Associations Between Early Structural Magnetic Resonance Imaging, Hammersmith Infant Neurological Examination, and General Movements Assessment in Infants Born Very Preterm

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Objective To evaluate the prevalence and associations between structural magnetic resonance imaging (sMRI) injury/abnormality at term-equivalent age and absent fidgety General Movements Assessment (GMA) and abnormal Hammersmith Infant Neurological Examination (HINE) scores among infants born very preterm at 3-4 months of corrected age.

Study design This prospective cohort study enrolled 392 infants born ≤2 weeks of gestation from 5 neonatal intensive care units in the greater Cincinnati area between September 2016 and October 2019. Infants completed sMRI at term-equivalent age and GMA and HINE at 3-4 months of corrected age. All assessors were blinded.

Results Of 392 infants, 375 (96%) had complete data. Of these, 44 (12%) exhibited moderate or severe brain abnormalities, 17 (4.5%) had abnormal GMA, and 77 (20.3%) had abnormal HINE. Global and regional abnormality scores on sMRI were significantly correlated with GMA (R^2 range 0.05-0.17) and HINE at 3-4 months of corrected age (R^2 range 0.01-0.17). These associations remained significant in multivariable analyses after adjusting for gestational age and sex. There was a significant but low correlation (R^2 0.14) between GMA and HINE.

Conclusions We observed a low prevalence of moderate or severe brain abnormalities in survivors born very preterm in this geographically defined cohort. The much greater prevalence of abnormal motor examination on the HINE compared with GMA and their low correlation suggests that these tests evaluate different constructs and, thus, should be used in combination with sMRI rather than interchangeably. *(J Pediatr 2021;232:80-6)*.

Cerebral palsy (CP) is the most common cause of childhood physical disability. Although CP originates from a brain abnormality or injury occurring during the prenatal, perinatal, or postnatal period, this motor disability is not commonly diagnosed until 12-24 months of age when clinical deficits are apparent.[1-3] However, recent advances in neuroimaging and early prognostic testing are expected to result in more accurate identification of infants at risk of CP by 3-4 months of corrected age.[1,4,5] Early detection and diagnosis are high priorities because neuroplasticity and opportunity for intervention are greatest in infants and diminish over time.[6] Early intervention is critical to reduce the progression of motor deficits, prevent secondary impairments, and improve independence.

The tools with the best predictive validity to detect CP in infants younger than 5 months of corrected age include structural magnetic resonance imaging (sMRI) at term, Prechtl Qualitative Assessment of General Movements (GMA) during the fidgety period, and Hammersmith Infant Neurological Examination (HINE) at 3-4 months of corrected age.[1,7-9] However, the sensitivity and specificity for these assessments vary vastly and are insufficient in isolation for diagnosing CP. In addition, how these tests complement each other is unclear.[10] The recommendation from an international panel of experts for early CP diagnosis is to use sMRI at term in combination with fidgety GMA and/or HINE.[1] However, there is little evidence regarding how these 3 assessments are associated to predict CP in combination. A few studies have examined associations between 2 of the 3 assessments prospectively,[11-14] and 1 study examined the tests retrospectively using a case-control study.[15] To our knowledge, there

CCHMC	Cincinnati Children's Hospital Medical Center
CP	Cerebral palsy
GMA	Prechtl Qualitative Assessment of General Movements
HINE	Hammersmith Infant Neurological Examination
NICU	Neonatal intensive care unit
sMRI	Structural magnetic resonance imaging
TE	Echo time
TR	Repetition time

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are no prospective, population-based cohort studies using sMRI, GMA, and HINE to examine the associations between these structural and functional assessments. Understanding this relationship is critical to establishing the combined prognostic properties of these assessments to predict CP accurately. The objectives of this study were to evaluate (1) the prevalence of sMRI injury/abnormality at term-equivalent age and absent fidgety GMA and abnormal HINE at 3-4 months of corrected age and (2) how these tests correlate with one another in a large, geographically based prospective cohort of infants born very preterm.

Methods

Participants

We conducted a prospective longitudinal cohort study in infants born very preterm recruited from 5 level III/IV neonatal intensive care units (NICUs) in the greater Cincinnati area. We prospectively enrolled 392 infants between September 2016 and October 2019 (**Figure 1**; available at www.jpeds.com). Inclusion criteria included gestational age ≤32 weeks and hospital care at a greater Cincinnati NICU. We excluded infants with known chromosomal or congenital anomalies affecting the central nervous system or cyanotic heart disease. See **Appendix 1** for acknowledgments to participants and other acknowledgments (**Appendix 1**; available at www.jpeds.com). The study was approved by all 5 hospital institutional review boards. All families consented to the study before any study procedures. Maternal and infant clinical variables were obtained by trained research coordinators via chart review using standardized definitions (**Table I**).[16]

Measures

MRI. sMRI scans were obtained strictly between 40 and 44[6/7] weeks of postmenstrual age. All infants recruited from sites other than Cincinnati Children's Hospital Medical Center (CCHMC) were scanned as outpatients. Infants from CCHMC were scanned as outpatients and inpatients, with 47 (12%) scans occurring while inpatient. All infants were scanned on the same 3-Tesla MRI magnet (Philips Ingenia) using a 32-channel head coil, located in the CCHMC Imaging Research Center. Infants were not sedated for the scan. Silicone earplugs, blanket swaddle, vacuum immobilization (MedVac; CFI Medical Solutions), and feeding before MRI were strategies to promote natural sleep and successful scanning. High-resolution anatomical T2-weighted images (repetition time [TR]/echo time [TE] = 18567/166 milliseconds, flip angle = 90°, in-plane resolution = 1 × 1 × 1 mm), magnetization-prepared rapid acquisition with gradient echo T1-weighted images (3D fast-field echo, TR/TE/inversion time = 8.5/3/1610 milliseconds, flip angle = 13°, in-plane resolution = 1 × 1 × 1 mm), and susceptibility weighted images (TE/TR = 7.2/29 milliseconds, resolution = 0.6 × 0.6 × 2 mm) were acquired.

Table I. Cohort maternal and infant baseline characteristics

Characteristics	Infants born very preterm (N = 392)
Maternal age, y, mean (SD)	29.2 (5.4)
Maternal hypertension, n (%)	154 (39.3%)
Maternal diabetes, n (%)	22 (5.6%)
Antenatal steroids, n (%)	361 (92.1%)
Magnesium, n (%)	329 (83.9%)
Infant Hispanic/Latino, n (%)*	36 (7.2%)
Infant race, n (%)†	
Black	104 (26.5%)
White	255 (65.1%)
Asian	8 (2.0%)
Other	20 (5.1%)
Singleton, n (%)	252 (64.3%)
Male sex, n (%)	210 (53.6%)
Apgar score at 5 min <5, n (%)	48 (12.4%)
Gestational age, wk, mean (SD)	29.3 (2.5)
Birth weight, g, mean (SD)	1293.0 (448.9)
Patent ductus arteriosus, n (%)	101 (25.8%)
Rates of culture positive sepsis, n (%)	43 (11.0%)
Bronchopulmonary dysplasia, n (%)‡	166 (42.4%)
Retinopathy of prematurity, n (%)	134 (34.2%)
Germinal matrix/intraventricular hemorrhage, n (%)	68 (17.4%)
Postmenstrual age at MRI scan, wk, mean (SD)	42.7 (1.4)

*In total, 29 mothers chose not to respond to ethnicity question.
†Six mothers did not respond to infant race question.
‡Bronchopulmonary dysplasia was defined as any respiratory support, including nasal cannula or higher, irrespective of oxygen need, at 36 weeks of postmenstrual age.[16]

A single pediatric neuroradiologist, masked to clinical history, performed all qualitative and quantitative assessments of MRI using a standardized assessment (**Appendix 2**; available at www.jpeds.com). Brain abnormalities were defined using a standardized scoring system (**Table II**; available at www.jpeds.com).[17] For the quantitative scoring system, we adjusted for the infant's age at MRI using a linear regression analysis equation: corrected brain measurement = measured brain measurement + slope (40 − postmenstrual age at MRI scan).[17] The scores were summed to generate separate white matter abnormality, gray matter abnormalities, deep gray matter, and cerebellar abnormality scores, with greater values reflecting more abnormalities; descriptive data are reported in **Table III**.

A categorical global brain abnormality score was computed per Kidokoro et al by summing abnormalities, with categories of normal (total score 0-3), mild (total score 4-7), moderate (total score 8-11), and severe (total score ≥12).[17] In addition, we examined sMRI abnormalities not included in the Kidokoro scores, including presence of germinal matrix hemorrhage and intraventricular hemorrhage and measurement of the pons (anterior–posterior), cerebellar vermis (anterior–posterior and cranio–caudal dimension), and frontal extra-axial space. Structural measurements of the pons and cerebellar vermis were collected as continuous variables and assessments of germinal matrix hemorrhage, intraventricular hemorrhage (present/absent), and frontal extra-axial space (≤5 mm/≥5 mm) were categorical (**Figure 2**, A-D; available at www.jpeds.com). A random sample of 20 MRI scans was reread by the same

Table III. Descriptive statistics for brain abnormalities variables

Brain abnormality variables	Range	Median	IQR	Intrarater reliability ICC (95% CI)
White matter abnormality score	0-20	1.0	0-3	0.87 (0.67-0.95)
Grey matter abnormality score	0-4	0	0-3	0.90 (0.74-0.96)
Cerebellar abnormality score	0-8	0	0-7	0.76 (0.39-0.90)
Global brain abnormality score	0-36	2.0	1-5	0.89 (0.73-0.96)
Pons thickness, mm	8.8-45.6	14.3	10.5-16.9	0.96 (0.91-0.99)
Cerebellar vermis (anterior–posterior), mm	5.5-28.6	16.5	9.3-24	0.85 (0.64-0.94)
Cerebellar vermis (cranio–caudal), mm	15-34.3	26.9	17.2-32	0.88 (0.70-0.95)

ICC, intraclass correlation coefficient.

neuroradiologist more than 1 month later to assess intra-rater reliability.

Prechtl Qualitative Assessment of General Movements. General movements were video recorded as recommended by Prechtl et al for 5 minutes in a clinic setting with the undressed, calm infant placed supine.[18-20] All GMAs were completed within the fidgety period, with 97% between 12 and 16 weeks of corrected age and the remaining 3% at 11-12 or 17-18 weeks. Infants with variable, complex, and multiplanar movements were scored as normal fidgety. Infants with no fidgety movements (absent) or few movements (sporadic) were scored absent. All videos were scored within 48-72 hours following the recording by a single, certified examiner (via General Movements Trust advanced course) masked to clinical history and MRI findings but not HINE score. For questionable videos, a second rating was obtained by a General Movements Trust trainer. Thirty random GMA videos were rescored by the same examiner 6 months later to assess intra-rater reliability.

HINE. The HINE is a standardized neurologic examination for infants 2-24 months of age consisting of 26 items (5 domains).[21] Each item is scored individually (0-3), and items are summed to obtain domain scores and an overall HINE score (range 0-78), with cut-off scores <56 considered abnormal.[22] The right and left limbs were scored separately for items testing both sides of the body. All HINEs were performed by a single examiner masked to clinical history and MRI findings, during the GMA visit. Fifteen randomly selected infants were assessed again for intrarater reliability, within 2-4 weeks of initial examination.

Statistical Analyses

Intrarater reliability was assessed using kappa statistics for dichotomous variables and intraclass correlation coefficient for continuous variables. We performed linear regression analyses to determine correlations (R^2) between sMRI global abnormality score, GMA, and HINE. All analyses were adjusted for gestational age at birth and sex. In multivariable linear regression analyses, we assessed the association between global abnormality MRI score (continuous dependent variable)[17] and GMA as well as HINE (continuous). Additional regression analyses examined sMRI subscores (eg, total WM score) with GMA and HINE. HINE global score was compared with the domain scores using the Spearman rho (ρ) correlation coefficient. In secondary analyses, we used multivariable logistic and linear regression to examine the relationship between the additional sMRI variables not included as part of the Kidokoro score with GMA and HINE. Two-sided P values <.05 were used for statistical significance. All 3 primary analyses were adjusted for multiple comparisons. Analyses were performed using STATA 16.0 (Stata Corp).

Results

From the original cohort of 392 infants, 375 (96%) had full data and were included in this study. Twelve infants (3%) did not return for follow-up at 3 months, 3 infants were excluded due to suboptimal sMRI image quality, and 2 infants did not have GMA scores due to suboptimal state. The mean (SD) gestational age at birth was 29.3 (2.5) weeks, and mean birth weight was 1294 (449) g. The median NICU length of stay was 64.2 (IQR 18-91) days. Demographic characteristics are reported in Table I.

sMRI data were collected at mean (SD) of 42.3 (1.3) weeks of postmenstrual age with no difference detected between age at scan for patients scanned as inpatients 42.58 (1.46) compared with outpatients 42.63 (1.33) (P = .97). There were 254 infants (67.7%) classified as having no brain abnormality, 82 with mild abnormality (21.9%), 24 with moderate abnormality (6.4%), and 15 with severe abnormality (4.0%). Regional scores, structural measurements, and intrarater reliabilities are presented in Table III. At 3 months of corrected age, 17 infants had absent fidgety movements (4.5%). Intrarater reliability for GMA was 96.7% (kappa 0.89). Abnormal HINE scores were detected in 77 infants (20.3%). HINE scores ranged from 30.5 to 73 (median 60), and an IQR of 7.0. Intrarater reliability assessed after mean (SD) of 26.8 (5.16) days between assessments for HINE resulted in an intraclass correlation coefficient of 0.79. The HINE score was highly (P < .001) correlated with the domain scores; cranial nerve: ρ = 0.55, posture: ρ = 0.66, movements: ρ = 0.31, tone: ρ = 0.77, and reflexes/reactions: ρ = 0.52. Twenty-seven infants (7.2%) were diagnosed with an abnormality on at least 2 of the 3 study tests (moderate-severe sMRI, absent fidgety movements

and/or HINE score <56), and 9 (2.4%) exhibited abnormalities on all 3 tests.

Association between MRI and GMA

Global and regional abnormality scores on sMRI at term-equivalent age were significantly correlated with GMA at 3 months of corrected age ($P < .001$ for all analyses; Table IV). In multivariable analyses, adjusting for gestational age and sex, we identified a significant and independent correlation between global and regional brain abnormality scores and absent fidgety GMA ($P < .001$; Table V). In secondary analyses, additional MRI abnormalities/structural measurements not part of the Kidokoro score were associated with GMA in univariable analyses. In multivariable analyses adjusting for gestational age, sex, and global brain abnormality score, 2 MRI variables were significantly and independently associated with GMA (N = 358): increasing thickness of the pons reduced the odds (OR 0.42, 95% CI 0.22-0.81; $P < .01$) and increased extra-axial space (greater than 5 mm) (OR 3.54, 95% CI 1.09-11.53; $P = .036$) increased the odds of absent fidgety movements.

Association between MRI and HINE

Global and regional abnormality scores on sMRI at term-equivalent age were significantly correlated with HINE at 3 months of corrected age ($P < .001$; Table IV). We identified a significant and independent correlation between global and regional brain abnormality scores and HINE ($P < .001$; Table V). All 5 HINE domains were significantly associated with MRI global score and most MRI regional scores. In secondary analyses, additional MRI abnormalities/structural measurements not part of the Kidokoro score were associated with HINE in univariable analyses. In multivariable analyses controlling for global brain abnormality score, gestational age and sex, size of the cerebellar vermis (in anterior–posterior) was directly associated ($\beta = 0.37$, 95% CI 0.10-0.65; $P = .007$) and increased extra-axial space showed a negative trend ($\beta = -1.57$, 95% CI −3.19, 0.05; $P = .058$) toward association with HINE (N = 360).

Association between MRI and GMA Plus HINE

There was a significant but relatively low correlation between GMA and HINE ($R^2 = 0.14$; Table IV). Both GMA and HINE were independently and significantly correlated with MRI global abnormality scores ($P < .001$; Table V) when adjusting for gestational age and sex, further underscoring the independent nature of GMA vs HINE as related to sMRI. White matter, cerebellum, cortical gray matter, and deep gray matter abnormality scores were also significantly and independently associated with GMA and HINE (Table V).

Discussion

Early detection and diagnosis of CP is a high priority in rehabilitation. There is consensus that early detection of CP should occur before 6 months of corrected age using sMRI, GMA, and/or HINE assessments, with purported high sensitivity and specificity and complementary in prognostic properties.[1] However, none of these tests are sufficiently accurate in isolation, and the accuracy of these assessments performed in combination to predict CP remains uncertain. Although this key question remains unresolved, our study advances our understanding of how these tests are inter-related. We identified significant correlations between structural abnormalities on sMRI and functional deficits on GMA and HINE. Our findings are in line with 2 previous studies showing that sMRI/cranial ultrasound were highly correlated with GMA.[23,24] These studies examined the individual and combined values of these tests for predicting CP, indicating that the addition of GMA findings to abnormal neuroimaging at term did not improve prognostic accuracy of CP, likely because they were highly correlated.[23,24] The addition of GMA to sMRI injury lowered the specificity and positive likelihood ratio for CP prediction in one study.[23] In contrast, the addition of GMA to cranial ultrasound reduced the sensitivity and negative likelihood ratio in the other study.[24] Our results suggest considerable overlap may exist in what these prognostic tests are measuring, and therefore their performance in combination may not add much to the prognostic precision for early CP diagnosis if the degree of correlation overshadows the unique information sMRI provides independent of GMA and HINE.

Table IV. Correlations (R^2) between sMRI abnormality scores at term-equivalent age and absent fidgety GMA and HINE at 3 months of corrected age

	General movements*		HINE global score	
	R^2	β (95% CI)	R^2	β (95% CI)
Global abnormality	0.155	7.67 (5.85-9.50)†	0.169	−0.57 (−0.70, −0.45)†
White matter	0.165	5.12 (3.95-6.28)†	0.113	−0.83 (−1.07, −0.60)†
Cerebellum	0.050	1.52 (0.84-2.19)†	0.082	−1.32 (−1.76, −0.87)†
Cortical gray matter	0.005	0.35 (−0.16, 0.85)	0.011	−0.67 (−1.30, −0.03)‡
Deep gray matter	0.103	1.81 (1.27-2.36)†	0.169	−2.30 (−2.81, −1.78)†

*Correlation (R^2) between GMA and HINE was 0.142 ($P < .001$).
†$P < .001$.
‡$P < .05$.

Table V. Multivariable linear regression results of relationships between sMRI global and regional abnormality scores at term-equivalent age and absent fidgety GMA and HINE at 3 months of corrected age, after adjustment for gestational age and infant sex

Tests at 3 months of corrected age	sMRI abnormality scores at term-equivalent age									
	Global abnormality		White matter		Cerebellum		Cortical gray matter		Deep gray matter	
	β	95% CI	β	95% CI	β	95% CI	β	95% CI	β	95% CI
GMA	8.11	6.08-10.15*	4.87	3.70-6.05*	1.25	0.61-1.91*	0.87	0.39-1.35*	1.65	1.12-2.19*
HINE										
Cranial nerve function	−0.65	−0.90, −0.41*	−0.32	−0.47, −0.18*	−0.11	−0.18, −0.03†	−0.04	−0.1, 0.02	−0.17	−0.23, −0.11*
Posture	−0.36	−0.56, −0.16*	−0.17	−0.29, −0.05†	−0.09	−0.15, −0.02†	−.002	−0.05, 0.04	−0.09	−0.14, −0.04†
Movements	−1.61	−2.12, −1.09*	−0.83	−1.13, 0.53*	−0.32	−0.48, −0.16*	−0.13	−0.26, −0.01‡	−0.30	−0.43, −0.16*
Tone	−0.41	−0.55, −0.29*	−0.23	−0.30, −0.15*	−0.06	−0.10, −0.02†	−0.03	−0.06, .004	−0.09	−0.12, −0.06*
Reflexes and reactions	−0.48	−0.77, −0.18*	−0.26	−0.43, −0.09†	−0.08	−0.17, .005	.001	−0.07, 0.07	−0.11	−0.19, −0.04†
Global score	−0.26	−0.33, −0.19*	−0.12	−0.16, −0.08*	−0.05	−0.07, −0.03*	−0.02	−0.04, −0.01*	−0.07	−0.08, −0.05*
Combined										
GMA	5.99	3.88-8.09*	4.03	2.80-5.27*	0.78	0.09-1.47‡	0.73	0.22-1.25†	1.09	0.55-1.62*
HINE (global)	−0.19	−0.26, −0.12*	−0.08	−0.12, −0.04*	−0.04	−0.7, −0.02*	−0.01	−0.02, 0.01	−0.06	−0.07, −0.04*

*$P < .001$.
†$P < .01$.
‡$P < .05$.

Neuroimaging, GMA, and/or HINE are proposed as the most accurate tools to detect CP before 5 months of age.[1] However, previous studies have not used all tests prospectively within the same cohort. Most studies report the prognostic value of 1 test in isolation, and few have examined 2 of the assessments together. By examining the association between sMRI, GMA, and HINE within the same cohort, our study lends greater understanding of how these assessments inter-relate and may help determine the best combination of tools for early CP identification. Our study demonstrated that abnormal sMRI findings at term-equivalent age were significantly associated with absent fidgety GMA and abnormal HINE at 3-4 months of corrected age in infants born very preterm. Of the 4 large regions that contribute to the global brain abnormality score, white matter and deep gray matter abnormalities were the most correlated with abnormal GMA and HINE. White matter abnormalities were the most closely associated with abnormal GMA at 3 months of corrected age, suggesting that white matter may play a greater role in generating normal fidgety movements than the deep gray matter, cortical gray matter, or cerebellum. Conversely, abnormalities in deep gray matter were the most closely associated with abnormal HINE at 3 months of corrected age. This significant association was driven largely by the movements and cranial nerve function subscores of the HINE (Table V). The greater correlations with white matter and deep nuclear gray matter are consistent with previous literature in infants born preterm and at term that has demonstrated the importance of injury to the periventricular white matter and basal ganglia/thalamus in the development of CP. Our findings also suggest that thickness of the pons, cerebellar vermis size, and enlarged extra-axial space are additional sMRI variables that may improve our ability to predict CP.

In our study, GMA and HINE were both independently associated with sMRI abnormalities. Furthermore, we found a low degree of correlation between GMA and HINE, suggesting that these tests are unlikely to provide similar prognostic information and should not be used interchangeably. Our data support the idea that the GMA and HINE likely evaluate different constructs and, therefore, should be used in combination rather than isolation for early CP detection. This idea is supported by several recent papers. A systematic review found that the fidgety GMA had greatest sensitivity (97%) and specificity (89%) but should not be used in isolation because of false-positive results for CP.[9] A large retrospective case-control study reported the test properties of combined neuroimaging, GMA, and HINE to predict CP. They reported high (>97%) combined sensitivity, specificity, and positive predictive value.[15] However, case-control studies are more biased than cohort studies[25] in identifying prognostic factors and cannot be used to calculate prognostic test values because the prevalence of the outcome is artificially determined by the study design (ie, 50% in 1:1 case-control matching) rather than natural disease prevalence.[16] The prevalence of CP in the study by Morgan et al was 33% (1:2 case-control matching), which is approximately 5-fold greater than observed in infants born very preterm, thus resulting in overinflated estimates of sensitivity, specificity, and positive predictive value.[15] It will be crucial to follow our population-based cohort to determine CP diagnosis at 2 years of corrected age to determine the prognostic test properties of each tests individually and combined to verify the strengths and limitations of this approach.

Our study adds a unique contribution to the literature because our work evaluates a cohort of infants born very preterm using sMRI, GMA, and HINE from a geographically defined region, thus limiting sampling bias. Our sMRI results indicate that 23% of infants exhibited mild brain injury/abnormality, and 12% had moderate or severe brain injury/abnormality. The prevalence of brain injury measured by sMRI in our sample was less compared with a study from Hintz

et al, finding that 58% of infants had mild brain injury, and 19% had moderate or severe brain injury in a cohort of 480 infants with extremely low birth weight.[26] In addition to the key difference in inclusion criteria (extremely low birth weight vs very preterm), the choice of recruiting from academic NICUs only compared with our sampling from academic and community NICUs from a geographically defined region likely contributed to these differences. For our sample, 4.5% of infants exhibited absent fidgety GMA. Comparing our findings to another large geographically recruited cohort showed similar findings, with 6% of infants having absent fidgety movements.[21] In contrast, comparing these data with another large cohort that was not geographically recruited, the presence of absent fidgety movements was much greater at 15%.[24]

In our study, 17% of infants exhibited mild, 6% moderate, and 6% severe white matter injury on sMRI. White matter injury and intraventricular hemorrhage have been shown by others as strong prognostic factors for CP.[27] White matter injury also has been associated with aberrant GMA.[13] Understanding the mechanism and severity of injury at term-equivalent age can be helpful in determining the most appropriate early interventions. Our study showed 3 sMRI findings independently correlated with HINE in addition to 2 new regional structural measurements that were significantly associated with GMA. These findings could be important in early CP detection. The regional structural measurements included the thickness of the pons and size of extra-axial space. One previous study found an association between a smaller pons in older children and periventricular leukomalacia.[28] However, no other studies have identified the pons as a potential predictor for later CP. Our finding associating the GMA with increased extra-axial space is important as several previous studies have shown the association between microcephaly and poorer neurodevelopmental outcome.[29,30] Our data suggest that an assessment battery consisting of sMRI, GMA, and HINE provides a comprehensive, early assessment of neurological development.

Our study has several strengths. We used a longitudinal cohort study design and recruited all eligible infants born very preterm from all regional academic and community level III/IV NICUs encompassing a geographically defined region. The race composition of our cohort was similar to recent state of Ohio census data (eg, percentage of Ohioans who self-identified as Black or White in 2018 was 33.3% and 63.5%, respectively; see **Table V** for analogous cohort data).[31] This refection of state demographics permitted unbiased inferences about disease prevalence and associations between our prognostic tests. We collected data at term-equivalent age (sMRI) and 3 months of corrected age (GMA and HINE), which represented uniform time points known to be optimal for test performance. All assessments also were performed with high reliability and masked to clinical history. The sample in this cohort study collecting all 3 assessments in concert is very large. In addition, using the Kidokoro scoring system, a more semiquantitative and less-subjective approach to evaluating neonatal sMRI, made our results more rigorous and reproducible. Study limitations include wide CIs for the intrarater reliability for the cerebellar abnormality scores. Although our study identifies important associations between sMRI and GMA and HINE, the correlations were small and it does not yet report long-term data. It will be important to continue to follow this cohort to understand how these significant associations between sMRI, GMA, and HINE will affect their combined ability to accurately predict CP at 2 years of corrected age, before definitive recommendations can be made.

In conclusion, we observed a low prevalence of moderate or severe brain abnormalities and absent fidgety GMA in survivors born very preterm in this geographically defined cohort. The much greater prevalence of abnormal motor examination on the HINE compared with the GMA and their low correlation suggests that these tests evaluate different constructs and thus might need to be used in combination with sMRI rather than interchangeably for early detection of CP. Determining the combined value of these tests in predicting CP at 2 years of corrected age is an important next step. ■

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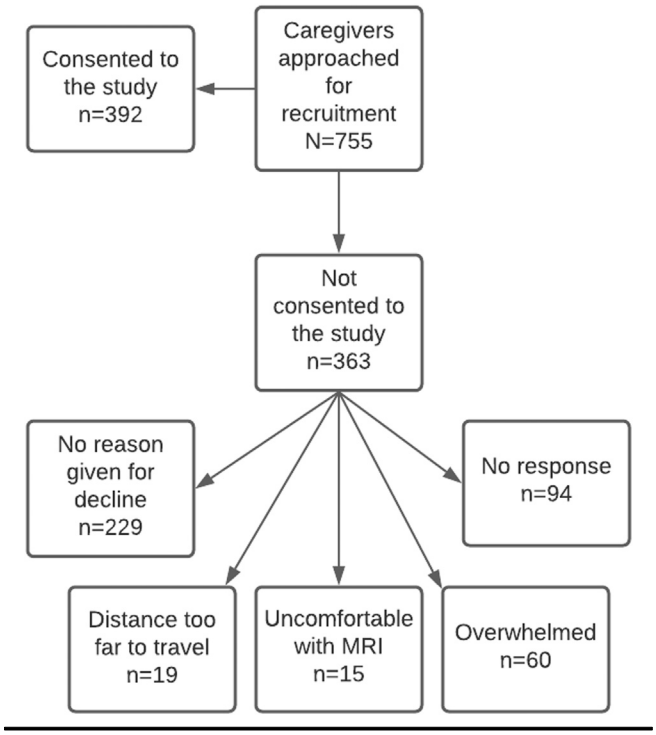

Figure 1. Study flowchart.

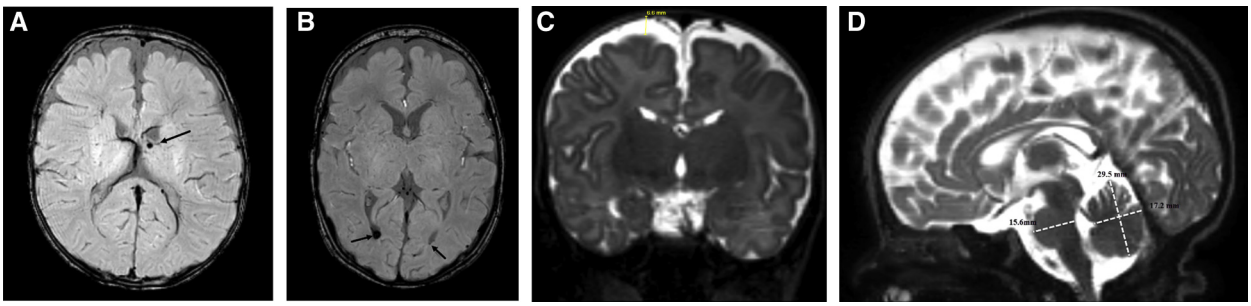

Figure 2. **A,** Axial image demonstrates an artifact at the left caudothalamic groove (*arrow*), consistent with germinal matrix hemorrhage. **B,** Axial susceptibility weighted image demonstrating a susceptibility artifact (*arrows*) at the posterior horns of the lateral ventricles, demonstrating evidence for intraventricular hemorrhage. **C,** Coronal T2 image measuring large frontal extra-axial space. **D,** Sagittal T2 image measuring anterior to posterior and craniocaudal dimension of the cerebellar vermis and anterior to posterior dimension of the pons.

Table II. Description for Kidokoro global abnormality scoring system

Brain abnormality variables[11]	Scale	Brain abnormalities	Total score range
Cerebral white matter abnormality	0-4	1. Cystic degeneration 2. Focal signal abnormalities 3. Delayed myelination 4. Thinning of the corpus callosum 5. Dilated lateral ventricles 6. Reduction of white matter volume	0-24
Cortical gray matter abnormalities	0-4	1. Signal abnormality 2. Delayed gyration 3. Dilated extracerebral CSF space	0-12
Deep gray matter	0-4	1. Signal abnormalities 2. Reduced volume	0-8
Cerebellar abnormalities	0-4	1. Signal abnormalities 2. Reduced volume	0-8

CSF, cerebrospinal fluid.