE scores in infants with CP during the first year of age. Moreover, we have shown that by HINE it could be possible to differentiate infants with diplegia from those with quadriplegia by a lower scoring of the latter in the subsections tone and posture. A further result of this retrospective study is that HINE scores, at all evaluation ages, were strongly correlated to GMFCS levels recorded at 2 years of age.

A critical point of this study is the age of diagnosis of CP. In our study design we made the diagnosis of CP at 2 years, because this age is usually chosen as endpoint of the follow-up outcome for assessing high risk newborns.[21] In fact, the minimum age at which an infant can be reliably considered to have CP can vary from 2 to 10 years.[22] On the other hand, the age of 2 years has the advantage of maintaining cohort compliance and a better identification of infants for comprehensive early intervention services.[23] Furthermore, diagnosis at this age is very effective for identifying infants with CP as noted by other authors,[24] who showed that changes in the diagnosis of CP between 2 and 5 years of age occurred in only 3 of 209 extremely low birth-weight infants. A possible limitation of this study is that, due to the retrospective design, it was not possible to accurately standardize the physiotherapy program. In fact, at the moment of diagnosis, infants were under the care of physical therapists working in different health structures and it was not possible to elaborate and to check a common standard protocol for all of them.

A prognostic value of neurological optimality scores has been reported by Haataja et al.[15] in a population of 53 infants with hypoxic-ischemic encephalopathy (24 of them with a diagnosis of CP at 2 years of age). They have shown that HINE can provide additional information to distinguish the infants who will walk from those who will not walk from the age of 9–14 months. The results of our study provide a detailed information on neurological assessment in infants who developed CP by the first year of age, but the experimental

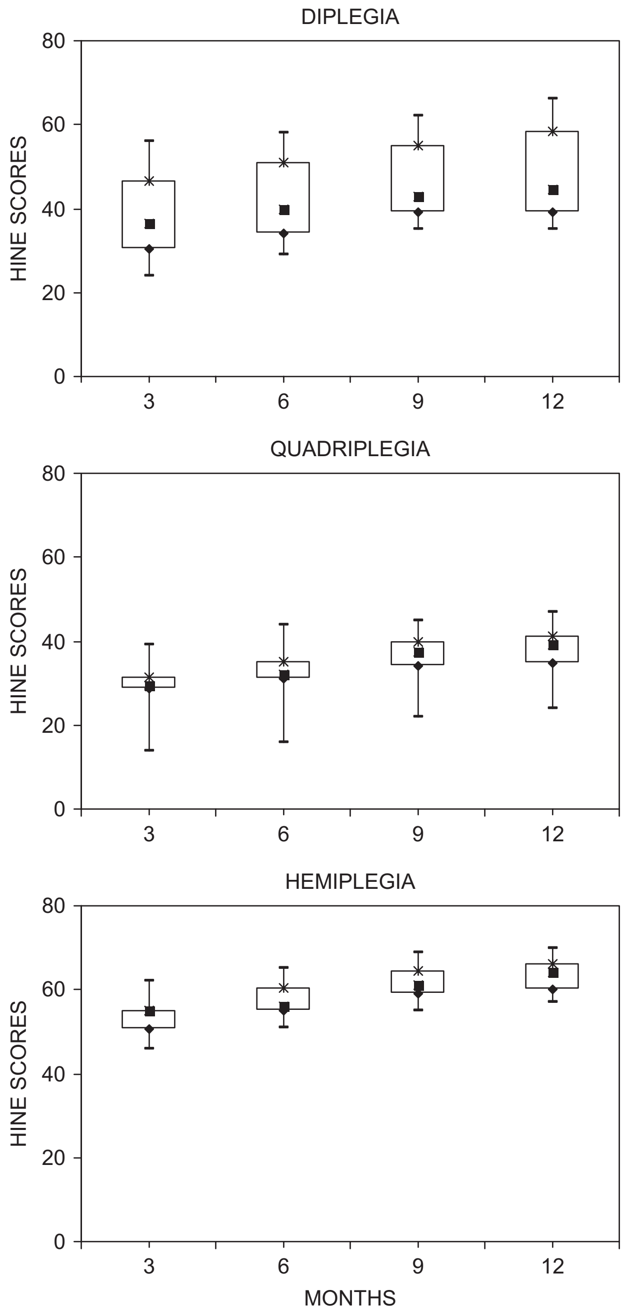

Fig. 1 – HINE scoring of infants with different forms of CP, throughout the first year of age (evaluations at 3, 6, 9 and 12 months). Scatter plots show Min–Max (-) Median (■) 25 th centiles (♦) and 75 th centiles (*).

design does not allow us to give a significance of predictivity to our results. However, from an observational point of view, we recorded some interesting data showing that, in our populations, there were some significant inter-group differences, as early as at the age of 3–6 months. In fact, the infants who scored between 67–72, at 9 and 12 months, and >60 at 3 and 6 months mainly had a hemiplegia, whereas those scoring below 40 had a severe diplegia (level III) or a quadriplegia. Furthermore, analysis of infants with hemiplegia showed that they scored much higher than the others with diplegia or quadriplegia in all subsections and namely in that of movements. Interestingly, the main differences between infants with quadriplegia and diplegia were represented by the subsections tone and posture, whereas movements, reflexes and cranial nerve were not significantly different. This observation could be explained by considering that one of the main features of the HINE is that the items are the same at all ages of testing. Consequently, infants score progressively better in accordance with their neuromotor development. In fact, although the items of HINE were considered not age-dependent, when used at 12 and 18 months of age in healthy term infants,[12] a further study[13] showed that in a similar cohort of infants there was a progressive reduction of the median and optimality scores with decreasing postnatal age. In particular, the lowest scores were observed in the posture (trunk and legs posture, head in sitting) and tone items (pulled to sit and popliteal angle) as well as in the reflexes and reaction ones (parachute and arm protection). Furthermore, Frisone et al.[14] identified some maturational and tone items, that were more frequently sub-optimal in preterm infants with a normal motor outcome. In our study, the results of HINE scores confirmed these observations even in a CP population. The changes of neurodevelopmental functioning observed during the first year of age are not surprising. In fact, infants with CP show different strategies during their neuromuscular response patterns, with a slight but continuous improvement of their motor performance,[25,26] although the presence of excessive co-activations of antagonist muscles and the reversal of normal distal to proximal muscle response patterns.[27] Moreover, infants with severe CP have considerable delay in the development of locomotion, but this occurs to only a minor extent when the degree of cerebral palsy is mild or moderate.[25] The differences observed between infants with diplegia and quadriplegia are consequently related to the inability of infants with quadriplegia to perform the requested performances at the same level of infants with diplegia. We observed that infants with quadriplegia always scored lower than infants with diplegia for the items "tone of adductors" and "trunk and legs in sitting" thus indicating that they are possibly "key items" for a differentiation between quadriplegia and diplegia.

The rate of motor development throughout the first year of age, evaluated by HINE, in our population of infants with CP seems to be progressive until the 9th month of age. After this month we observed only small increases of scoring. This could have a twofold explanation. Firstly, after the 9th month there could be a delay or arrest of the neuromotor development in these infants with CP, because they were not able to develop some complex activities, such as posture and standing, for which the central nervous system is physiologically "timed" after the third trimester of postnatal life. Secondly, it is possible that a period of three months is too short for a statistical comparison of scoring values, as observed for infants with quadriplegia or hemiplegia. Consequently, in order to have more reliable data about the rate of development, it can be suggested that intra-group comparisons should be done with an interval of at least six months (3 vs 9 month or 6 vs 12 month).

In the last decade, the gross motor functioning of infants with CP has been described by the GMFCS, which is

Table 3 – Items of Hammersmith Infant Neurological Examination in the total population

	Cranial nerve	Posture	Movements	Tone	Reflexes
	Median (range)	Median (range)	Median (range)	Median (range)	Median (range)
3 months					
Diplegia	11 (7–15)ns	10 (5–14)[a]	1 (0–2)ns	12.5 (6–18)[a]	3 (1–7)ns
Quadriplegia	10 (7–13)[c]	9 (3–11)[c]	0 (0–1)[c]	9 (3–13)[c]	2.5 (1–5)[c]
Hemiplegia	13 (11–15)[b]	14 (11–16)[b]	4 (2–5)[b]	16 (13–22)[b]	7 (4–9)[b]
6 months					
Diplegia	12 (8–15)ns	11 (8–16)[a]	1 (0–2)ns	13 (7–20)[a]	4 (1–7)ns
Quadriplegia	11 (7–14)[c]	9 (4.5–12)[c]	0 (0–1)[c]	9.5 (3.5–15)[c]	3 (1–5)[c]
Hemiplegia	14 (12–15)[b]	14 (12–16)[b]	4 (2–5)[b]	18 (13–22)[b]	7 (4–9)[b]
9 months					
Diplegia	13.5 (9–15)ns	12.5 (9–16)[a]	1 (0–3)ns	14 (10–21)[a]	4 (2–8)ns
Quadriplegia	12.5 (9–15)[c]	10 (6–12)[c]	1 (0–2)[c]	11 (6–15)[c]	3.5 (1–6)[c]
Hemiplegia	15 (13–15)[b]	15 (13–17)[b]	4 (2–5)[b]	20 (14–23)[b]	8 (4–10)[b]
12 months					
Diplegia	13.5 (10–15)ns	13 (9–18)[a]	1 (0–3)ns	14.5 (10–22)[a]	5 (2–9)ns
Quadriplegia	12.5 (9–15)[c]	10 (6–13)[c]	1 (0–2)[c]	12 (7–16)[c]	4 (1–6)[c]
Hemiplegia	15 (13–15)[b]	16 (15–18)[b]	4 (3–5)[b]	21 (17–23)[b]	8 (5–11)[b]

ns = no statistical significance on difference between diplegia and quadriplegia.
[a] Diplegia vs quadriplegia ($p<0.001$).
[b] Diplegia vs hemiplegia ($p<0.001$).
[c] Quadriplegia vs hemiplegia ($p<0.0001$).

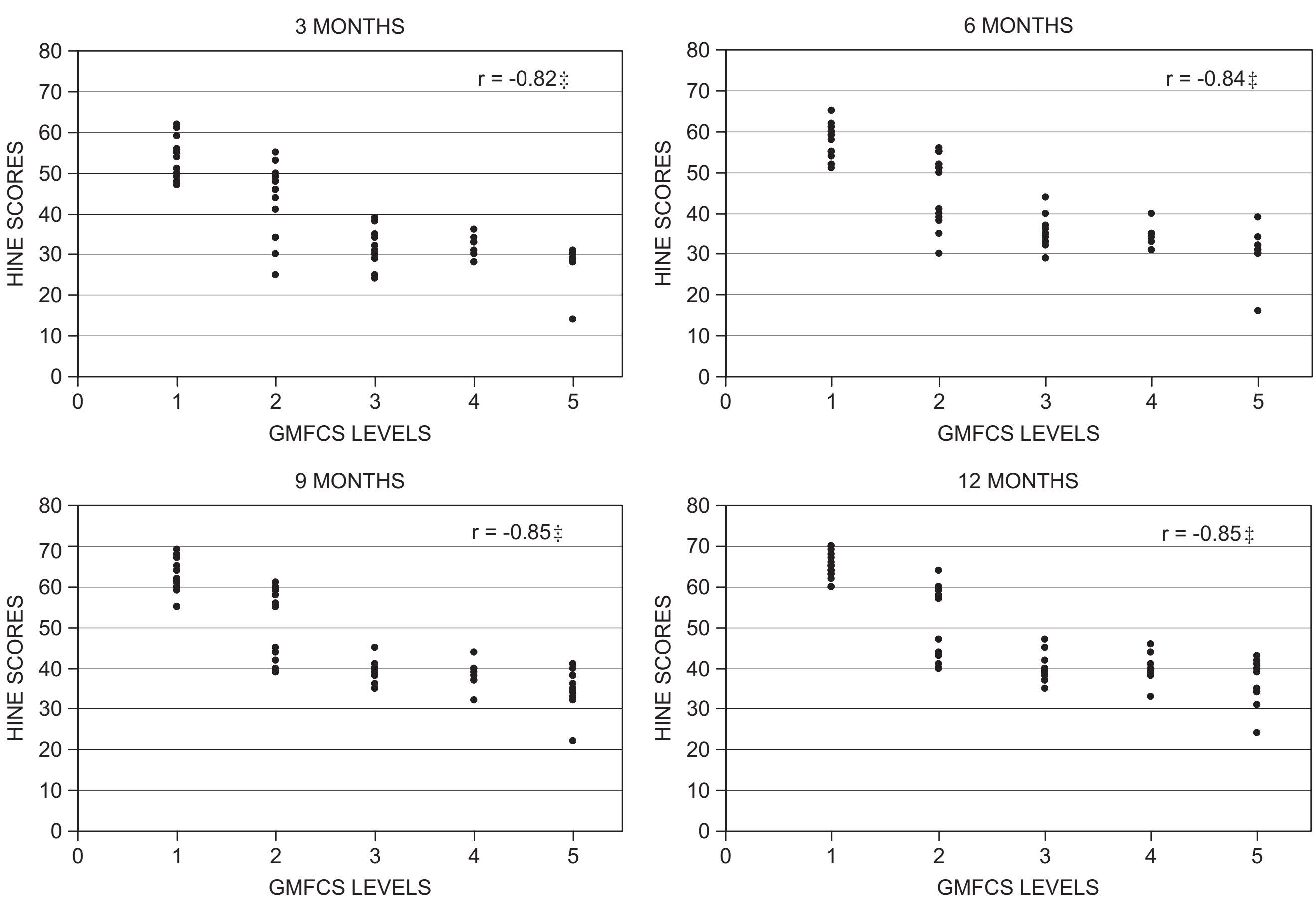

Fig. 2 – Correlations between the HINE scoring and the level of GMFCS in infants with CP at different ages (‡$p<0.0001$).

considered the only descriptive, reliable and predictive classification.[28,29] Our results for the relations between the topographical distribution of motor impairment and GMFCS are in accordance with other studies showing that infants with hemiplegia were usually in levels I and II, those with diplegia in levels I–III and those with quadriplegia in levels III–V.[23,28] In this line of evidence, we have shown a strong and significant negative correlation ($p<0.0001$) between HINE scores and GMFCS levels. In fact, all infants who scored >60 were in level I (infants with hemiplegia and mild diplegia) , whereas those scoring between 48–60 were in levels I–II (infants with hemiplegia and moderate diplegia) and those scoring below 48 (quadriplegia or diplegia) were in levels II–V. Our results, are in the same line of evidence of those reported by other authors,[14] showing that preterm infants who scored<52 between 6 and 15 months corrected age were unable to walk or sit unsupported at 2 years. Similarly those infants with hypoxic-ischemic encephalopathy scoring<40 at 9 and 14 months of age were severely limited in self abilities at 2 and 4 years of age, whereas those scoring between 40 and 66 were able to sit independently, but with some form of self mobility by 4 years.[15] Recently Ricci et al.[20] confirmed these observations by showing that between 6 and 9 months scores below 40 were associated with the inability to sit independently at 2 years, while scores between 41 and 60 were usually associated with independent sitting, but not with walking. Our data seem particularly interesting because for the first time we have shown a link between scoring values obtained by HINE during the first year of age and the most recognized and used evaluation scale of functional motor abilities of children with CP.

In conclusion, our data point out that by HINE we can have some additional information for the complex diagnostic strategy leading to the precocious diagnosis of CP and to an early physical therapy intervention.[30,31] Further developments of this study would be firstly to verify the possibility that the HINE could allow to predict not only the development of a CP, but more interestingly of a specific type of CP, and secondly to extend the follow-up program at school age to relate the optimality scores to a careful and detailed neurodevelopment assessment.

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