# Hammersmith Infant Neurological Examination for infants born preterm: predicting outcomes other than cerebral palsy

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**ABBREVIATIONS**

| | |
|---|---|
| BSID-II | Bayley Scales of Infant Development, Second Edition |
| HINE | Hammersmith Infant Neurological Examination |
| MDI | Mental Development Index |

**AIM** We explored the ability of the Hammersmith Infant Neurological Examination (HINE) to identify typical and delayed cognitive performance in a large population of infants born preterm, both with and without cerebral palsy (CP).
**METHOD** We conducted a retrospective study of infants born preterm who had repeated HINEs between 3 and 12 months corrected age. At 2 years, cognition was assessed using the Mental Development Index (MDI; from the Bayley Scales of Infant Development, Second Edition) and the presence and severity of CP was determined. All children were classified as cognitively typical/mildly delayed or significantly delayed (MDI <70) and CP. The predictive validity of HINE scores for significantly delayed cognitive performance, in children with and without CP, was calculated using specific cut-off scores according to age at assessment.
**RESULTS** Of 1229 eligible infants (gestational age 25–36wks, mean [SD] 34.9 [2.3]; 646 males, 583 females), 1108 did not develop CP, 891 had an MDI that was typical/mildly delayed, and 217 had an MDI less than 70. Of the 121 infants who developed CP, the MDI was typical in 28, mildly delayed in 27, and less than 70 in 66. HINE scores showed a good sensitivity and specificity, especially after 3 months, for detecting significantly delayed cognitive performance in infants without CP. In those who developed CP, the score was associated with their cognitive level.
**INTERPRETATION** The HINE provides information about the risk of delayed cognitive performance in infants born preterm with and without CP.

Several studies have investigated the relation between early and later motor development; in addition, recently, specific guidelines defining the tools that show the highest predictive value for cerebral palsy (CP) have been published.[1,2] Together with neuroimaging, the Hammersmith Infant Neurological Examination (HINE)[3–8] has proven to be the assessment with the highest predictive power after 5 months of age, while general movements[1,2,9] showed a higher predictive power in the first 3 months from birth. Much less has been published on a possible relation between early neuromotor performance and later non-motor outcome, although such information could help to better organize follow-up programmes for infants at risk. The research into significant early signs in this regard is even more challenging as no clear association between pathological findings based on conventional neuroimaging and cognitive functions has been detected yet[9,10] in the absence of lesions leading to CP. Only advanced diffusion-based brain imaging techniques, not available everywhere, have given information predicting non-motor outcomes but mostly only in group analysis and not specifically for an individual.[11] General movements have, however, been used in infants born preterm to find specific early signs evidencing that quality of motor repertoire relates to brain areas involved not only in motor but also in cognitive development.[9] However, these studies included a relatively low number of infants, and a conclusive relation between general movements and cognitive dysfunction remains to be further confirmed. More recently, the Standardized Infant Neuro Developmental Assessment neurological scale, an assessment that places considerable emphasis on the quality of movements, has been proposed as a tool for predicting both CP and other atypical outcome;[12,13] however, the scale

needs to be more fully explored, specifically in the low-risk population for which it was designed.[14]

The HINE is a simple to use neurological examination consisting of 26 items each scored on a scale of 0 to 3, designed for evaluating infants between 2 and 24 months of age.[3,8] It has been largely used for the early diagnosis of motor impairment and several studies have reported its use in both infants with brain lesions born preterm and at term,[3–8] showing that the examination can be used to predict sitting and walking ability, CP, and provide more detailed information on the type and severity of motor impairment. These studies have also shown that the HINE can, to some extent, predict the presence and the severity of other sequelae, including visual and feeding disorders.[3,15] However, its value in identifying infants at high risk for other atypical outcomes has not been systematically investigated.

In this study, our primary aim was to explore the ability of the HINE (both global and subsection scores) to identify typical and delayed performance assessed using the Mental Development Index (MDI) from the Bayley Scales of Infant Development, Second Edition (BSID-II) at 2 years in a large population of infants born preterm. Our secondary aim was to explore how HINE scores overlap in groups of children with typical and low MDI scores, who did and did not develop CP.

## METHOD

All the infants described in this study were part of a follow-up research project done for infants born preterm at the Neonatal Unit of the University of Catania and at the Fondazione Policlinico Gemelli IRCCS of Rome between January 2006 and December 2012. These are level II (specialty care) and level III (subspecialty) neonatal centres, admitting infants affected by preterm birth, low birthweight, asphyxia/seizures, infection, congenital heart disease, cerebral malformations, and those needing surgery. Infants were enrolled routinely to a 2-year follow-up research protocol.

Infants with a gestational age less than 37 weeks were eligible for the present study. The specific inclusion criteria were neurological assessments on four occasions in the first year (3, 6, 9, and 12mo) and a neurodevelopmental assessment at 2 years. Exclusion criteria were the presence of congenital anomalies, transfer to another hospital, or an incomplete follow-up programme.

The study protocol was approved by the Ethics Committee of the Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy, and signed informed consent was obtained from the parents in all cases.

In this retrospective study, the charts of 1441 infants born preterm consecutively discharged from our neonatal units were reviewed. Of these 1441 infants, 212 were excluded from the study: 21 because of the presence of congenital anomalies, 44 because of transfer to their local level II hospitals after stabilization of their clinical condition, and 147 because they did not complete the follow-up programme. There were no statistical differences in the patient characteristics in this patient group compared with those in the study group. Thus 1229 infants (gestational age range 25.0–36wks, mean [SD] 34.8 [2.3]) were included in the study. A proportion (almost 50%) of these infants have been described in an earlier paper with different aims.[5]

**What this paper adds**

- The Hammersmith Infant Neurological Examination (HINE) can be used in the first year to identify infants born preterm at risk for delayed cognitive performance.
- Age-dependent HINE cut-off scores are proposed for detecting increased risk of delayed cognitive performance.

### Neurological examination

The HINE was used for the clinical neurological examinations. It includes 26 items that assess five different aspects of a neurological examination: cranial nerve function, posture, movements, tone, and reflexes. Each item can be given a score from 0 to 3, 3 being optimal, giving a maximum total score of 78. The HINE is readily performed and accessible to all clinicians with a good interobserver reliability.[3–8,15] An optimality score[7] was obtained by calculating the distribution of the frequency of the scores in the typically developing term-born population, defining as optimal all the scores found in at least 90% of the cohort. At 9 and 12 months, scores of at least 73 are regarded as optimal, less than 73 as suboptimal; at 3 and 6 months, typically developing term-born infants scored at least 67 and at least 70 (median) respectively.[16] For infants born preterm, the concept of optimality is difficult but equivalent scores have been determined from infants with typical cranial ultrasound scans and typical 2-year outcomes.[3,7]

In this retrospective study, we analysed data from patients with HINE assessments at 3, 6, 9, and 12 months corrected age using both the score from the five subsections and the global score, which is the sum of subsection scores, for each time period.

### Outcomes

At 2 years corrected age, all infants were assessed using a structured neurological examination[17] and the BSID-II.[18] The BSID-II comprises two outcome scores, the Psychomotor Developmental Index and the MDI, with a mean of 100 and a standard deviation of 15. For the present study, we only used the MDI. An MDI score of 50 was apportioned to those infants who could not be tested because of physical or other difficulties. Two child neurologists (DMR, CB) with experience in neurodevelopmental examination administered the BSID-II. The examiners were blind to the HINE results.

The presence of CP was determined from the neurological examination. CP was defined as a developmental disorder of movement and posture, causing activity limitation, attributed to non-progressive disturbances related to brain injury early in development[19] and classified according to

the Gross Motor Function Classification System (GMFCS) with levels of I to V as developed by Palisano and colleagues[20] with good stability over time.

Outcomes were classified as being within the typical range (Bayley MDI scores >84 and no CP), mildly delayed performance (Bayley MDI scores 70–84 without CP), and significantly delayed performance (MDI <70 without CP). Children who developed CP were classified similarly according to their MDI score.

### Statistical analysis

Birthweight and gestational age are reported as mean and standard deviation (SD). HINE scores are reported as median and interquartile range (for data that are not normally distributed) at the four different ages, for four groups of infants (those with typical performance, mildly delayed performance, significantly delayed performance, and those with CP). Intergroup comparisons were done, as appropriate, by parametric (one-way analysis of variance performed separately for each age group, followed by post hoc analysis for multiple comparisons using Bonferroni's method) or by non-parametric test (Kruskall–Wallis test followed by Dunn's test of multiple comparisons). Spearman's rank correlation coefficient ($r_s$) was used to correlate the HINE global and subsection scores obtained at 3, 6, 9, and 12 months with the MDI scores at 2 years.

Sensitivity and specificity were used to assess the predictive value of cut-off HINE global and subsection scores, according to the age at assessment, for two different outcomes (significantly delayed performance and CP). Areas under the operating characteristic curve were obtained and cut-off values were estimated using the Liu method which maximizes the product of the sensitivity and specificity.[21] The level of significance was set at $p<0.05$. The analysis was performed with the software Stata Statistical Software, release 15 (StataCorp LLC 2017, College Station, TX, USA).

## RESULTS

Of the 1229 eligible infants, 1108 did not develop CP identified at 2 years; of these infants, 851 had MDI results classified as typical (MDI ≥85), 40 were mildly delayed (MDI 70–84), and 217 significantly delayed (MDI <70). Infants with typical and mildly delayed performance had similar findings in terms of gestational age, birthweight, and HINE scores; we therefore combined these two groups for analysis and refer to them as having typical/mildly delayed performance ($n$=891).

A total of 121 infants developed CP, of whom 28 had an MDI of at least 85, 27 had an MDI between 70 and 84, and 66 had an MDI less than 70 including the 33 infants given a score of 50 because a structured cognitive assessment was not possible. Infants with CP and MDI scores of at least 85 and between 70 and 84 were not similar in terms of HINE scores and were therefore not combined for the analysis.

Table 1 gives the clinical characteristics of the population related to outcome at 2 years. Infants with typical/mildly delayed performance (MDI ≥70) and without CP had a significantly higher mean gestational age ($p<0.001$) and mean birthweight ($p<0.05$) than the other groups. Infants with significantly delayed performance without CP had a significantly higher mean gestational age and mean birthweight ($p<0.01$) than those with CP. No differences ($p<0.05$) were observed for mean gestational age and birthweight in infants with CP when subdivided according to the MDI. However mean MDI scores differed according to the severity of CP, children with milder CP having higher MDI scores and vice versa (Table 2).

### HINE scores

At each evaluation age (Fig. 1), infants with a typical/mildly delayed performance at 2 years had significantly higher ($p<0.001$) HINE global scores than those with significantly delayed performance and those with CP; infants with significantly delayed performance had higher HINE global scores ($p<0.001$) than those with CP; of infants with CP and MDI, at least 85 had significantly higher HINE global scores ($p<0.001$) than those with CP (with or without low MDI scores). Numerical details of these data are given in Table S1 (online supporting information).

In our population, the sensitivity and specificity of HINE global cut-off scores estimated according to Liu et al.[21] at the four assessment ages (3mo, 58 out of 78; 6mo, 64 out of 78; 9mo, 69 out of 78; 12mo, 69 out of 78), for detecting firstly significantly delayed performance, then significantly delayed performance or CP and CP versus no CP, are given in Tables 3 and Table S2 (online supporting information). An age-dependency of the predictive values is reported with lower sensitivity and specificity at 3 months.

We found a significant ($p<0.001$) correlation between HINE global scores at 3 months corrected age ($r_s$=0.42), 6 months corrected age ($r_s$=0.47), 9 months corrected age ($r_s$=0.51), and 12 months corrected age ($r_s$=0.59) and MDI at 2 years corrected age (Fig. S1, online supporting information).

The sensitivity and specificity of cut-off scores for the five HINE subsections at each assessment age for detecting significantly delayed performance, and significantly delayed performance and/or CP are given in Table 4. At all ages the scores for the movements subsection showed the highest sensitivity and specificity. Additionally, the movements subsection scores had the most significant correlation at all four assessment ages (3mo corrected age $r_s$=0.65; 6mo corrected age $r_s$=0.67; 9mo corrected age $r_s$=0.69; 12mo corrected age $r_s$=0.69) with 2-year MDI scores (Table 5).

## DISCUSSION

In the present study we aimed to determine whether the HINE, already used to predict CP in young infants,[1–8] could also be used to identify infants at risk of cognitive delay. Few studies have attempted the early prediction of

**Table 1:** Infant background characteristics during the neonatal period

| | No CP | | CP | All children |
|---|---|---|---|---|
| | Typical/mildly delayed performance (*n*=891, 72%) | Significantly delayed performance (*n*=217, 18%) | All MDI levels[a] (*n*=121, 10%) | Total (*n*=1229, 100%) |
| Sex (male) | 463 | 120 | 63 | 646 |
| Mean (SD) gestational age, wks (range) | 35.3 (1.8)[b,c] (25–36) | 34.3 (2.8)[d] (26–36) | 32.2 (2.7) (26–36) | 34.9 (2.4) (25–36) |
| Mean (SD) birthweight, g (range) | 2312 (542)[c] (720–4350) | 2282 (663)[d] (630–4570) | 1749 (541) (630–3500) | 2256 (585) (630–4570) |
| Neonatal seizures (*n*) | 10 | 33 | 85 | 128 |
| Surgery (*n*) | 4 | 12 | 12 | 28 |
| Necrotizing enterocolitis (*n*) | 1 | 9 | 6 | 16 |
| Small for gestational age (*n*) | 15 | 22 | 18 | 55 |
| Bronchopulmonary dysplasia (*n*) | 4 | 20 | 16 | 40 |

Typical/mildly delayed, Mental Development Index (MDI) scores ≥70 without cerebral palsy (CP); significantly delayed performance, MDI <70 without CP. [a]No significant differences in gestational age and birthweight between infants with CP when subdivided by MDI scores. [b]$p<0.001$ statistical difference between typical/mildly vs significantly delayed. [c]$p<0.001$ statistical difference between typical/mildly vs CP. [d]$p<0.001$ statistical difference between significantly delayed vs CP.

**Table 2:** Gross Motor Function Classification System (GMFCS) levels of children with cerebral palsy (CP) according to the Mental Development Index (MDI)

| GMFCS level | CP and MDI ≥85 (*n*=28) | CP and MDI=70–84 (*n*=27) | CP and MDI <70 (*n*=66) |
|---|---|---|---|
| I | 21 (75%) | 10 (37%) | 3 (4%) |
| II | 6 (21%) | 11 (41%) | 11 (17%) |
| III | 1 (4%) | 4 (15%) | 23 (35%) |
| IV | 0 (0%) | 2 (7%) | 13 (20%) |
| V | 0 (0%) | 0 (0%) | 16 (24%) |

delayed neurodevelopmental outcomes.[8,22–26] We found that the HINE at 3, 6, 9, and 12 months corrected age could provide prognostic information on neurodevelopmental outcome in a population of infants born preterm with and without CP. First, we found a significant correlation between the HINE global score and the 2-year MDI scores, with a better correlation at 9 and 12 months. The relatively lower correlation of the HINE with 2-year outcome at 3 months is probably because, as previously reported,[4,5] this tool was designed for and validated in older infants, and some of the items are age-dependent.[4]

When we subdivided the outcome at 2 years in this large preterm cohort on the basis of the presence of significantly delayed performance, with or without CP, we were able to confirm and extend previous observations[3,5,6,22] that infants with typical/mildly delayed performance at 2 years had higher mean HINE global scores during the first year compared with those who had delayed performance at 2 years. Furthermore we were able to identify subpopulations of infants with CP according to the MDI score; infants with CP and an MDI of at least 85 had, in general, a better motor outcome, with 75% being in GMFCS level I, while only 37% and 4% of infants with an MDI between 70 and 84 and less than 70 respectively, were classified in such low GMFCS levels (Table 2), as also previously reported by others.[27] Although the infants with CP and an MDI of at least 85 had higher HINE global scores than those with CP and a low MDI, their HINE scores were still lower than those infants with significantly delayed performance without CP and obviously lower than those with typical/mildly delayed performance. These data demonstrate that the early pattern of neurological findings show a gradient related both to later motor outcome and to cognitive performance. On the other hand, the MDI scores for those with CP may be affected by their motor skills and therefore the MDI score may not be a true reflection of their non-motor skills.

Although some HINE global scores overlapped within the groups of children according to the outcome at 2 years, we identified specific HINE cut-off scores for infants who did not develop CP but who had delayed performance at 2 years. While, as previously reported,[1,3] single cut-off scores could identify patients with CP, further cut-off points could help to distinguish infants with typical outcomes from those with neurodevelopmental impairments (CP and/or with significant delay). Therefore, if a clinician's aim is to identify infants developing CP, the cut-off scores of less than 57 at 3 months and less than 66 at 12 months have the best sensitivity and specificity, as previously reported;[3] to identify infants with significantly delayed performance and/or with CP, the cut-off of 58 at 3 months, 64 at 6 months, and 69 at 9 to 12 months could be used. The good prediction of HINE cut-off scores even for infants with significantly delayed performance without CP shows that this tool is a useful early screener not only for detecting infants at risk of CP but also for those at risk of low general developmental scores. However, owing to a wide variation in the range of scores, in individual cases it may be difficult to clearly differentiate the type of

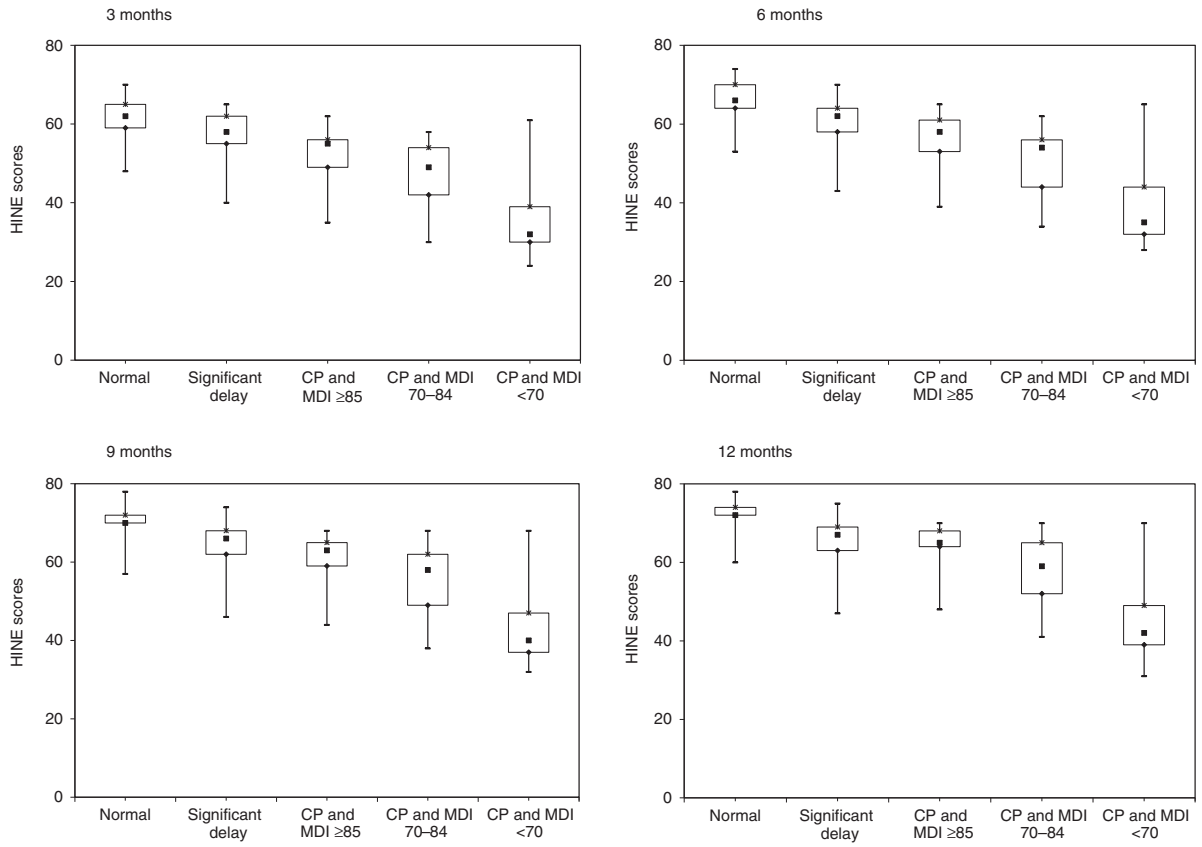


**Figure 1:** Global Hammersmith Infant Neurological Examination (HINE) median score and outcome. HINE scores from throughout the first year (evaluations at 3, 6, 9, and 12mo) in the study infants grouped by outcome. Scatter plots show 25th to 75th centiles with median. CP, cerebral palsy; MDI, Mental Development Index.

diagnosis. Therefore, these cut-off scores should be used with caution and not in isolation, but as part of a comprehensive clinical evaluation and one particularly making use of brain imaging data.

The HINE subsection with the best sensitivity and specificity for significantly delayed performance and/or with CP was 'movements' at all assessment ages. Furthermore, the scores from this subsection had the highest correlation with the MDI scores at 2 years at all assessment ages. This is consistent with the literature demonstrating the role of movements assessment for detecting infants at risk of CP[23] and with recent studies showing that abnormal movements may also be associated with other developmental disorders such as intellectual disability and autism spectrum disorder.[9,10,13,24,25]

One of the advantages of the HINE is that it is a structured examination including many aspects of neurological function, such as posture, tone, motility, and reflexes and reactions. A more detailed analysis of individual items, such as spontaneous motility, visual function, or achievement of postures, may increase the sensitivity for predicting cognitive outcome as they may better reflect the maturation of cortical networks, also linking with the cerebellum and basal ganglia and thalami, that are more relevant for the development of cognitive aspects.[9,25,28]

Recently, Hadders-Algra and colleagues[12,13] validated a new tool, the Standardized Infant Neuro Developmental Assessment, for assessing infants under 12 months of age at risk of neurodevelopment disorders. As with the HINE, the Standardized Infant Neuro Developmental Assessment proved to be a good tool not only for detecting infants at risk of CP, but also for those at high risk for developmental delay determined using the BSID-II, largely related to the inclusion of several items evaluating the quality of spontaneous movements.[12–14] The Standardized Infant Neuro Developmental Assessment has the same cut-offs and good prediction at all test ages whereas the HINE's predictive value for neurodevelopmental delay is age-dependent, including a moderate predictive value at 3 months. However, both these tools demonstrate that a well-structured neurological examination that includes the assessment of spontaneous motility is useful in terms of

**Table 3:** Cut-off scores for typical/mildly delayed performance according to the corrected age at assessment and outcome at 2y

| Age at assessment | Cut-off | Typical/mildly delayed (*n*=891) vs significantly delayed (*n*=217) | Typical/mildly delayed (*n*=891) vs significantly delayed or CP (*n*= 338) | CP (*n*=121) vs no CP (*n*=1108) |
|---|---|---|---|---|
| 3mo corrected age | 58 | Se 51, Sp 90 (AUC 0.71; accuracy 0.83) | Se 70, Sp 90 (AUC 0.80; accuracy 0.85) | Se 96, Sp 90 (AUC 0.93; accuracy 0.91) |
| 6mo corrected age | 64 | Se 81, Sp 71 (AUC 0.76; accuracy 0.73) | Se 88, Sp 71 (AUC 0.79; accuracy 0.76) | Se 97, Sp 70 (AUC 0.91; accuracy 0.75) |
| 9mo corrected age | 69 | Se 82, Sp 81 (AUC 0.82; accuracy 0.81) | Se 90, Sp 81 (AUC 0.86; accuracy 0.84) | Se 100, Sp 81 (AUC 0.92; accuracy 0.84) |
| 12mo corrected age | 69 | Se 76, Sp 93 (AUC 0.85; accuracy 0.90) | Se 84, Sp 93 (AUC 0.89; accuracy 0.91) | Se 96, Sp 93 (AUC 0.95; accuracy 0.94) |

CP, cerebral palsy; Se, sensitivity; Sp, specificity; AUC, area under receiver-operator curve.

**Table 4:** Hammersmith Infant Neurological Examination subsections: cut-off scores for typical performance according age at assessment and outcome at 2y

| Age (mo) at assessment | Cut-off | Typical/mildly delayed (*n*=891) vs significantly delayed or CP (*n*=338) | Typical/mildly delayed (*n*=891) vs significantly delayed (*n*=217) | CP (*n*=121) vs no CP (*n*=1108) |
|---|---|---|---|---|
| *3mo corrected age* | | | | |
| Cranial nerves | 13 | Se 66, Sp 89 | Se 62, Sp 89 | Se 54, Sp 91 |
| Posture | 13 | Se 47, Sp 69 | Se 34, Sp 70 | Se 90, Sp 90 |
| Movements | 5 | Se 86, Sp 75 | Se 80, Sp 75 | Se 88, Sp 85 |
| Tone | 18 | Se 65, Sp 82 | Se 51, Sp 82 | Se 75, Sp 81 |
| Reflexes | 7 | Se 54, Sp 71 | Se 36, Sp 71 | Se 61, Sp 81 |
| *6mo corrected age* | | | | |
| Cranial nerves | 14 | Se 79, Sp 67 | Se 77, Sp 67 | Se 62, Sp 86 |
| Posture | 14 | Se 64, Sp 72 | Se 60, Sp 72 | Se 56, Sp 84 |
| Movements | 5 | Se 84, Sp 85 | Se 77, Sp 85 | Se 86, Sp 91 |
| Tone | 19 | Se 62, Sp 82 | Se 47, Sp 82 | Se 86, Sp 86 |
| Reflexes | 11 | Se 83, Sp 53 | Se 93, Sp 40 | Se 99, Sp 47 |
| *9mo corrected age* | | | | |
| Cranial nerves | 14 | Se 52, Sp 76 | Se 39, Sp 76 | Se 56, Sp 92 |
| Posture | 15 | Se 58, Sp 73 | Se 55, Sp 73 | Se 56, Sp 85 |
| Movements | 5 | Se 82, Sp 95 | Se 74, Sp 95 | Se 82, Sp 92 |
| Tone | 20 | Se 64, Sp 84 | Se 54, Sp 89 | Se 73, Sp 87 |
| Reflexes | 11 | Se 79, Sp 64 | Se 71, Sp 64 | Se 92, Sp 71 |
| *12mo corrected age* | | | | |
| Cranial nerves | 14 | Se 51, Sp 79 | Se 38, Sp 79 | Se 56, Sp 94 |
| Posture | 16 | Se 76, Sp 73 | Se 73, Sp 73 | Se 58, Sp 87 |
| Movements | 5 | Se 80, Sp 97 | Se 72, Sp 97 | Se 81, Sp 82 |
| Tone | 21 | Se 68, Sp 76 | Se 60, Sp 76 | Se 73, Sp 84 |
| Reflexes | 12 | Se 92, Sp 63 | Se 89, Sp 63 | Se 90, Sp 69 |

CP, cerebral palsy; Se, sensitivity; Sp, specificity.

**Table 5:** Correlations between subsection Hammersmith Infant Neurological Examination scores and Mental Development Index at each age of assessment

| *n*=1229 | Cranial nerves $r_s$ (95% CI) | Posture $r_s$ (95% CI) | Movements $r_s$ (95% CI) | Tone $r_s$ (95% CI) | Reflexes and reactions $r_s$ (95% CI) |
|---|---|---|---|---|---|
| 3mo corrected age | 0.58 (0.543–0.617) | 0.30 (0.257–0.358) | 0.65 (0.623–0.687) | 0.52 (0.480–0.561) | 0.40 (0.354–0.448) |
| 6mo corrected age | 0.53 (0.495–0.575) | 0.44 (0.399–0.488) | 0.67 (0.647–0.707) | 0.50 (0.459–0.543) | 0.47 (0.430–0.517) |
| 9mo corrected age | 0.45 (0.409–0.497) | 0.46 (0.417–0.505) | 0.69 (0.667–0.725) | 0.56 (0.527–0.603) | 0.52 (0.487–0.568) |
| 12mo corrected age | 0.46 (0.417–0.505) | 0.56 (0.521–0.597) | 0.69 (0.666–0.724) | 0.58 (0.546–0.619) | 0.58 (0.551–0.624) |

$r_s$, Spearman rank correlation coefficient; CI, confidence interval.

prediction not only for those at high risk of CP, but also for high risk of developmental delay without CP.[12]

A limitation of this study, when considering cognitive outcome, is the relatively short follow-up period of 24 months although with the advantage of a high follow-up rate. Some infants with significantly delayed performance at this age may catch up and later have cognitive development in or nearer the typical range, and some with MDI scores within the typical range may be found to have, for example, learning difficulties at an older age when more detailed testing is possible.[29] Furthermore, in the present study the neurodevelopmental outcome was performed using the BSID-II, which is not now used; at the time of our study, the Italian norms of the Bayley Scales of Infant and Toddler Development, Third Edition or Fourth Edition were not available. Recent studies comparing the BSID-II and Bayley Scales of Infant and Toddler Development, Third Edition report higher-than-expected scores using the Third Edition,[30] suggesting that it may underestimate neurodevelopmental disability compared with the BSID-II, especially in infants born extremely preterm.[31]

In conclusion, our results suggest that the HINE can be used to assess infants at risk of more general neurodevelopmental disabilities, not only CP. The different age-dependent predictive value of scores should be considered in clinical practice to potentially differentiate infants at risk of CP from other disabilities. In practice, the likely development of CP will be identified early from a combination of neurological examination, general movements, and magnetic resonance imaging,[1,2] and the HINE cut-off scores proposed in the present study assist in differentiating infants who will have a significantly delayed performance.


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## Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

## SUPPORTING INFORMATION

The following additional material may be found online:

**Table S1:** Global HINE scores and developmental outcome

**Table S2:** Cut-off scores for predicting significantly delayed performance compared to infants with CP and those with CP and an MDI ≥85 according to corrected age at assessment

**Figure S1:** Correlations between the HINE and MDI score at different ages.

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