ARTICLE

Neurodevelopmental and Perinatal Correlates of Simple Brain Metrics in Very Preterm Infants

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Objective: To explore perinatal correlates of 3 simple measures of brain size, known as metrics, in very preterm infants at term-equivalent age and their relationship to 2-year neurodevelopmental outcomes.

Design: Prospective cohort study of preterm infants born at a gestational age of less than 30 weeks or a weight of less than 1250 g between April 1, 2001, and December 31, 2003, and followed up at 2 years of corrected age.

Setting: The Royal Women's Hospital and the magnetic resonance imaging unit at the Royal Children's Hospital.

Patients: Two hundred thirty-six preterm infants.

Interventions: Brain metrics—biparietal, bifrontal, and transverse cerebellar diameters—on magnetic resonance imaging for preterm infants at term-equivalent age and neurodevelopmental assessments at 2 years of corrected age.

Main Outcome Measures: Mental Development Index and the Psychomotor Development Index of the Bayley Scales of Infant Development–Revised.

Results: Higher birth weight *z* score, shorter duration of assisted ventilation, and postmenstrual age at magnetic resonance imaging were independently associated with increases in the 3 brain metrics, and male sex was associated with larger bifrontal and biparietal diameters. Only the biparietal diameter was predictive of cognitive and motor indices after adjustment for perinatal variables and social risk.

Conclusion: This study provides further evidence of altered brain growth in preterm infants, relating to growth restriction and severity of illness, that in turn relate to neurodevelopmental outcome.

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THE PAST 2 DECADES HAVE seen dramatic improvements in the survival rates of very preterm infants (<30 weeks gestational age). Although the rates of severe neurosensory disabilities in preterm survivors are stable or decreasing, milder cognitive impairments and behavioral deficits remain common.[1]

The neuropathological mechanisms underlying cognitive and behavioral deficits in preterm children are poorly understood, and early sensitive biomarkers are lacking. Brain volume measurements on magnetic resonance imaging (MRI) are potential predictors of altered regional cerebral development.[2] Reductions in cerebral volumes in preterm survivors during childhood and adolescence have been related to abnormal cognitive functioning.[3] However, volumetric methods are not practical on a routine basis given the expertise and infrastructure required to apply such techniques. An alternative biometric approach to cerebral growth has been developed in fetal brain imaging by applying a set of measurements to the conventional qualitative MRI, known as *brain metrics*.[4] We recently adapted brain metrics for a simple quantitative determinant of brain size in preterm infants approaching term age and found that simple brain metrics were reproducible, correlated strongly with volumetric measurements, and differentiated preterm and term infants.[5] More specifically, we found that preterm infants had smaller bifrontal, biparietal, and transverse cerebellar diameters than term infants.

The primary objectives of this subsequent study of very preterm infants were to (1) explore perinatal exposures, including brain injury, as predictors of brain metrics at term-equivalent age and (2) to delineate the relationship between brain metrics at term and 2-year neurodevelopmental outcomes.

METHODS

STUDY SAMPLE

Preterm infants with birth weights of less than 1250 g and/or gestational ages of less than 30 weeks at birth admitted between April 1, 2001, and December 31, 2003, to the Royal Women's Hospital were included in a prospective cohort study, after informed parental consent, as previously described.[6] The study was approved by the local hospital ethics committee.

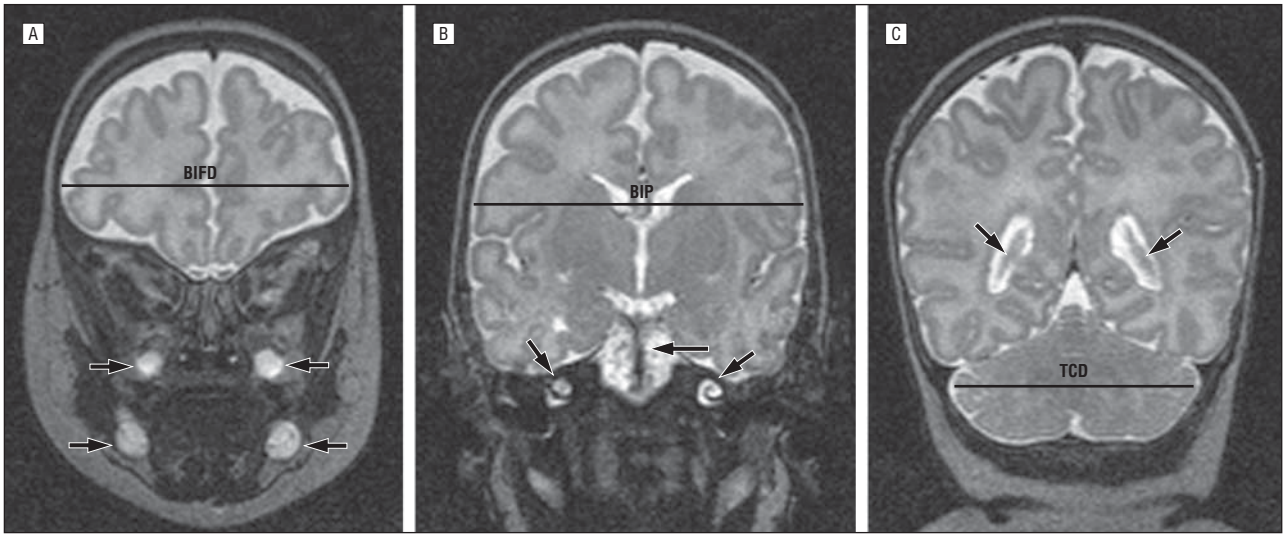

Figure. Landmarks (indicated by arrows) for brain metrics on magnetic resonance imaging. A, Bifrontal diameter (BIFD) (landmarks: teeth). B, Biparietal diameter (BIP) (landmarks: cochleas [left and right arrows] and basilar trunci [center arrow]). C, Transverse cerebellar diameter (TCD) (landmarks: posterior part of the lateral ventricle).

Sociodemographic, obstetric, and infant birth data as well as neonatal therapies and morbidities were obtained by medical record review. Birth weight *z* scores for gestational age and sex were computed relative to the British Growth Reference data.[7] Cranial ultrasonographic images were obtained serially throughout the neonatal intensive care course in all infants within the first 48 hours and at ages 4 to 7 days and 4 to 6 weeks; additional ultrasonographic images were obtained if abnormalities were detected. All ultrasonographic images were reported by a clinical pediatric radiologist before the MRI evaluation. The highest grade of intraventricular hemorrhage (IVH) on all cranial ultrasonographic images was recorded in the database.

Social risk was assessed using a 12-point index consisting of 6 aspects of social status, including family structure, education of the primary caregiver, occupation of the primary income earner, employment status of the primary income earner, language spoken at home, and maternal age at birth.[8] Total scores of less than 3 represent lower risk, whereas scores of 3 or more represent higher risk.

MAGNETIC RESONANCE IMAGING

The brain was imaged using MRI without sedation at a term-equivalent age with a 1.5-T system (Signa system; GE Medical Systems, Milwaukee, Wisconsin). Infants were fed, swaddled, outfitted with earphones, and placed in a vacuum-fixation bean bag. The weight and head circumference at the time of MRI were recorded.

The following sequences were acquired: (1) a 3-dimensional Fourier transformed spoiled gradient-recalled sequence (1.5-mm coronal slices; flip angle, 45°; repetition time, 35 milliseconds; echo time, 5 milliseconds; field of view, 18 cm; matrix, 256 × 256) and (2) a double-echo (proton density and T2-weighted) spin-echo sequence (dual-echo) (3-mm axial slices; repetition time, 3000 milliseconds; echo time, 36 and 162 milliseconds; field of view, 18 cm; matrix 256 × 256; interleaved acquisition).

The MRIs were scored using a standardized system[9] by 2 independent raters (R.W.H. and T.E.I.) who were blinded to the clinical history and the cranial ultrasonographic findings. Qualitative abnormalities were classified according to the degree of white matter and gray matter abnormality. White matter abnormality was graded from 1 to 3 on each of the following 5 items: (1) the nature and extent of white matter signal abnormality, (2) loss of periventricular white matter, (3) presence and extent of cysts, (4) degree of ventricular dilatation, and (5) thinning of the corpus callosum. The scores from individual items were then combined to give an overall white matter injury (WMI) score categorized as normal (5-7), mild (8-10), moderate (11 or 12), or severe (13-15). Gray matter abnormality was graded from 1 to 3 on each of 3 items that assessed (1) the presence of cortical gray matter signal abnormality, (2) quality of gyral maturation, and (3) size of subarachnoid space. The individual scores were combined and categorized as normal (3-5) or abnormal (6-9) gray matter.

BRAIN METRICS

The MRIs were displayed using a browser (DicomWorks, available at http://dicom. online.fr/). Length variables, including tissue measures (ie, bifrontal diameter, left and right frontal height, brain and bone biparietal diameter, fronto-occipital diameter, and transverse cerebellar diameter) and fluid measures of the pericerebral space (interhemispheric distance and craniocaudal left and right interopercular distances) and the intracerebral spaces (diameter of the left and right lateral ventricles and third ventricle diameter), were manually measured on 3 selected sections. In a previous report[5] comparing preterm infants with term control infants (36 infants; mean gestational age, 38.9 [SD, 1.2] weeks; mean birth weight, 3277 [SD, 524] g; and mean head circumference at MRI, 36 [SD, 1.4] cm), we showed that the bifrontal, biparietal, and transverse cerebellar diameters were the most reduced measurements in preterm infants and were significantly associated with the brain tissue volume calculated by volumetric analysis but less strongly with the head circumference.[5] Owing to a lack of any difference in the other metrics between preterm infants at term-equivalent age and term infants and a lack of sagittal acquisition in some infants (>50% not acquired), we focused the analysis on the 3 brain metrics that demonstrated marked differences between the preterm population at term-equivalent age and term infants. These measurements were tested for intrarater and interrater reliability and showed intraclass correlation coefficients greater than 0.8. The sections and landmarks for (1) bifrontal, (2) biparietal, and (3) transverse cerebellar diameter were, respectively, (1) the level of the olfactory sulci (4 teeth apparent), maximal distance perpendicular to the interhemispheric fissure; (2) the level of the third ventricle (cochlea and basilar truncus apparent), maximal diameter perpendicular to the interhemispheric fissure, not including the cerebrospinal fluid; and (3) the level of the atria (plexus choroid apparent), maximal horizontal distance (**Figure**).

Table 1. Socioeconomic, Perinatal, MRI, and 2-Year Outcome Data[a]

Variable	Total Cohort (n=187)
Perinatal variables	
Higher social risk	77 (41.2)
Antenatal corticosteroid therapy (n=186)	164 (88.2)
Male sex	96 (51.3)
Multiple birth	80 (42.8)
Gestational age at birth, mean (SD), wk	27.6 (1.9)
Birth weight, mean (SD), g	962 (218)
Birth weight *z* score, mean (SD)	–0.60 (–0.99)
Intrauterine growth restriction	21 (11.2)
Neonatal variables	
IPPV, median (25th-75th percentile), h	80 (6-269)
Oxygen administration, median (25th-75th percentile), h	334 (50-1385)
Total PN, median (25th-75th percentile), d	11 (6-17)
Inotropic support	72 (38.5)
Indomethacin to treat a patent ductus arteriosus	62 (33.2)
Necrotizing enterocolitis	20 (10.7)
Sepsis	78 (41.7)
Postnatal corticosteroids	16 (8.6)
Outcome variables at term-equivalent age (n=187)	
IVH grade 3 or 4 (n=185)	7 (3.8)
WMI grade 3 or 4 (n=184)	34 (18.5)
Gestational age at MRI, mean (SD), wk	40.0 (1.3)
Weight at MRI, mean (SD), g	3006 (553)
Weight SD score at MRI, mean (SD)	–0.95 (1.13)
Head circumference at MRI, mean (SD), cm	34.9 (2.1)
Brain metrics (n=187), mean (SD), mm	
Bifrontal diameter	64.1 (4.6)
Biparietal diameter	75.2 (5.0)
Transverse cerebellar diameter	50.8 (3.3)
Bayley Scales of Infant Development–Revised at 2 y, mean (SD) (n=177)	
MDI	83.4 (19.3)
PDI	87.9 (17.1)

Abbreviations: IPPV, intermittent positive pressure ventilation; IVH, intraventricular hemorrhage; MDI, Mental Development Index; MRI, magnetic resonance imaging; PDI, Psychomotor Development Index; PN, parenteral nutrition; WMI, white matter injury.

[a] Unless otherwise indicated, data are expressed as number (percentage) of patients.

NEURODEVELOPMENTAL OUTCOMES

The neurosensory and developmental outcomes were assessed at 24 months' corrected age (range, 22-26 months) using the Bayley Scales of Infant Development–Revised.[10] The Mental Development Index (MDI), assessing cognitive and language development, and the Psychomotor Development Index (PDI), assessing fine and gross motor development, were obtained and a standardized physical examination was performed. The MDI and PDI are reported as age-standardized scores with a mean (SD) of 100 (15).

STATISTICAL ANALYSIS

Data were analyzed using commercially available software (SPSS for Windows, version 15 [SPSS, Inc, Chicago, Illinois] and Stata, version 10 [StataCorp, College Station, Texas]). Perinatal and neonatal variables were initially assessed as predictors of brain metrics using univariable linear regression models for each variable. Univariable predictors were then combined into a multivariable model, removing any variables that were no longer significant and checking for additional predictors in the multivariable model that were not univariable predictors. All multivariable models included adjustment for postmenstrual age at the time of MRI as a potential confounder, with sicker infants being more likely to undergo imaging at later ages when brain growth may be greater. We also retained head circumference at MRI for multivariable analysis to test the hypothesis that brain metrics provide independent information.

To assess the effects of brain injury, these brain metrics were compared between children with different levels of WMI using analysis of variance and between those with and without gray matter abnormality and with IVH of grades 3 or 4 using unpaired 2-tailed *t* tests.

Finally, brain metrics were assessed as predictors of MDI and PDI at age 2 years after adjusting for perinatal and neonatal predictors, checking for a potential interaction between sex and brain metrics on the 2-year outcome. Again, univariable models were used to assess the predictive nature of the variables before building multivariable regression models to assess independent predictors, checking for potential interactions between brain metrics and sex. In both analyses, predictors that were highly skewed were log-transformed to produce a linear relationship with the outcome.

The results presented assume that the observations are independent. In fact, there were a significant number of twins and triplets in the data set (42.8%); however, analysis using random effects to adjust for a lack of independence between multiple births made little difference to the analysis. Hence, we present the results assuming independence only.

RESULTS

During the study period, 348 eligible preterm infants were admitted to the neonatal intensive care unit, and 236 were recruited into the study. The most common reasons for failure to recruit were inability to obtain parental consent because of early hospital transfer or long distance from the hospital. There were no significant differences between participants and nonparticipants in relation to sex, multiple births, gestational age at delivery, IVH, or bronchopulmonary dysplasia (defined as oxygen requirement at 36 weeks corrected gestational age). Infants with known or suspected brain malformation or congenital abnormalities (n=6) were excluded. Infants with MRI data of insufficient or suboptimal quality (n=43) were also excluded. Thus, MRIs were studied for 187 preterm infants. Neurodevelopmental assessments were completed on all but 5 of these children, and we were able to complete the MDI and PDI from the Bayley Scales of Infant Development–Revised for 177 and 182 children, respectively. The characteristics of the preterm cohort are presented in **Table 1**.

BRAIN METRICS AND PERINATAL VARIABLES

On univariable analysis, larger birth weight *z* scores; not receiving inotropic agents; shorter duration of assisted ventilation, oxygen, and total parenteral nutrition; and older postmenstrual age at the time of MRI were all predictors of increased length in each of the 3 brain metrics (**Table 2**). Other individual variables were associated with only 1 or 2 of the brain metrics, but not all 3; notably, male sex was associated with higher values for bifrontal and biparietal diameters but not transverse cer-

Table 2. Significant Predictors in Brain Metrics Related to Perinatal and Neonatal Variables

Variable	Differences in Brain Diameters, Mean (95% CI), mm		
	Bifrontal	Biparietal	Transverse Cerebellar
Univariable Analysis			
Perinatal			
Gestational age at birth[a]	0.43 (0.08 to 0.77)[b]	0.09 (–0.29 to 0.47)	0.22 (–0.02 to 0.47)
Male sex	2.6 (1.3 to 3.8)[c]	2.1 (0.7 to 3.5)[d]	0.6 (–0.4 to 1.5)
Multiple pregnancy	–0.7 (–2.0 to 0.7)	–1.1 (–2.5 to 0.4)	–0.6 (–1.5 to 0.4)
Birth weight SD *z* score[e]	1.14 (0.49 to 1.78)[d]	1.41 (0.70 to 2.12)[c]	0.78 (0.31 to 1.25)[d]
Antenatal corticosteroid therapy	0.8 (–1.3 to 2.8)	0.1 (–2.2 to 2.3)	1.3 (–0.2 to 2.8)
Neonatal			
Inotropic agents	–2.3 (–3.6 to –1.0)[d]	–2.4 (–3.9 to –0.9)[d]	–2.2 (–3.2 to –1.3)[c]
Indomethacin	–1.4 (–2.7 to 0.03)	–1.4 (–2.9 to 0.1)	–1.7 (–2.7 to –0.7)[d]
Sepsis	–0.7 (–2.1 to 0.6)	–0.4 (–1.9 to 1.1)	–0.9 (–1.8 to 0.1)
Postnatal corticosteroid therapy	–2.2 (–4.5 to 0.2)	–2.1 (–4.7 to 0.4)	–1.6 (–3.2 to 0.1)
NEC	–1.7 (–3.9 to 0.4)	–1.9 (–4.3 to 0.4)	–1.7 (–3.2 to –0.2)[b]
Duration of IPPV (log scale)[f]	–0.53 (–0.76 to –0.29)[c]	–0.47 (–0.74 to –0.21)[c]	–0.41 (–0.58 to –0.25)[c,g]
Duration of oxygen (log scale)[f]	–0.33 (–0.61 to –0.05)[b]	–0.34 (–0.65 to –0.03)[b]	–0.40 (–0.59 to –0.20)[c]
Duration of PN (log scale)[f]	–1.33 (–1.90 to –0.75)[c]	–0.84 (–1.50 to –0.19)[b]	–0.90 (–1.31 to –0.48)[c]
Postmenstrual age at time of MRI[a]	1.00 (0.53 to 1.48)[c]	1.39 (0.88 to 1.90)[c]	1.31 (1.01 to 1.62)[c]
Multivariable Analysis			
Perinatal			
Gestational age at birth[a]	0.42 (0.03 to 0.80)[b]		
Male sex	2.3 (1.2 to 3.4)[c]	1.9 (0.7 to 3.1)[d]	
Birth weight SD *z* score[e]	1.69 (1.07 to 2.30)[c]	1.67 (0.65 to 3.06)[c]	0.96 (0.61 to 1.31)[c]
Neonatal			
Duration of IPPV (log-scale)[f]	–0.39 (–0.64 to –0.15)[d,h]	–0.50 (–0.72 to –0.27)[c,i]	–0.32 (–0.47 to –0.12)[c]
Postmenstrual age at time of MRI[a]	0.96 (0.55 to 1.36)[c]	1.37 (0.91 to 1.82)[c]	1.32 (1.06 to 1.57)[c]

Abbreviations: CI, confidence interval; IPPV, intermittent positive pressure ventilation; MRI, magnetic resonance imaging; NEC, not elsewhere classified; PN, parenteral nutrition; SD, standard deviation.

[a] Indicates per week.

[b] $P < .05$.

[c] $P < .001$.

[d] $P < .01$.

[e] Indicates per SD.

[f] Indicates per day.

[g] This equates to a reduction of –0.22 (95% CI –0.33 to –0.12) mm in the traverse cerebellar diameter for a doubling of duration of IPPV.

[h] This equates to a reduction of –0.27 (95% CI, –0.44 to –0.10) mm in the bifrontal diameter for a doubling of duration of IPPV.

[i] This equates to a reduction of –0.34 (95% CI –0.50 to –0.19) mm in the biparietal diameter for a doubling of duration of IPPV.

ebellar diameter. On multivariable analysis, only larger birth weight *z* score, shorter duration of assisted ventilation, and older postmenstrual age at MRI were predictive of larger brain metrics, along with male sex for bifrontal and biparietal diameters and immaturity at birth for the bifrontal diameter.

BRAIN METRICS AND QUALITATIVE MRI INTERPRETATION

There was no evidence that bifrontal and biparietal diameters were associated with white or gray matter abnormality or IVH grades 3 or 4. However, lower transverse cerebellar diameters were associated with moderate to severe white matter abnormalities, whereas gray matter abnormalities and IVH status had no effect on this cerebellar metric (**Table 3**).

BRAIN METRICS AND NEURODEVELOPMENTAL OUTCOME

On univariable analysis, both MDI and PDI were positively associated with each of the 3 brain metrics. Lower MDI was also associated with being male, being at higher social risk, having a lower birth weight *z* score, receiving postnatal corticosteroids, and having moderate or severe WMI. A lower PDI was associated only with postnatal corticosteroid therapy and moderate/severe WMI (**Table 4**). The remaining variables in Table 2 were also explored as independent predictors, although none were found to have a predictive effect on the outcome (results not shown).

On multivariable analysis for MDI, each of the social and perinatal variables found to be predictive in the univariable analyses were found to be independent predictors. However, of the brain metrics, only the biparietal diameter remained significantly associated with the MDI. The high correlation between brain metrics meant that once one was adjusted for, there was nothing to be gained by adding the others. On removing the effect of biparietal diameter from the models, there was strong evidence that a higher MDI was related to increased bifrontal diameter (increase in MDI for each millimeter increase, 0.84 [95% confidence interval (CI), 0.26-1.42]; $P = .005$) and also increased transverse cerebellar diameter (increase in MDI for each millimeter increase, 0.93 [0.10-

Table 3. Brain Metrics and Qualitative MRI Interpretation

	Diameter, mm					
	Bifrontal		Biparietal		Transverse Cerebellar	
	Mean (SD)	*P* Value	Mean (SD)	*P* Value	Mean (SD)	*P* Value
Gray matter category (3 missing)[a]						
Normal (n=133)	64.1 (4.6)	.87	75.3 (5.1)	.57	51.0 (3.1)	.14
Abnormal (n=51)	63.5 (5.1)		74.9 (4.9)		50.2 (3.8)	
IVH grade 3 or 4 (2 missing)[a]						
Yes (n=7)	63.5 (5.1)	.71	75.8 (3.4)	.75	49.5 (2.4)	.27
No (n=178)	64.1 (4.6)		75.2 (5.1)		50.9 (3.3)	
White matter lesion[b]						
None (n=70)	64.3 (4.9)	.27	75.3 (4.9)	.74	51.2 (2.7)	.02
Mild (n=83)	64.5 (4.0)		75.4 (4.8)		51.1 (3.3)	
Moderate (n=27)	62.9 (5.3)		74.3 (6.3)		49.4 (3.9)	
Severe (n=7)	62.2 (4.1)		74.1 (2.1)		48.7 (3.9)	

Abbreviations: IVH, intraventricular hemorrhage; MRI, magnetic resonance imaging.
[a] *P* values are calculated by unpaired 2-tailed *t* test.
[b] *P* values are calculated by analysis of variance.

Table 4. Brain Metrics and Other Perinatal Variables Related to BSID-II Scores at 2 Years in 177 Children

	BSID-II Score[a]			
	MDI		PDI	
	Univariable	Multivariable	Univariable	Multivariable
Brain diameter				
Bifrontal	0.86 (0.25 to 1.47)[b]	NA	0.73 (0.19 to 1.28)[b]	NA
Biparietal	0.95 (0.40 to 1.50)[b]	1.00 (0.45 to 1.60)[c]	0.87 (0.38 to 1.35)[b]	0.99 (0.45 to 1.50)[b]
Transverse cerebellum	1.23 (0.35 to 2.10)[b]	NA	1.43 (0.66 to 2.19)[c]	NA
Higher social risk	−8.8 (−14.5 to −3.1)[b]	−11.9 (−16.8 to −6.9)[c]	−1.2 (−6.4 to 4.0)	NA
Perinatal and neonatal variables				
Male sex	−7.9 (−13.5 to −2.3)[b]	−9.9 (−14.9 to −6.9)[c]	−4.0 (−9.0 to 1.1)	−5.9 (−10.7 to −1.1)[d]
Birth weight *z* score	4.58 (1.71 to 7.44)[b]	3.56 (0.80 to 6.32)[d]	2.21 (−0.39 to 4.80)	NA
Duration of IPPV (log-scale)	−0.95 (−2.01 to 0.10)	NA	−0.66 (−1.60 to 0.28)	NA
Postnatal corticosteroid therapy	−18.2 (−27.8 to −8.5)[c]	−11.7 (−20.4 to −3.1)[b]	−15.8 (−24.4 to −7.2)[c]	−11.9 (−20.2 to −3.7)[b]
Head circumference	NA	−0.40 (−1.80 to 0.90)	NA	−0.02 (−1.33 to 1.29)
Moderate to severe WMI	−16.9 (−24.1 to −9.7)[c]	−14.3 (−20.7 to −7.9)[c]	−12.4 (−18.9 to −5.8)[c]	−10.1 (−16.3 to −3.8)[b]

Abbreviations: BSID-II, Bayley Scales of Infant Development–Revised; IPPV, intermittent positive pressure ventilation; MDI, Mental Development Index; NA, not applicable; PDI, Psychomotor Development Index; WMI, white matter injury.
[a] Data are expressed as mean differences (95% confidence intervals) in MDI or PDI for each unit change in independent variable.
[b] $P<.01$.
[c] $P<.001$.
[d] $P<.05$.

1.76]; $P=.03$), although again these effects were not independent.

For PDI, male sex, postnatal corticosteroid therapy, and moderate/severe WMI were independent predictors for the PDI, with again only the biparietal diameter as an independent predictor. In this case, after removing the biparietal diameter, higher PDI was related to larger bifrontal diameter (increase in PDI for each millimeter increase, 0.70 [95% CI, 0.16-1.24]; $P=.01$) and larger transverse cerebellar diameter (increase in PDI for each millimeter increase, 1.13 [−0.38 to 1.88]; $P=.01$). There was no evidence of an interaction between sex and the effect of the brain metrics on the MDI or the PDI.

Similar results were seen for all analysis with adjustment for the infants who were multiple births (data not shown).

COMMENT

Our study demonstrates that 3 simple brain metrics (bifrontal, biparietal, and transverse cerebellar diameters), which are easily measured on T2-weighted coronal MRI sequences, were associated with the perinatal factors in the preterm infant that reflect in utero growth and the degree of illness, as measured by the duration of assisted ventilation and total parenteral nutrition and by the requirement of inotropic agents. Furthermore, there was some suggestion that more severe white matter abnormalities were associated with smaller cerebellar diameter, with no effect on other metrics. Brain metrics were also predictive of neurodevelopmental outcome at 2 years of corrected age. In multivariable analysis, although all metrics were predic-

tive of MDI and PDI independently of perinatal variables, the biparietal diameter was the brain metric that was most associated with the MDI and PDI. Finally, although there were sex differences with regard to brain metrics and 2-year outcomes, male sex and brain metrics were independent predictors of cognitive and motor development, with no evidence that the impact of brain metrics on outcomes varied between male and female infants.

Cerebral growth occurs in a linear fashion from 24 to 40 weeks' gestation, with a 4- to 5-fold increase in total brain volume during this period.[11] In preterm infants, this rapid growth is likely to be impaired by insults that occur before birth and during the early postnatal period.[12] In our study, smaller diameters were associated with lower birth weight and with severity of respiratory disease after birth, as reflected by the duration of assisted ventilation and oxygen use.

Few data are available about the brain regions' relative growth rate during the last trimester of gestation; however, it has been reported that the cerebellum has a faster growth rate than the rest of the brain and that its rate is negatively correlated with the duration of the mechanical ventilation.[13] Differential frontal and parietal growth patterns have not been described during the neonatal period but exist later in childhood along with sex differences.[14] The brain volume growth rate assessed by serial volumetric MRIs follows an inverted U-shaped curve that peaks during the teenage years, with a total brain volume being 6% to 10% greater in boys.[15] The peak brain volume occurs 4 years earlier in girls than in boys and earlier in the parietal lobes than in the frontal lobes. These changes and sex differences are probably associated with pubertal maturation, emphasizing the role of the hormonal environment on brain growth. Our results suggest that some mechanisms of sex-dependent brain growth trajectories may already be active during pregnancy and may be influenced by the extrauterine environment, especially in boys. This is in accordance with the study of sex differences by Hintz et al,[16] who demonstrated that preterm boys have perinatal risk factors similar to those of girls and concluded that their cognitive disadvantage may result from higher constitutional vulnerability to the perinatal events.

We failed to find an effect of postnatal corticosteroid therapy with low-dose dexamethasone on the 3 brain metrics. Previous research has suggested that decreased total brain volume at term-equivalent age has been associated with postnatal dexamethasone therapy.[17] In contrast, hydrocortisone use has been associated with only a trend toward smaller hippocampal volume but conserved total brain volumes.[18,19] In our study, postnatal corticosteroids were given in much lower doses than in the study by Murphy et al[17] and were restricted to a very small number of infants (8.6%), limiting our statistical power for these analyses.

The results from this study suggest that the duration of assisted ventilation was an independent predictor of the brain metrics, raising questions about the direct role of respiratory status on brain growth, perhaps through apnea or through oxygen and carbon dioxide levels. Severe respiratory illness requiring prolonged ventilation and oxygen exposure are also associated with increased handling and procedures for the infants; increased exposure to drugs, including sedatives and anxiolytics; and prolonged parenteral nutrition. It is likely that stress, drug exposures, and impaired nutrition may all contribute to alterations in the trajectory of typical cerebral development, although few data currently exist.

Our study also identified growth restriction at birth as having a persistent effect on brain growth by term-equivalent age. The impact of intrauterine growth restriction on impairing cerebral growth has been shown with cerebral volumetry[11] and has been related mostly to a decrease in gray matter volume that persisted at term-equivalent age.[20] Growth-restricted preterm infants are also exposed to an additional extrauterine growth restriction that is common in the neonatal intensive care unit.[21]

The association of poor growth and/or severe illness with reduced lateral brain metrics (bifrontal and biparietal measures) may be rationally thought to merely reflect the often scaphocephalic head of the preterm infant. However, we have previously documented that, although the preterm infants at term-equivalent age demonstrate reduced bifrontal and biparietal measures, there is no difference in fronto-occipital diameter, indicating no compensatory increase in skull length.[5] This study also reported strong correlations between volumetric analysis and brain metrics in this population (total tissue volume [without cerebrospinal fluid] to bifrontal diameter, $r=0.66$; to biparietal diameter, $r=0.63$; and to transverse cerebellar diameter, $r=0.71$; all significant at $P<.001$), confirming that these metrics reflect total brain tissue.

It may also be rationally questioned whether a measure of head circumference at term-equivalent age would render information similar to the brain metrics without the necessity of MRI. The relationship between head circumference and clinical outcome in this cohort has been addressed in a recent report in the same cohort.[22] In that study, we demonstrated that there was no significant relationship between head circumference at term-equivalent age and early motor and cognitive development. However, there was a relationship between head circumference at 1 year of age and outcomes. This difference may reflect enlarged periventricular spaces in preterm children at term-equivalent age. Although head circumference was a nonsignificant predictor of outcome in univariable analysis in our study, we adjusted for it in multivariable analysis to explore the effect of brain metrics beyond head circumference (Table 4).

There was little evidence that white and gray matter abnormalities were associated with brain metrics, with the exception of cerebellar diameter, which was reduced in children with WMI, an association previously described.[13,23] This aspect underscores the fact that morphologic changes on MRI may represent only a small part of the consequences of a preterm birth on the brain. Poor brain growth with no apparent WMI or gray matter injury may represent another aspect of the impact of preterm birth on the brain.

Cognitive development (measured by the MDI) was associated with a number of perinatal variables, including sex, social risk, growth status at birth, duration of

ventilation, postnatal corticosteroid therapy, and WMI, whereas motor development (measured by the PDI) was mainly related to sex, postnatal corticosteroid therapy, and WMI. Bifrontal, biparietal, and transverse cerebellar diameters were all predictors of cognitive and motor development at 2 years' corrected age beyond these perinatal variables, although they were interrelated and shared variance. Biparietal diameter appeared to be the most predictive, with the effects of bifrontal and transverse cerebellar diameters disappearing once biparietal diameter was adjusted for. Knowing that the sensitivity of moderate to severe qualitative MRI scores for predicting adverse long-term outcomes remains relatively low (sensitivity, 38% [95% CI, 25%-51%]),[9] brain metrics may complement the qualitative analysis of MRI and assist in identifying the infants at risk for poor outcome.

Our study has several limitations. The brain metrics were obtained using raw, nonrealigned MRIs, lowering the precision of the measure. However, the reproducibility was high and, because the objective was to provide a routine usable method, it was our intention to avoid time-consuming reconstructions. Developmental assessments such as the Bayley Scales of Infant Development are designed to evaluate developmental delay and as such are only moderate predictors of later general intellectual ability.[24] A strength of the study is that the cohort was large, and the follow-up rate to 2 years of age was high. A further strength is that all perinatal and follow-up observations were recorded independent of knowledge of the results of MRI.

In conclusion, our study provides important information regarding a new widely accessible quantitative technique for routine MRI examinations in preterm infants. These measures may help in understanding the factors associated with early brain development in preterm infants and may provide additional prognostic information that could be helpful in identifying children at risk for adverse developmental outcomes.

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