Hammersmith Infant Neurological Examination and long-term cognitive outcome in children born very preterm

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ABBREVIATIONS

DCD	Developmental coordination disorder
HINE	Hammersmith Infant Neurological Examination
MABC-2	Movement Assessment Battery for Children, Second Edition
MND	Minor neurological dysfunction
WISC-IV	Wechsler Intelligence Scale for Children, Fourth Edition

AIM To study the association between the Hammersmith Infant Neurological Examination (HINE) at age 2 years and neurocognition at age 11 years in children born very preterm. We hypothesized that the HINE at 2 years would be associated with neurocognition, that is, neurological, motor, and cognitive outcomes at 11 years.

METHOD A total of 174 children (mean gestational age 29.0wks, SD 2.7; minimum 23.0, maximum 35.9; 95 [55%] males, 79 [45%] females) born very preterm (birthweight ≤1500g/gestational age <32wks), were included in a prospective cohort recruited from 2001 to 2006 in Turku, Finland. The HINE was performed at 2 years' corrected age. Neurocognition at 11 years was assessed with the Touwen neurological examination, Movement Assessment Battery for Children, Second Edition (MABC-2), and full-scale IQ (Wechsler Intelligence Scale for Children, Fourth Edition).

RESULTS The HINE global score was associated with the results of the Touwen neurological examination (odds ratio [OR]=0.9, 95% confidence interval [CI] 0.8–0.9, p=0.001), MABC-2 (β=1.4, 95% CI 0.7–2.2, p<0.001), and full-scale IQ (β=1.2, 95% CI 0.8–1.7, p<0.001), even when adjusted. When children with cerebral palsy (CP) were excluded, the HINE was still associated with full-scale IQ (unadjusted β=1.2, 95% CI 0.3–2.1, p=0.01).

INTERPRETATION A higher HINE global score at 2 years was associated with better general intelligence at 11 years even in children without CP. The HINE may be a useful tool to detect children at risk for later cognitive impairment.

The incidence of cerebral palsy (CP) in children born preterm is decreasing[1,2] whereas other neurodevelopmental impairments, such as minor neurological dysfunction (MND) and developmental coordination disorder (DCD), are still prevalent in children born preterm compared to their peers.[3,4] Both MND and DCD commonly co-occur with other developmental difficulties, such as problems with learning, behaviour, and attention;[5–7] this underlines the importance of recognizing these conditions even in the absence of CP. A structured neurological examination of the newborn has been shown to be an efficient tool to predict early neurodevelopmental outcome.[8,9] The Hammersmith Infant Neurological Examination (HINE) is a simple and standardized method for assessing children between 3 and 24 months of age.[10] It has a strong predictive validity for CP even before 5 months, particularly when combined with brain magnetic resonance imaging (MRI).[8] Although CP can usually be diagnosed by 2 years,[8,9] early developmental scales might underestimate the rate of non-CP neurodevelopmental impairments compared to later, more specific assessments.[1]

Children born very preterm are also at risk for different levels of cognitive impairment.[1,11–13] Neurological assessment at a term-equivalent age has been shown to associate with cognitive development at 2 years in children born preterm.[14] To our knowledge, no studies have been conducted on the association between the HINE in early childhood and non-CP neurocognitive impairments at middle-school age. Our aim was to study the association between the HINE at 2 years' corrected age and neurocognition, that is, neurological, motor, and cognitive outcomes at 11 years in children born very preterm. The hypothesis was that the HINE at 2 years would be associated with neurocognition at 11 years. In addition, we expected the neurological outcome at 11 years to associate with the concurrent cognitive outcome.

METHOD

Participants

This prospective regional cohort study is part of the multidisciplinary PIPARI study (The Development and

Functioning of Very Low Birth Weight Infants from Infancy to School Age) of infants born very preterm.[15] Participants were born from January 2001 to December 2006 to Finnish- or Swedish-speaking families at Turku University Hospital, Finland. From 2001 to 2003, the inclusion criteria were a birthweight equal to or less than 1500 grams and preterm birth (<37wks gestation). From 2004, the inclusion criteria were extended to all infants born at less than 32 weeks of gestational age irrespective of birthweight. Exclusion criteria were severe congenital anomalies or diagnosed syndromes affecting development. The flow chart showing participant selection is shown in Figure S1 (online supporting information).

Ethical approval

The ethics review committee of the Hospital District of South-West Finland approved the study protocol in 2000 and 2012. Written informed consent was provided by parents and children.

HINE at 2 years' corrected age

The structured neurological examination at 2 years' corrected age was performed by an experienced physician and physiotherapists using the HINE.[10] The sequential Hammersmith Neonatal Neurological Examination was performed in all children during the neonatal period, but the HINE was not performed before 2 years unless there was a high risk or clinical suspicion of CP. The HINE consists of three sections: (1) neurological examination; (2) developmental milestones; and (3) behaviour. The first section includes 26 items that evaluate five subsections: cranial nerve function; posture; movements; tone; and reflexes. The second section includes eight items that describe developmental milestones and the third section includes three items that evaluate behaviour during assessment. Each item of the first section is scored individually and these item scores are summed up to calculate the subsection scores and then the global score (minimum 0, maximum 78). In this study, HINE scores were analysed as a continuous variable. If there was a diagnosis of CP, it was confirmed after a systematic clinical follow-up at 2 years' corrected age by an experienced child neurologist. To classify the severity of CP, the Gross Motor Function Classification System (GMFCS) was used.[16]

Neurocognition at 11 years of age

Touwen Neurological Examination

The neurological outcome at 11 years was assessed with the Touwen neurological examination.[6] It was performed by one of three physicians except for the ophthalmological part, which was performed by an ophthalmologist as part of a comprehensive ophthalmological assessment. The Touwen neurological examination includes eight domains: posture and muscle tone; reflexes; fine manipulation; involuntary movements; associated movements; coordination and balance; sensory function; and cranial nerve function. All Touwen neurological examination tests were video recorded; in case of any uncertainty regarding the examinations, the videos were reassessed together with an experienced child neurologist. The examinations were classified according to the classification criteria set out by Hadders-Algra[6] using computerized scoring. The result was considered neurologically typical if the child had no abnormal domains; if the child had one or two dysfunctional domains, it was regarded as simple MND. For complex MND, more than two domains had to be dysfunctional. Children who had a result of neurologically typical or simple MND were classified as having a neurological condition within the typical range, unlike children with complex MND. This classification was done to highlight the clinically important features of complex MND.[17]

What this paper adds

- A Hammersmith Infant Neurological Examination (HINE) global score at 2 years was associated with long-term neurocognitive function.
- Severe cognitive impairment was significantly more common in 11-year-old children with complex minor neurological dysfunction compared to typically developing children.
- The HINE performed at 2 years detects risks of cognitive impairment at 11 years in children born very preterm.
- A higher HINE score at 2 years was associated with better general intelligence at 11 years.

Movement Assessment Battery for Children, Second Edition

Motor development at 11 years was evaluated with the Movement Assessment Battery for Children, Second Edition (MABC-2)[18,19] by the same physician who performed the Touwen neurological examination. The MABC-2 includes three subscales: manual dexterity; aiming and catching; and balance. The raw scores of the subscales were converted into total standard and centile scores according to the test manual using age band 3 (11–16y) and the norms for 11-year-old children. A total score greater than the fifth centile indicated typical motor development. A score equal to or less than the fifth centile, together with motor problems that interfered with activities of daily living, denoted DCD.[19] The Developmental Coordination Disorder Questionnaire 2007 was used to assess how motor problems interfered with activities of daily living. The results of the questionnaire have been published elsewhere.[20]

Wechsler Intelligence Scale for Children, Fourth Edition

Cognitive outcome at 11 years was assessed with the Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV), Finnish translation.[21,22] The assessment was performed in Finnish or Swedish according to the child's native language. Finnish assessments were performed by one of two Finnish-speaking psychologists and the Swedish assessments by a native-speaking Swedish psychologist. General intelligence was measured with a full-scale IQ that consisted of four indexes: verbal comprehension; perceptual reasoning; working memory; and processing speed. Based on the test manual,[21,22] a full-scale IQ of less than 70 (≤2SD) was classified as severe cognitive impairment.

Table 1: Characteristics of children born very preterm (birth weight ≤1500g or gestational age <32wks) compared to children born very preterm who withdrew from the study

Characteristic	Total study cohort (*n*=174)	Children who withdrew (*n*=47)	*p*
Gestational age mean (SD), (minimum, maximum), wks	29.0 (2.7) (23.0, 35.9)	29.2 (2.7) (23.7, 34.1)	0.6
Birth weight mean (SD), (minimum, maximum), g	1119.2 (314.4) (400.0, 2120.0)	1226.3 (375.1) (580.0, 1970.0)	0.05
Small for gestational age (≤2SD), *n* (%)	58 (33)	10 (21)	0.1
Birth weight z-score, mean (SD), (minimum, maximum)	−1.4 (1.5) (−4.9, 3.4)	1.2 (1.3) (−3.9, 1.1)	0.3
Male, *n* (%)	95 (55)	30 (64)	0.3
Caesarean delivery, *n* (%)	106 (61)	28 (60)	0.9
Multiple birth, *n* (%)	58 (33)	9 (19)	0.06
Bronchopulmonary dysplasia, *n* (%)	24 (14)	6 (13)	0.9
Operated necrotizing enterocolitis, *n* (%)	7 out of 171 (4)	3 out of 46 (7)	0.4
Sepsis, *n* (%)	31 (18)	6 (13)	0.4
Laser-treated retinopathy of prematurity, *n* (%)	5 out of 163 (3)	3 out of 44 (7)	0.4
Major brain pathologies on MRI at term age,[a] *n* (%)	45 out of 169 (27)	11 out of 46 (24)	0.7
Mother's education >12y, *n* (%)	109 out of 172 (63)	20 out of 43 (47)	0.04
Father's education >12y, *n* (%)	56 out of 170 (33)	12 out of 41 (29)	0.7

[a]The specific MRI protocol and details about the classification of the findings have been described by Setänen et al.[20] MRI, magnetic resonance imaging.

Statistical analysis

Differences in continuous background characteristics (gestational age and birthweight) between participating children and children who withdrew from the study were studied using an independent samples *t*-test (Table 1). For the categorical background characteristics, a χ^2 or Fisher's exact test was used, as appropriate. Differences in HINE global score according to the 11-year outcomes (typical neurological outcome or complex MND, typical motor development or DCD, and full-scale IQ≥70 or full-scale IQ<70) were studied using a Mann–Whitney *U* test (Tables 2–4). Associations between the continuous HINE global score and continuous outcome variables (MABC-2, full-scale IQ, and four indexes of the WISC-IV) were studied using linear regression analysis. The association between the continuous HINE global score and categorical outcome variable (typical neurological outcome or complex MND) was studied using logistic regression analysis. The association between the 11-year outcome (typical neurological outcome or complex MND and continuous full-scale IQ) was studied using linear regression. The analyses were adjusted for sex, brain MRI findings at term, paternal education, and birthweight z-score since these have previously been found to be associated with cognition at 11 years in children born very preterm in this cohort.[12] Goodness of fit was reported according to the Akaike information criterion, where information criteria are in smaller-is-better form (Table 5). Residuals were checked to justify the analysis. Possible multicollinearity was checked; a correlation coefficient equal to or greater than 0.8 and/or tolerance value less than 0.1 and/or Phi and Cramer's V equal to or greater than 0.8 was considered a sign of multicollinearity. Statistical analysis was performed using SPSS v27.0 (IBM Corp., Armonk, NY, USA). A two-tailed $p<0.05$ was considered statistically significant.

RESULTS

All 174 study children were examined with the HINE at 2 years' corrected age. The characteristics of the study children and children who withdrew from the study are shown in Table 1. The median HINE global score was 74.1 (minimum 38.0, maximum 78.0). Nine (5%) children were diagnosed with CP by 2 years' corrected age. In children with CP, the median HINE global score was 56.0 (minimum 38.0, maximum 74.0) and the median (minimum, maximum) subsection scores were 15.00 (12.0, 15.0) for cranial nerve function, 9.5 (7.5, 16.0) for posture, 19.5 (10.0, 24.0) for tone, 3.0 (0.0, 6.0) for movements, and 9.0 (4.5, 14.0) for reflexes. Of the children with CP, four were classified in GMFCS level I, three in GMFCS level II, and two in GMFCS level IV. All children with CP were diagnosed by 2 years' corrected age and the diagnosis was confirmed at 11 years in all cases.

Neurocognition at 11 years of age

Touwen neurological examination

Neurological outcome at 11 years was assessed in 166 (95%) children using the Touwen neurological examination. Of these children, 127 (77%) were within the typical range, including 63 (38%) children with a neurologically typical result and 64 (39%) children with simple MND. A total of 31 (19%) children had a complex MND and eight

Table 2: HINE global score and subsection scores at 2 years' corrected age according to the outcome of the Touwen Neurological Examination at 11 years in children born very preterm without cerebral palsy

	Children with typical neurological development (*n*=127)	Children with complex MND (*n*=31)	*p*
HINE global score	74.5 (67.5, 78.0)	74.0 (66.0, 78.0)	0.3
Cranial nerve function	15.0 (12.0, 15.0)	15.0 (12.5, 15.0)	0.8
Posture	17.0 (13.5, 18.0)	16.5 (14.0, 18.0)	0.002
Tone	24.0 (18.0, 24.0)	24.0 (20.0, 24.0)	0.3
Movements	6.0 (3.0, 6.0)	6.0 (5.0, 6.0)	0.6
Reflexes	14.0 (9.0, 15.0)	14.0 (11.0, 15.0)	0.3

Data are median (minimum, maximum). HINE, Hammersmith Infant Neurological Examination; MND, minor neurological dysfunction.

Table 3: HINE global score and subsection scores at 2 years' corrected age according to the outcome of the MABC-2 at 11 years in children without cerebral palsy born very preterm

	Children with typical motor development (*n*=140)	Children with DCD (*n*=18)	*p*
HINE global score	74.5 (67.5, 78.0)	74.3 (66.0, 76.5)	0.5
Cranial nerve function	15.0 (12.0, 15.0)	15.0 (13.0, 15.0)	0.3
Posture	17.0 (14.0, 18.0)	16.5 (13.5, 18.0)	0.06
Tone	24.0 (18.0, 24.0)	24.0 (20.0, 24.0)	0.7
Movements	6.0 (3.0, 6.0)	6.0 (5.0, 6.0)	0.2
Reflexes	14.0 (9.0, 15.0)	14.0 (11.0, 15.0)	0.7

Data are median (minimum, maximum). HINE, Hammersmith Infant Neurological Examination; MABC-2, Movement Assessment Battery for Children, Second Edition; DCD, developmental coordination disorder.

Table 4: HINE global score and subsection scores at 2 years' corrected age according to the outcome of the WISC-IV at 11 years (children with cerebral palsy are included)

	Children with full-scale IQ≥70 (*n*=150)	Children with full-scale IQ<70 (*n*=15)	*p*
HINE global score	74.5 (67.5, 78.0)	73.0 (66.0, 75.5)	0.02
Cranial nerve function	15.0 (12.0, 15.0)	15.0 (13.0, 15.0)	0.9
Posture	17.0 (13.5, 18.0)	16.0 (14.0, 18.0)	0.007
Tone	24.0 (18.0, 24.0)	23.0 (19.0, 24.0)	0.1
Movements	6.0 (3.0, 6.0)	6.0 (5.0, 6.0)	0.1
Reflexes	14.0 (9.0, 15.0)	14.0 (11.0, 15.0)	0.3

Data are median (minimum, maximum). HINE, Hammersmith Infant Neurological Examination; WISC-IV, Wechsler Intelligence Scale for Children, Fourth Edition.

(5%) had CP. All but one of the children with CP were successfully examined.

A higher HINE global score at 2 years was associated with a decreased risk for complex MND in the Touwen neurological examination at 11 years when all study children were included; this was confirmed when adjusted for sex, brain MRI findings at term, paternal education, and birthweight z-score (Table 5). When children with CP were excluded, the association did not remain. Table 2 presents the median values of the HINE global score and subsection scores at 2 years according to the Touwen neurological examination at 11 years.

MABC-2

The motor outcome of the 166 (95%) children was assessed with the MABC-2 at 11 years. Of these children, 140 (84%) had typical motor development, 18 (11%) had DCD, and eight (5%) had CP. All but one of the children with CP were successfully examined.

A higher HINE global score was associated with higher centiles in the MABC-2 even when adjusted (Table 5). When children with CP were excluded, the association did not remain. The median values of the HINE scores at 2 years according to the MABC-2 outcome at 11 years are shown in Table 3.

WISC-IV

The cognitive outcome of all 174 (100%) children was assessed with the WISC-IV at 11 years. Of the 165 children without CP, 150 (91%) had a full-scale IQ equal to or greater than 70. Of the children with CP, four (44%) had a full-scale IQ equal to or greater than 70. The mean values of the full-scale IQ and four indexes at 11 years are shown in Table 6. In addition, Table 6 shows the associations between the HINE global score at 2 years and full-scale IQ and four indexes at 11 years. The full-scale IQ improved by 1.2 points when the HINE global score increased by one point (β=1.2, 95% confidence interval [CI] 0.8–1.7, p<0.001). The scatter plot of the HINE global score at 2 years and full-scale IQ at 11 years is shown in Figure 1. The median values of the HINE global score and subsection scores at 2 years according to the outcome of the WISC-IV at 11 years are shown in Table 6.

At 11 years, typical neurological development was associated with higher full-scale IQ (β=14.1, 95% CI 8.5–19.8, p<0.001); this was also the case when adjusted and when children with CP were excluded (β=10.6, 95% CI 4.7–16.4, p<0.001). Children with complex MND, compared to children with typical neurological development, had lower scores in full-scale IQ (81.3 vs 91.9, p=0.001), perceptual reasoning (86.1 vs 95.6, p=0.002), and working memory (82.1 vs 96.2, p<0.001); however, the difference was not

Table 5: Associations between the HINE global score at 2 years' corrected age and complex MND or centiles in the MABC-2 in all 11-year-old children born very preterm and children without cerebral palsy

	All study children				Children without CP			
Outcome variable	OR	95% CI	*p*	AIC	OR	95% CI	*p*	AIC
Complex MND								
Unadjusted	0.8	0.8–0.9	0.001	69.4 (*n*=166)	1.1	0.9–1.2	0.4	64.3 (*n*=158)
Adjusted	0.8	0.7–0.9	0.001	140.7 (*n*=157)	1.1	0.9–1.3	0.4	131.5 (*n*=149)
MABC-2								
Unadjusted	1.4	0.7–2.1	<0.001	1519.2 (*n*=166)	1.1	−0.3 to 2.6	0.1	1449.2 (*n*=158)
Adjusted	0.9	0.2–1.7	0.02	1426.4 (*n*=157)	0.5	−0.8 to 1.9	0.4	1356.6 (*n*=149)

HINE, Hammersmith Infant Neurological Examination; MND, minor neurological dysfunction; MABC-2, Movement Assessment Battery for Children, Second Edition; CP, cerebral palsy; OR, odds ratio; CI, confidence interval; AIC, Akaike information criterion (smaller-is-better form).

Table 6: Mean values of full-scale IQ and four indexes assessed with the WISC-IV at 11 years in children born very preterm and their association with the HINE global score at 2 years' corrected age

			HINE global score at 2 years							
			All study children (*n*=174)				Children without CP (*n*=165)			
	All study children (*n*=174)	Children without CP (*n*=165)	R^2	β	95% CI	*p*	R^2	β	95% CI	*p*
Full-scale IQ	87.7 (17.6) (40.0, 131.0)	89.1 (16.2) (40.0, 131.0)	0.14	1.2	0.8–1.7	<0.001	0.04	1.2	0.3–2.1	0.01
Verbal comprehension	89.8 (14.9) (46.0, 122.0)	90.6 (14.1) (46.0, 122.0)	0.07	0.7	0.4–1.1	<0.001[a]	0.03	1.0	0.2–1.8	0.02
Perceptual reasoning	91.6 (17.3) (40.0, 122.0)	93.1 (15.8) (51.0, 122.0)	0.16	1.3	0.8–1.7	<0.001[a]	0.05	1.3	0.4–2.2	0.006[a]
Working memory	92.2 (16.7) (46.0, 133.0)	93.1 (16.1) (46.0, 133.0)	0.04	0.6	0.2–1.1	0.008	0.01	0.5	−0.5 to 1.4	0.3
Processing speed	93.6 (17.6) (47.0, 153.0)	94.7 (16.7) (47.0, 153.0)	0.11	1.1	0.6–1.5	<0.001[a]	0.01	0.7	−0.3 to 1.7	0.2

Data are mean (SD) (minimum, maximum), unless otherwise stated. [a]$p<0.05$ adjusted for sex, brain MRI findings at term, paternal education, and birth weight z-score.[12]WISC-IV, Wechsler Intelligence Scale for Children, Fourth Edition; HINE, Hammersmith Infant Neurological Examination; CP, cerebral palsy; CI, confidence interval; MRI, magnetic resonance imaging.

statistically significant for verbal comprehension (88.5 vs 91.7, $p=0.3$) and processing speed (90.0 vs 96.3, $p=0.06$). Severe cognitive impairment was more common in children with complex MND compared to children with a neurological outcome within the typical range at 11 years (26% vs 3%, $p<0.001$).

DISCUSSION

This study showed that a structured neurological examination at 2 years' corrected age was associated with cognitive development at 11 years in a regional cohort of children born very preterm from 2001 to 2006 in Turku, Finland. To our knowledge, this is the first study to show an association between the HINE at 2 years and general intelligence at middle-school age. When the HINE global score increased by 1 point, the subsequent full-scale IQ was improved by 1.2 points. In addition, severe cognitive impairment was significantly more common in 11-year-old children with complex MND compared to children with typical neurological development at 11 years.

A higher HINE global score at 2 years was associated with better general intelligence, verbal comprehension, perceptual reasoning, and processing speed at 11 years even when adjusted for sex, brain MRI findings at term, paternal education, and birthweight z-score. Associations with reasoning abilities, that is, verbal comprehension and perceptual reasoning, were evident even when the children with CP were excluded. A structured neurological examination at 2 years seems to tap aspects of cognitive development even at 11 years. Our results are in line with the findings by Romeo et al.,[23,24] which showed that the HINE at 3, 6, 9, and 12 months of corrected age provides information about the cognitive outcome at 2 years of corrected age in children born preterm with and without CP.

The association between complex MND and adverse cognitive development is consistent with previous data.[7,17] In our study, the prevalence of severe cognitive impairment in 11-year-olds with complex MND was as high as 26%. In contrast, the prevalence of severe cognitive impairment in children with typical neurological development was 3%,

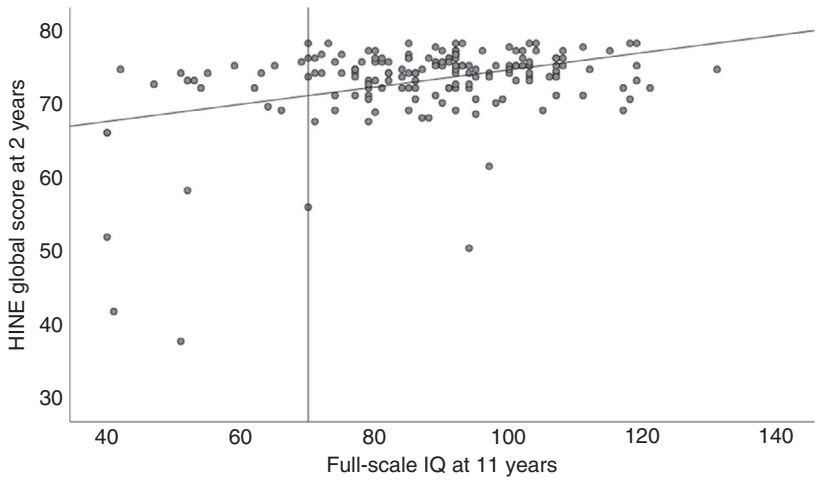

Figure 1: Scatter plot of the Hammersmith Infant Neurological Examination (HINE) global score at 2 years' corrected age and full-scale IQ at 11 years in children born very preterm (*n*=174). The vertical line represents a full-scale IQ of 70.

which is in line with a national register study that reported a severe cognitive impairment prevalence rate of 2.5% in 7-year-olds born very preterm.[13] The high rate of severe cognitive impairment underlines not only the clinical relevance of complex MND but also the importance of its early detection that launches the targeted support services.

A higher HINE score at 2 years was associated with better neurological and motor outcomes at 11 years and was statistically significant even when adjusted. These associations were not statistically significant when children with CP were excluded. In this study and in line with clinical experience, complex MND or DCD at 11 years in children without CP could not be predicted based on a single HINE assessment performed at 2 years. However, studies have shown that the HINE is a reliable tool for the early identification of CP[8] and correlates with neonatal brain MRI findings.[25] These results are supported by a recent systematic review by Caesar et al.,[26] which showed that although the HINE has high sensitivity and specificity for the prediction of severe motor impairments, it was not as discriminative for mild-to-moderate motor impairments. Thus, it is reasonable that the association between the HINE and neurological and motor development was not statistically significant when children with CP were excluded.[27]

In this study, we did not assess HINE scores at 2 years according to the brain imaging findings at term age because we previously reported that the negative predictive value of normal findings or minor pathologies in brain MRI for a HINE global score greater than 70 was 90.3% and the positive predictive value of major pathologies for a HINE global score equal to or less than 70 was 31.5%.[28] According to Hadders-Algra, complex MND is likely to associate with structural brain deficit and may be considered as a borderline form of CP.[17] Despite the emergence of more information regarding the possible alterations in brain structure and function behind non-CP neurodevelopmental impairments,[6,29] the connection is not as well known as with CP and its brain pathology.

The HINE subscale score of posture was statistically significantly lower in children with complex MND and children with severe cognitive impairment compared to children without these impairments. This is in line with previous data showing that children at high risk for neurodevelopmental impairments exhibit more challenges in postural control compared to children with typical neurodevelopment, who seem to have a better repertoire of postural control mechanisms.[30]

Compared to CP, the identification of infants at risk for subsequent MND, DCD, or cognitive disability is challenging. A suboptimal outcome on neonatal neurological examination and severe pathologies on neonatal brain MRI increase the risk for cognitive delay at 2 years.[14,31] Early diagnosis of CP involves a combination of neuroimaging and standardized neurological and motor assessments. In this study, the HINE was performed primarily to evaluate neurological condition at 2 years' corrected age and confirm that all children with CP were diagnosed correctly. To evaluate cognition at 2 years, the Bayley Scales of Infant Development, Second Edition, was conducted in the study cohort as described by Munck et al.[32] However, the HINE together with a parental questionnaire, for example, the Parent Report of Children's Abilities-Revised,[33] could offer an alternative method to identify children at risk for subsequent cognitive impairment in clinical settings where comprehensive cognitive assessments are not available.

The strength of our study is that it was a longitudinal prospective cohort study. Retention rate was reasonably high. The assessments of neurocognitive outcomes were performed by trained specialists. All assessments were conducted using the latest full versions instead of abbreviated measures. Regarding the WISC-IV, up-to-date national norms were used to classify severe cognitive impairment. This study had some limitations. It was a single-centre study with a relatively small subgroup of children with adverse outcomes, which might limit the generalizability of the findings. It was not possible to compare the results with peers born at term in the absence of a control group. Another potential limitation was that the MABC-2 was not done repeatedly as suggested in the latest recommendations.[5] However, the most recent guidelines were published after the data collection of this study. In addition, the numbers of children with CP, complex MND, DCD, and severe cognitive impairment were moderate, which might limit the generalizability of the findings.

In conclusion, the HINE performed at 2 years helped to detect the risk of cognitive impairment at 11 years in children born very preterm even in the absence of CP. Interestingly, the HINE, which is primarily used to assess neurological status at an early age, was associated with cognitive outcome at middle-school age, but not with neurological and motor developmental outcomes in children without CP. The clinical importance of this finding should be explored in future studies. We emphasize the risk of neurocognitive impairments even in the absence of CP and the importance of their early recognition and initiation of targeted support services in due time to optimize the development of neurocognition.

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DATA AVAILABILITY STATEMENT

Data available on request from the authors.

SUPPORTING INFORMATION

The following additional material may be found online:

Appendix S1: Study flow chart showing participant selection.

Figure S1: The PIPARI Study Group.

REFERENCES

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