Ventricular Volume in Infants Born Very Preterm: Relationship with Brain Maturation and Neurodevelopment at Age 4.5 Years

Min Sheng, MD[1], Ting Guo, PhD[1], Connor Mabbott, MSc[1], Vann Chau, MD[1], Anne Synnes, MDCM, MHSc[2], Linda S. de Vries, MD, PhD[3], Ruth E. Grunau, PhD[2], and Steven P. Miller, MDCM[1,2]

Objective To evaluate the relationship of quantitative ventricular volume with brain maturation and neurodevelopmental outcomes at age 4.5 years in children born very preterm.

Study design T1-weighted imaging, diffusion tensor imaging, and magnetic resonance spectroscopy were performed shortly after birth (n = 212) and at term-equivalent age (TEA) (n = 194). Intraventricular hemorrhage (IVH) grade and white matter injury (WMI) volume were measured on early T1-weighted magnetic resonance imaging (MRI) scans. Total cerebral volume and ventricular volume were quantified using the Multiple Automatically Generated Templates-Brain pipeline. At age 4.5 years, 178 children (84%) underwent cognitive and motor assessments. Multivariable linear regression was used to examine the relationships between ventricular volume and neurodevelopmental outcomes. Generalized estimating equations were used to account for repeated measures when analyzing neonatal MRI data. All models accounted for sex, postmenstrual age at scan, WMI volume, IVH grade, and total cerebral volume and were corrected for multiple comparisons.

Results On early MRI, 97 infants had IVH (grade 1, n = 22; grade 2, n = 66; grade 3, n = 9), and 68 had WMI (median, 44 mm^3; IQR, 21-296 mm^3). IQ at 4.5 years was associated with MRI ventricular volume at the early ($\beta = -0.64$; $P < .001$) and TEA ($\beta = -0.44$, $P < .001$) time points. Motor outcomes were associated with ventricular volume at TEA ($\beta = -0.84$, $P = .01$). Greater ventricular volume independently predicted lower fractional anisotropy in corpus callosum (genu: $\beta = -0.0008$, $P = .002$; splenium: $\beta = -0.003$, $P < .001$) and optic radiations ($\beta = -0.001$, $P = .004$); ventricular volume did not predict the N-acetylaspartate/choline ratio.

Conclusions In children born very preterm, neonatal ventricular size was associated with 4.5-year neurodevelopmental outcomes. Our findings suggest that white matter maturation may be abnormal in the setting of enlarged ventricular size beyond that expected from concurrent brain injuries. *(J Pediatr 2022;248:51-8)*.

Enlarged ventricular size (dilatation) is one of the most common brain abnormalities in infants born preterm and is often associated with concurrent brain injury.[1-4] Previous studies assessing the association of ventricular dilatation with neurodevelopmental outcomes have reported inconsistent results owing to the different techniques and variables applied to measure ventricular size.[1,5-7] In addition, recent studies have shown that ventricular measurements on ultrasound, the most common imaging method used in routine clinical practice, do not correlate well with magnetic resonance imaging (MRI) measurements of ventricular size.[8,9] Ventricular dilatation is often detected with concurrent intraventricular hemorrhage (IVH) and periventricular hemorrhagic infarction. In this setting, ventricular dilatation itself is associated with an increased risk of neurodevelopmental sequelae,[2,10-14] such as cerebral palsy,[12] visual performance deficits,[2] and learning challenges.[13,14] However, because the reported neurodevelopmental outcomes of infants with ventricular dilatation in the absence of brain hemorrhage vary across studies, a more in-depth understanding of the relationship between ventricular size and neurodevelopmental outcome is needed.

We studied a prospective cohort of infants born very preterm with a wide range of ventricular sizes to accurately measure ventricular volume and investigate the independent association of ventricular volume with neonatal brain maturation and long-term neurodevelopmental outcomes. We focused specifically on infants

2D	Two-dimensional	MRI	Magnetic resonance imaging
3D	Three-dimensional	NAA/Cho	N-acetylaspartate/choline ratio
DTI	Diffusion tensor imaging	PLIC	Posterior limb of the internal capsule
FA	Fractional anisotropy		
FSIQ	Full-scale IQ	PMA	Postmenstrual age
IVH	Intraventricular hemorrhage	ROI	Region of interest
MABC-2	Movement Assessment Battery for Children, Second Edition	TEA	Term-equivalent age
		WMI	White matter injury

From the [1]Department of Paediatrics, University of Toronto and the Hospital for Sick Children, Toronto, Ontario, Canada; [2]Department of Pediatrics, University of British Columbia and BC Children's Hospital Research Institute, Vancouver, British Columbia, Canada; and [3]Department of Neonatology, University Medical Center Utrecht, Utrecht, The Netherlands

Funded by the Canadian Institutes of Health Research (Operating Grants MOP-79262, to S.M., and MOP-86489, to R.G.) and the Kids Brain Health Network. S.M. was supported by the Bloorview Children's Hospital Chair in Paediatric Neuroscience, and R.G. was supported by the BC Children's Hospital Research Institute. The authors declare no conflicts of interest.

Portions of this study were presented as an abstract during the Pediatric Academic Society meeting, May 1-4, 2021 (Virtual).

https://doi.org/10.1016/j.jpeds.2022.05.003

born preterm, because ventriculomegaly is uncommon in full-term infants. Our aims were to determine the relationship of ventricular volume with neonatal brain maturation and neurodevelopmental outcomes at age 4.5 years, accounting for total cerebral volume and concurrent brain abnormalities.

Methods

The study was approved by the University of British Columbia/BC Children's and Women's Health Centre Research Ethics Board. Infants (n = 234; 122 boys) born between 24 and 32 weeks of gestation (median, 27.7 weeks; IQR, 26.0-29.6 weeks) were recruited. Infants with a congenital infection, congenital malformation or syndrome, or large parenchymal hemorrhagic infarction (>2 cm on ultrasound) were excluded. Clinical and demographic data, including head circumference, Score for Neonatal Physiology Version II, neonatal hypotension, infection, patent ductus arteriosus, and maternal education level, were collected from a detailed chart review.[15] Neonatal hypotension was defined as sustained low blood pressure necessitating intervention with fluid bolus or inotropes. Maternal education level was categorized into 3 groups: primary/secondary school, undergraduate degree, and postgraduate degree.[15]

Brain Imaging and Segmentation

All brain MRI acquisitions were carried out without sedation on a 1.5T Siemens Avanto scanner (Siemens) at 2 time points, with the first scan performed shortly after birth (n = 212) and the second scan performed at term-equivalent age (TEA; n = 188). Three-dimensional (3D) volumetric T1-weighted imaging, diffusion tensor imaging (DTI), and magnetic resonance spectroscopy were performed at each time point. Details of sequence variables have been reported previously.[16-18] White matter injury (WMI) volumes were obtained as described previously,[19,20] and IVH was graded according to the system of Papile et al on early scans, the period at which these injuries are most apparent.[3]

Ventricular volume and total cerebral volume were segmented using the Multiple Automatically Generated Templates-Brain pipeline[21] on 3D T1-weighted images and then inspected and manually revised by an experienced radiologist to ensure that only target structures were included. Segmentation details have been described previously.[16] Ventricular volume includes the supratentorial ventricular volume, consisting of the lateral ventricles and the third ventricle (**Figure 1**; available at www.jpeds.com).

DTI. Mean fractional anisotropy (FA), mean diffusivity, axial diffusivity, and radial diffusivity values were extracted from each of 10 regions of interest (ROIs) in each hemisphere[18,22] (**Figure 2**). The average of the DTI variables of each ROI from the left and right hemispheres was calculated. The 10 ROIs were classified into 3 groups according to similarities of anatomic connectivity or proximity: (1) deep gray matter: caudate, lentiform nuclei, and thalamus; (2) white matter tracts: genu and splenium

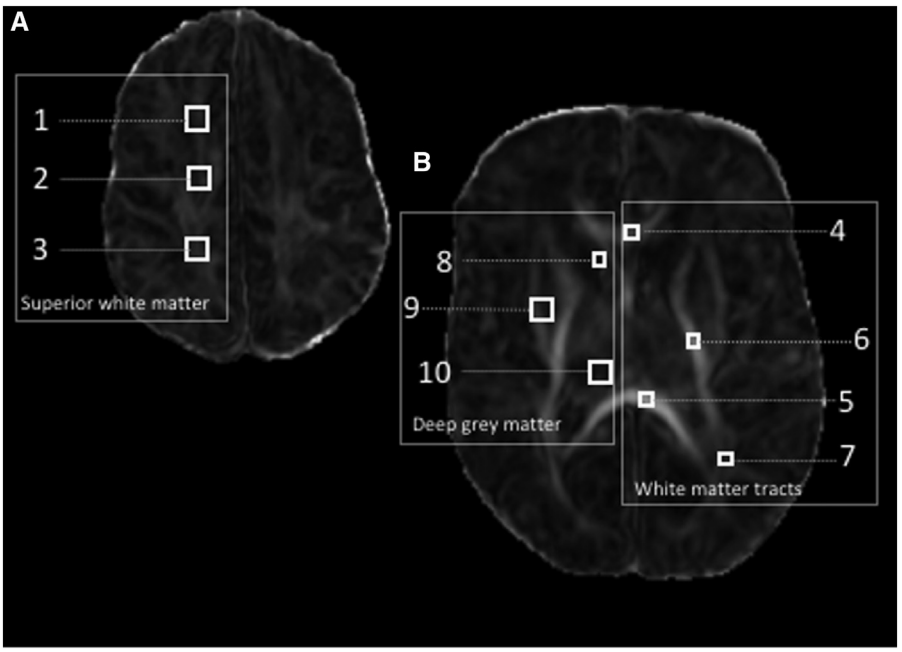

Figure 2. FA map derived from the DTI of an infant born at 29 weeks of gestation and scanned at 34 weeks PMA. Ten ROIs were identified at the levels of **A,** the high centrum semiovale and **B,** the basal ganglia. The value of each ROI was the average of bilateral values, and the ROIs were categorized into 3 groups: superior white matter (1) anterior, (2) central, and (3) posterior; white matter tracts (4) genu, (5) splenium, (6) PLIC, and (7) optic radiations; and deep gray matter (8) caudate nucleus, (9) lentiform nucleus, and (10) thalamus.

of the corpus callosum, posterior limb of the internal capsule (PLIC), and optic radiations; and (3) superior white matter: anterior, central, and posterior white matter.

Magnetic Resonance Spectroscopy. The N-acetylaspartate (NAA)/choline (Cho) ratio was calculated for each ROI bilaterally. The mean NAA/Cho ratio of each ROI was obtained by averaging values of both the left and right hemispheres. Four white matter ROIs (anterior, central, and posterior white matter and optic radiations) and 3 gray matter ROIs (caudate, lentiform nuclei, and thalamus) were measured and grouped as in the DTI analysis.

Neurodevelopmental Outcomes

Neurodevelopmental outcomes at age 4.5 years were assessed by experienced clinical staff in the Neonatal Follow-up Program who were blinded to the ventricular volume measurements. Cognitive outcome was measured using the Wechsler Primary and Preschool Scale of Intelligence, Third Edition, which provides the full-scale IQ (FSIQ). Ten children who could not be tested owing to severe cognitive impairment were assigned a score of 49. Motor skills were evaluated by experienced occupational therapists using the Movement Assessment Battery for Children, Second Edition (MABC-2).

Statistical Analyses

Statistical analysis was performed using R version 3.5.1 (R Foundation for Statistical Computing). To describe the cohort, we categorized children based on the 75th percentile of ventricular volume/total cerebral volume into normal and abnormal ventricular volume/total cerebral volume groups. Demographic and clinical characteristics in the normal and abnormal ventricular volume groups were compared using the χ^2 or Fisher exact test for categorical data and the Kruskal–Wallis test for continuous variables. For the remainder of the analyses, ventricular volume was modeled as the primary predictor, accounting for total cerebral volume as one of the covariates. Multiple linear regression models were used to investigate how ventricular volume related to neurodevelopmental outcomes, with ventricular volume as the primary predictor, FSIQ and motor scores as dependent variables, and sex, postmenstrual age (PMA) at scan, WMI volume, IVH grade, and total cerebral volume as covariates. Restricted cubic splines were then applied in these regression models to investigate whether there was a cutoff value of ventricular volume for predicting neurodevelopmental outcomes. We then examined the interaction term of WMI volume by ventricular volume in the linear regression models to determine whether the associations between ventricular volume and neurodevelopmental outcomes were modified by WMI volume. Because most children had 2 neonatal MRI scans, generalized estimating equations were used to determine the relationship between ventricular volume with FA, mean diffusivity, radial diffusivity, axial diffusivity, and NAA/Cho while accounting for repeated measures. These generalized estimating equation models used an independent correlation structure with robust standard error adjustment and included sex, PMA at scan, WMI volume, IVH grade, and total cerebral volume as covariates. To limit multiple comparisons across ROIs, we first analyzed the imaging metrics in the 3 ROI groups. For ROI groups with significant results, we then evaluated the individual ROIs within that group. The false discovery rate was used to correct for multiple comparisons for the ROI group and then in individual ROI analyses. Of note, only 2 subjects in this cohort had surgical ventricular drainage, thus surgery was not included as a covariate in our analyses. A P value $<.05$ was considered significant.

Results

Among the 212 infants with an early MRI, 208 with acceptable image quality had total cerebral volume and ventricular volume segmentations (median PMA, 32.0 weeks; IQR, 30.4-33.6 weeks). At TEA, 194 infants underwent MRI, and total cerebral volume and ventricular volume of 188 images were quantified successfully (median PMA, 40.3 weeks; IQR, 38.9-42.0 weeks). Four early scans and 6 TEA scans were excluded owing to excessive motion artifact. Of the 212 early MRIs, 68 (32.1%) showed punctate WMI (median WMI volume, 44 mm^3; IQR, 21-296 mm^3), 97 (45.8%) showed IVH (grade I, 22; grade II, 66; grade III, 9), and 43 (20.3%) showed both IVH and WMI.

Ventricular Volume and Total Cerebral Volume Quantification

The median ventricular volume and median total cerebral volume were 3.5 cm^3 (IQR, 2.6-5.6 cm^3) and 168.7 cm^3 (IQR, 146.6-200.8 cm^3), respectively, on early MRI and 6.6 cm^3 (IQR, 4.8-9.1 cm^3) and 349.1 cm^3 (IQR, 300.4-391.1 cm^3) at TEA. The median ventricular volume/total cerebral volume ratio was 2.1% (IQR, 1.5%-3.2%) early in life and 1.8% (IQR, 1.5%-2.7%) at TEA. Patients were categorized into normal and abnormal ventricular volume/total cerebral volume groups based on the 75th percentile of ventricular volume/total cerebral volume ratio (3.2%) using results of the early MRI. Infants in the abnormal ventricular volume/total cerebral volume group were more often male, were of younger gestational age, and had higher incidences of IVH and hypotension (Table I). Within the abnormal ventricular volume/total cerebral volume group, 33 of 41 infants (80.5%) with MRI data at both time points had reduction in ventricular volume/total cerebral volume ratio from the early MRI to the TEA MRI. Because no significant differences in ventricular volume or total cerebral volume were observed between the early life (P = .11 and .34, respectively) and TEA (P = .83 and .11, respectively) MRIs were observed across maternal education level groups, maternal education level was not adjusted for in subsequent analyses.

Ventricular Volume and Neurodevelopmental Outcomes

At age 4.5 years, 178 children (84%) returned for neurodevelopmental assessment (median age, 57.9 months; IQR,

Table I. Demographic and clinical characteristics of neonates with normal ventricular volume/total cerebral volume (<75th percentile) and abnormal ventricular volume/total cerebral volume (≥75th percentile)

Characteristics	Normal ventricular volume/total cerebral volume (N = 156)	Abnormal ventricular volume/total cerebral volume (N = 52)	*P*
Male sex, n (%)	73 (46.8)	34 (65.4)	.03
Gestational age, week, median (IQR)	28.6 (26.5-30.0)	26.6 (25.6-28.1)	<.001
PMA at early MRI, week, median (IQR)	32.3 (30.6-33.7)	31.3 (30.1-32.4)	.08
PMA at TEA MRI, week, median (IQR)	40.3 (39.0-41.9)	40.1 (37.7-41.9)	.33
WMI volume at early MRI, mm3, median (IQR)	41.2 (19.8-406.6)	49.5 (30.9-272.6)	.79
IVH, n (%)			<.001
Grade I-II	57 (36.5)	31 (59.6)	
Grade III	2 (1.3)	6 (11.5)	
Head circumference at birth, cm, median (IQR)	26.0 (24.0-27.5)	24.5 (22.5-26.5)	.06
Maternal education level, n (%)			.35
Primary/secondary	19 (10.7)	4 (2.2)	
Undergraduate	93 (52.2)	31 (17.4)	
Postgraduate	25 (14.0)	6 (3.3)	
SNAP-II, median (IQR)	9 (0-17)	9 (5-25)	.09
Hypotension, n (%)	47 (30.1)	26 (50.0)	.02
Culture-positive infection, n (%)	63 (40.4)	24 (46.2)	.59
Patent ductus arteriosus, n (%)	73 (46.8)	28 (53.8)	.47
WPPSI-III FSIQ score, median (IQR)	104 (95-112)	97 (89-107.8)	.02
MABC-2 total score, median (IQR)	74 (53-87)	72 (51-79.5)	.39

SNAP-II, Score for Neonatal Physiology, Version II; *WPPSI-III*, Wechsler Primary and Preschool Scale of Intelligence, Third Edition.
In the normal ventricular volume/total cerebral volume group, WPPSI-III FSIQ and MABC-2 scores were available for 127 and 123 children, respectively. In the abnormal ventricular volume/total cerebral volume group, WPPSI-III FSIQ and MABC-2 scores were available for 38 and 32 children, respectively.

57.0-58.9 months). The median Wechsler Primary and Preschool Scale of Intelligence, Third Edition FSIQ was 103 (IQR, 94.3-111), and the median MABC-2 total score was 74 (IQR, 53-85). Larger ventricular volume in early life ($\beta = -0.64$, $P < .001$) and at TEA ($\beta = -0.44$, $P < .001$) were associated with lower FSIQ scores. Larger ventricular volume at TEA also was associated with lower motor scores ($\beta = -0.84$, $P = .01$) (**Figure 3**). Examining the relationships with splines, no meaningful cutoff values of ventricular volume in relation to FSIQ and motor score were identified. Across the range of observed values, on the early MRI, every 1 cm^3 increase in ventricular volume was associated with a 0.6 point lower FSIQ, and on the TEA MRI, every 1 cm^3 increase in ventricular volume was associated with a 0.4 point lower FSIQ and a 0.8 point lower motor score. WMI volume significantly modified the relationship between ventricular volume in early life and FSIQ at 4.5 years ($P < .01$), where the negative association between ventricular volume and FSIQ was accentuated by greater WMI volume.

Ventricular Volume and MRI Measures of Brain Maturation

FA, mean diffusivity, and radial diffusivity values for the 3 groups of ROIs are presented in **Table II** (available at www.jpeds.com). Significant associations were observed between ventricular volume and FA, mean diffusivity, and radial diffusivity in white matter tract and gray matter groups after adjusting for sex, PMA at scan, WMI volume, IVH grade, and total cerebral volume and correcting for multiple comparisons (**Table III**; available at www.jpeds.com). We examined the relationships between ventricular volume and FA, mean diffusivity, and radial diffusivity in each individual ROI of these 2 groups (**Table IV**). Significant associations were observed between ventricular volume and FA in several white matter tracts (genu, splenium, optic radiations, and PLIC) and in the lentiform nucleus and thalamus after adjusting for sex, PMA at scan, WMI volume, IVH grade, and total cerebral volume and correcting for multiple comparisons. Ventricular volume was associated with mean diffusivity in the splenium, PLIC, and optic radiations. Significant associations between ventricular volume and radial diffusivity in the genu, splenium, optic radiations, and thalamus were observed as well. No significant association between ventricular volume and NAA/choline was observed after accounting for sex, PMA at scan, WMI volume, IVH grade, and total cerebral volume and correcting for multiple comparisons.

Discussion

We evaluated ventricular size in infants born very preterm both early in life and at TEA using quantitative volumetric measures, accounting for total cerebral volume and comprehensive assessment of concurrent brain injury, including WMI volumes. In our prospective cohort of children born preterm, larger ventricular volume in the neonatal period was associated with lower FSIQ and motor scores at preschool age. Our findings also suggest that enlarged ventricular volume is associated with alterations in white matter microstructure beyond that expected from a concurrent brain injury. It is important to note that ventricular volume was independently associated with neurodevelopmental outcomes regardless of the presence or absence of other brain injuries. This finding is consistent with conclusions from other contemporary reports identifying ventricular dilatation as a

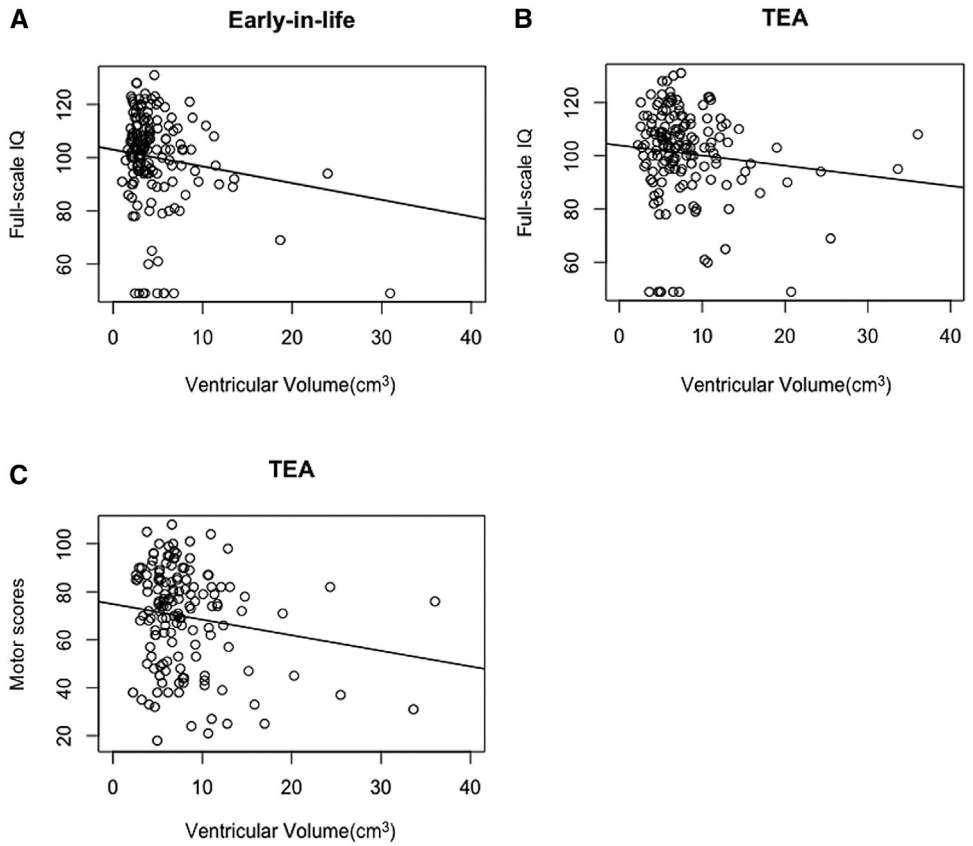

Figure 3. Relationships between **A,** ventricular volume at early in life and full-scale IQ; **B,** ventricular volume at TEA and full-scale IQ; and **C,** ventricular volume at TEA and motor score.

risk factor for adverse neurodevelopment in infants born preterm.[1,5,23-25] Fox et al reported that larger ventricular measurements acquired on neonatal ultrasound images predicted adverse motor and language development, but not cognitive composite scores, at age 2 years.[5] A recent study used the biparietal diameter-to-ventricle ratio measured on cranial ultrasound to calculate a total brain-to-ventricle ratio as a measure of relative ventricular size.[24] In that study of 482 infants born preterm, a reduced brain-to-ventricle ratio was associated with lower Mental Development Index and Psychomotor Development Index scores at 2 years.[24] Our study builds on these observations by acquiring accurate ventricular volumes during the neonatal period and investigating the relationships of these volumes early in life and at TEA with neurodevelopmental outcomes.

Table IV. Associations between DTI variables and ventricular volume in each ROI

	FA		Mean diffusivity		Radial diffusivity	
ROIs	*β*	***P***	*β*	***P***	*β*	***P***
Genu	−0.0008	**.002**	0.001	.08	0.002	**.002**
Splenium	−0.003	**<.001**	0.002	**<.001**	0.005	**.004**
PLIC	0.0005	**.01**	−0.0008	**.002**	−0.0008	.10
Optic radiations	−0.001	**.004**	0.001	**.01**	0.002	**.002**
Lentiform	0.0002	**<.001**	−0.0003	.90	−0.0003	.10
Thalamus	0.0005	**<.001**	−0.0004	.10	−0.0007	**<.001**

Independent variable: ventricular volume. Dependent variables: FA, mean diffusivity, and radial diffusivity in each ROI. Covariates: sex, PMA at scan, WMI volume, IVH grade, and total cerebral volume. *P* values are adjusted for false discovery rate. Significant *P* values are in bold type.

Two-dimensional (2D) ultrasound is the most common and accessible method for assessing ventricular size in neonatal intensive care units[26]; however, concerns have been raised regarding interobserver variability and poor correlation between 2D measurements and 3D ventricular volume. We conducted our study using 3D ventricular volume for several reasons. First, compared with ultrasound, MRI is more sensitive in WMI, which is the predominant brain injury in infants born preterm and is strongly associated with adverse neurodevelopment.[15,19,27] With MRI, WMI can be quantitively assessed and taken into account with the grade of IVH for the analyses of associations between ventricular volume and brain maturation, as well as with neurodevelopmental outcomes. Second, ventricular volume can be more accurately measured on 3D MRI compared with ultrasound and 2D measures.[16,20,28]

Ventricular volume was independently associated with cognitive and motor outcomes at age 4.5 years. This is consistent with findings of Ment et al showing that infants with ventriculomegaly had significantly lower IQ scores and a

higher rate of IQ scores <70.[25] In other studies, ventricular dilatation was associated with more neurodevelopmental impairment in children born preterm either with or without hemorrhage.[4,29,30] Our prospective cohort of children born very preterm was studied longitudinally with multimodal brain MRI from early in life to TEA, as well as neurodevelopmental outcomes at preschool age. The MRI studies enabled accurate quantitative measurements of ventricular size and its trajectory from early life to TEA and to investigate how ventricular size at each time point relates to neurodevelopmental outcomes. Of note, this cohort did not include neonates with severe periventricular hemorrhagic infarction; these neonates were excluded from enrollment because at the time their mortality was high and neurodevelopmental outcomes considered known.

Previous studies have demonstrated that infants born preterm are at high risk of brain injury, with the cerebral white matter particularly vulnerable. Both the extent and the severity of WMI were associated with adverse neurodevelopmental outcomes.[19] In our study, even after controlling for WMI volume, total cerebral volume, and other key factors, ventricular volume was independently associated with FSIQ and motor scores at preschool age, suggesting a contribution of ventricular size to cognitive and motor function in children born very preterm beyond what can be attributed to WMI.

The linear relationship between neonatal ventricular volume with preschool cognitive and motor outcomes suggests that there is no cutoff value of ventricular volume for predicting adverse neurodevelopmental outcomes. Thus, when considering intervention for ventricular dilatation, the etiology of the ventricular enlargement should be considered along with ventricular size. For example, in neonates with posthemorrhagic ventricular dilatation, those with an early neurosurgical intervention for this condition had essentially normal neurodevelopmental outcomes, whereas those receiving a late intervention did not.[31]

Larger ventricular volume was associated with lower FA in the corpus callosum and optic radiations, suggesting impaired white matter maturation in these regions. This is in line with a neonatal ultrasound study showing an association between hemorrhagic ventricular dilatation and white matter abnormalities.[32] Vollmer et al pointed out that even in MRI with reasonable image quality, isolated ventricular dilatation is likely to be associated with subtle WMIs that could not be identified on conventional neonatal MRI.[2] Furthermore, we found that larger ventricular volume was associated with higher mean diffusivity and radial diffusivity values in the splenium. Increased mean diffusivity values may be due to increased water content and decreased restriction of water diffusion observed in conditions of reduced membrane density.[33] White matter FA typically increases and mean diffusivity decreases along with PMA in the neonatal period[34,35]; these DTI changes have been linked to maturation of the oligodendroglial lineage in experimental models.[36] This increased regional mean diffusivity with decreased FA suggests abnormalities in the early events of white matter myelination in neonates with larger ventricular volume. Gilmore et al and Estrin et al reported decreased FA and increased mean diffusivity in neonates with a prenatal diagnosis of ventriculomegaly compared with full-term controls.[37,38]

In general, radial diffusivity decreases with increasing myelin development.[39] Increases in radial diffusivity have been linked to incomplete myelination[40] and loss of myelin following axonal injury.[41] The splenium is located adjacent to the trigone of the lateral ventricles, which is usually the earliest and the most pronounced part of the corpus callosum affected by lateral ventricle dilatation.[42] Therefore, it is not surprising to see the alterations in FA, mean diffusivity, and radial diffusivity with ventricular volume changes in the splenium, suggesting a particular vulnerability of the splenium in the context of ventricular dilatation. In contrast, ventricular volume was observed to be positively correlated with FA in the PLIC. Increased FA likely reflects the early myelination of the PLIC[43,44] and its relatively more distant location to ventricles. We hypothesize that ventricular dilatation may have resolved or decreased in our cohort before adversely impacting early myelination in the PLIC.

Deep gray matter maturation did not show pronounced alterations with ventricular dilatation. Experimental data suggest that hydrocephalus affects oligodendrocytes and myelin deposition first and results in axonal damage only when ventricle dilatation persists.[45] In our cohort, ventricular dilatation was reduced from early life to TEA in most (81%) neonates. Therefore, we hypothesize that ventricular dilatation resolved before inducing a pronounced abnormality in gray matter. Although the pathologic significance of FA in deep gray matter is controversial, abnormalities of radial diffusivity are generally considered to indicate axonal pathology.[46] The association of thalamus FA and radial diffusivity with ventricular volume suggests that this structure may be particularly vulnerable among deep gray nuclei in the patients with sustained ventricular dilatation. The association with higher FA suggests that changes other than myelination underlie these differences, although differences in axonal or glial development cannot be distinguished with the DTI methods used in this study. In our study, the absence of uniform longitudinal ultrasound measures of ventricular size precluded a detailed examination of the trajectory of ventricular size on the MRI scans in which ventricular volume was measured in relation to these measures of gray matter maturation.

Associations observed between ventricular volume and diffusion variables in splenium and optic radiations may reflect regional-specific vulnerability to ventricular dilatation. This work deepens our understanding of how neonatal ventricular dilatation after prematurity relates to neurodevelopmental outcomes at preschool age and highlights the importance of ventricular volume measurements during the neonatal period in relationship to longer-term neurodevelopmental outcomes. Furthermore, our findings contribute new insights into the brain changes that explain

the spectrum of neurodevelopment outcome in children born preterm. ■

We thank the participating children and families, the staff at the neonatal intensive care unit and Neonatal Follow-Up for their support, and the research staff for data collection.

Submitted for publication Oct 27, 2021; last revision received Apr 19, 2022; accepted May 5, 2022.

Reprint requests: Steven P. Miller, MDCM, Pediatric Medicine, BC Children's Hospital, 4500 Oak St, Vancouver, British Columbia V6H 3N1, Canada. E-mail: steven.miller@cw.bc.ca

References

1. Brouwer MJ, van Kooij BJM, van Haastert IC, Koopman-Esseboom C, Groenendaal F, de Vries LS, et al. Sequential cranial ultrasound and cerebellar diffusion-weighted imaging contribute to the early prognosis of neurodevelopmental outcome in preterm infants. PLoS One 2014;9:e109556.
2. Vollmer B, Roth S, Riley K, Sellwood MW, Baudin J, Neville BGR, et al. Neurodevelopmental outcome of preterm infants with ventricular dilatation with and without associated haemorrhage. Dev Med Child Neurol 2006;48:348-52.
3. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1500 g. J Pediatr 1978;92:529-34.
4. Luu TM, Ment LR, Schneider KC, Katz KH, Allan WC, Vohr BR. Lasting effects of preterm birth and neonatal brain hemorrhage at 12 years of age. Pediatrics 2009;123:1037-44.
5. Fox LM, Choo P, Rogerson SR, Spittle AJ, Anderson PJ, Doyle L, et al. The relationship between ventricular size at 1 month and outcome at 2 years in infants less than 30 weeks. Arch Dis Child Fetal Neonatal Ed 2014;99:F209-14.
6. Maunu J, Lehtonen L, Lapinleimu H, Matomäki J, Munck P, Rikalainen H, et al. Ventricular dilatation in relation to outcome at 2 years of age in very preterm infants: a prospective Finnish cohort study. Dev Med Child Neurol 2011;53:48-54.
7. Storbeck T, Bruns N, Weiss C, Felderhoff-Müser U, Müller H. Correlation of lateral ventricular size and deep gray matter volume in MRI at term equivalent age with neurodevelopmental outcome at a corrected age of 24 months and with handedness in preterm infants. Eur J Pediatr 2020;179:271-8.
8. Leijser LM, Srinivasan L, Rutherford MA, Counsell SJ, Allsop JM, Cowan FM. Structural linear measurements in the newborn brain: accuracy of cranial ultrasound compared to MRI. Pediatr Radiol 2007;37:640-8.
9. Anderson NG, Warfield SK, Wells S, Spencer C, Balasingham A, Volpe JJ, et al. A limited range of measures of 2-D ultrasound correlate with 3-D MRI cerebral volumes in the premature infant at term. Ultrasound Med Biol 2004;30:11-8.
10. Srinivasakumar P, Limbrick D, Munro R, Mercer D, Rao R, Inder T, et al. Posthemorrhagic ventricular dilatation: impact on early neurodevelopmental outcome. Am J Perinatol 2013;30:207-314.
11. Şimşek GK, Canpolat FE, Büyüktiryaki M, Okman E, Keser M, Üstünyurt Z, et al. Developmental outcomes of very low birthweight infants with non-hemorrhagic ventricular dilatations and the relationships thereof with absolute brain volumes measured via two-dimensional ultrasonography. Childs Nerv Syst 2020;36:1231-7.
12. Bolisetty S, Dhawan A, Abdel-Latif M, Bajuk B, Stack J, Oei J-L. Intraventricular hemorrhage and neurodevelopmental outcomes in extreme preterm infants. Pediatrics 2014;133:55-62.
13. Gilmore JH, van Tol JJ, Streicher HL, Williamson K, Cohen SB, Greenwood RS, et al. Outcome in children with fetal mild ventriculomegaly: a case series. Schizophr Res 2001;48:219-26.
14. Stewart AL, Rifkin L, Amess P, Kirkbride V, Townsend JP, Miller DH, et al. Brain structure and neurocognitive and behavioural function in adolescents who were born very preterm. Lancet 1999;353:1653-7.
15. Benavente-Fernández I, Synnes A, Grunau RE, Chau V, Ramraj C, Glass T, et al. Association of socioeconomic status and brain injury with neurodevelopmental outcomes of very preterm children. JAMA Netw Open 2019;2:e192914.
16. Guo T, Winterburn JL, Pipitone J, Duerden EG, Park MTM, Chau V, et al. Automatic segmentation of the hippocampus for preterm neonates from early-in-life to term-equivalent age. Neuroimage Clin 2015;9:176-93.
17. Chau V, Synnes A, Grunau RE, Poskitt KJ, Brant R, Miller SP. Abnormal brain maturation in preterm neonates associated with adverse developmental outcomes. Neurology 2013;81:2082-9.
18. Chau V, Poskitt KJ, McFadden DE, Bowen-Roberts T, Synnes A, Brant R, et al. Effect of chorioamnionitis on brain development and injury in premature newborns. Ann Neurol 2009;66:155-64.
19. Guo T, Duerden EG, Adams E, Chau V, Branson HM, Chakravarty MM, et al. Quantitative assessment of white matter injury in preterm neonates: association with outcomes. Neurology 2017;88:614-22.
20. Garfinkle J, Guo T, Synnes A, Chau V, Branson HM, Ufkes S, et al. Location and size of preterm cerebellar hemorrhage and childhood development. Ann Neurol 2020;88:1095-108.
21. Chakravarty MM, Steadman P, van Eede MC, Calcott RD, Gu V, Shaw P, et al. Performing label-fusion-based segmentation using multiple automatically generated templates. Hum Brain Mapp 2013;34:2635-54.
22. Chau V, Brant R, Poskitt KJ, Tam EWY, Synnes A, Miller SP. Postnatal infection is associated with widespread abnormalities of brain development in premature newborns. Pediatr Res 2012;71:274-9.
23. Hammerl M, Zagler M, Zimmermann M, Griesmaier E, Janjic T, Gizewski ER, et al. Supratentorial brain metrics predict neurodevelopmental outcome in very preterm infants without brain injury at age 2 years. Neonatology 2020;117:287-93.
24. Işık Ş, Büyüktiryaki M, Şimşek GK, Kutman HGK, Canpolat FE. Relationship between biparietal diameter/ventricular ratio and neurodevelopmental outcomes in non-handicapped very preterm infants. Childs Nerv Syst 2021;37:1121-6.
25. Ment LR, Vohr B, Allan W, Westerveld M, Katz KH, Schneider KC, et al. The etiology and outcome of cerebral ventriculomegaly at term in very low birth weight preterm infants. Pediatrics 1999;104:243-8.
26. Horsch S, Bengtsson J, Nordell A, Lagercrantz H, Ådén U, Blennow M. Lateral ventricular size in extremely premature infants: 3D MRI confirms 2D ultrasound measurements. Ultrasound Med Biol 2009;35:360-6.
27. Cayam-Rand D, Guo T, Grunau RE, Benavente-Fernández I, Synnes A, Chau V, et al. Predicting developmental outcomes in preterm infants: a simple white matter injury imaging rule. Neurology 2019;93:e1231-40.
28. Guillot M, Guo T, Ufkes S, Schneider J, Synnes A, Chau V, et al. Mechanical ventilation duration, brainstem development, and neurodevelopment in children born preterm: a prospective cohort study. J Pediatr 2020;226:87-95.E3.
29. Pappas A, Adams-Chapman I, Shankaran S, McDonald SA, Stoll BJ, Laptook AR, et al. Neurodevelopmental and behavioral outcomes in extremely premature neonates with ventriculomegaly in the absence of periventricular-intraventricular hemorrhage. JAMA Pediatr 2018;172:32-42.
30. Lucke AM, Hagan JL, Weiss MD. Does ventriculomegaly without hemorrhage impact neurologic and behavioral outcomes of premature neonates? J Perinatol 2019;39:1577-80.
31. Leijser LM, Miller SP, van Wezel-Meijler G, Brouwer AJ, Traubici J, van Haastert IC, et al. Posthemorrhagic ventricular dilatation in preterm infants: when best to intervene? Neurology 2018;90:e698-706.
32. Kuban K, Sanocka U, Leviton A, Allred EN, Pagano M, Dammann O, et al. White matter disorders of prematurity: association with intraventricular hemorrhage and ventriculomegaly. The Developmental Epidemiology Network. J Pediatr 1999;134:539-46.
33. Sen PN, Basser PJ. A model for diffusion in white matter in the brain. Biophys J 2005;89:2927-38.
34. Gilmore JH, Lin W, Corouge I, Vetsa YSK, Smith JK, Kang C, et al. Early postnatal development of corpus callosum and corticospinal white matter assessed with quantitative tractography. AJNR Am J Neuroradiol 2007;28:1789-95.

35. Neil JJ, Shiran SI, McKinstry RC, Schefft GL, Snyder AZ, Almli CR, et al. Normal brain in human newborns: apparent diffusion coefficient and diffusion anisotropy measured by using diffusion tensor MR imaging. Radiology 1998;209:57-66.
36. Drobyshevsky A, Song SK, Gamkrelidze G, Wyrwicz AM, Derrick M, Meng F, et al. Developmental changes in diffusion anisotropy coincide with immature oligodendrocyte progression and maturation of compound action potential. J Neurosci 2005;25:5988-97.
37. Gilmore JH, Smith LC, Wolfe HM, Hertzberg BS, Smith JK, Chescheir NC, et al. Prenatal mild ventriculomegaly predicts abnormal development of the neonatal brain. Biol Psychiatry 2008;64:1069-76.
38. Lockwood Estrin G, Kyriakopoulou V, Makropoulos A, Ball G, Kuhendran L, Chew A, et al. Altered white matter and cortical structure in neonates with antenatally diagnosed isolated ventriculomegaly. Neuroimage Clin 2016;11:139-48.
39. Bockhorst KH, Narayana PA, Liu R, Ahobila-Vijjula P, Ramu J, Kamel M, et al. Early postnatal development of rat brain: in vivo diffusion tensor imaging. J Neurosci Res 2008;86:1520-8.
40. Song SK, Sun SW, Ramsbottom MJ, Chang C, Russell J, Cross AH. Dysmyelination revealed through MRI as increased radial (but unchanged axial) diffusion of water. Neuroimage 2002;17:1429-36.
41. Song SK, Yoshino J, Le TQ, Lin SJ, Sun SW, Cross AH, et al. Demyelination increases radial diffusivity in corpus callosum of mouse brain. Neuroimage 2005;26:132-40.
42. Dorner RA, Burton VJ, Allen MC, Robinson S, Soares BP. Preterm neuroimaging and neurodevelopmental outcome: a focus on intraventricular hemorrhage, post-hemorrhagic hydrocephalus, and associated brain injury. J Perinatol 2018;38:1431-43.
43. Rogers CE, Smyser T, Smyser CD, Shimony J, Inder TE, Neil JJ. Regional white matter development in very preterm infants: perinatal predictors and early developmental outcomes. Pediatr Res 2016;79:87-95.
44. Ling X, Tang W, Liu G, Huang L, Li B, Li X, et al. Assessment of brain maturation in the preterm infants using diffusion tensor imaging (DTI) and enhanced T2 star weighted angiography (ESWAN). Eur J Radiol 2013;82:e476-83.
45. Del Bigio MR, Kanfer JN, Zhang YW. Myelination delay in the cerebral white matter of immature rats with kaolin-induced hydrocephalus is reversible. J Neuropathol Exp Neurol 1997;56:1053-66.
46. Nagasunder AC, Kinney HC, Blüml S, Tavaré CJ, Rosser T, Gilles FH, et al. Abnormal microstructure of the atrophic thalamus in preterm survivors with periventricular leukomalacia. AJNR Am J Neuroradiol 2011;32:185-91.

50 Years Ago in *THE JOURNAL OF PEDIATRICS*

Understanding Progressive Cholestatic Liver Disease

Linarelli LG, Williams CN, Phillips MJ. Byler's disease: fatal intrahepatic cholestasis. J Pediatr 1972;81:484-92.
Williams CN, Kaye R, Baker L, Hurwitz R, Senior JR. Progressive familial cholestatic cirrhosis and bile acid metabolism. J Pediatr 1972;81:493-500.

In 1972, Linarelli et al contributed findings to further understand Byler disease, the first described progressive familial cholestasis disorder; this was discovered in the Amish Byler family in the western Pennsylvania and eastern Ohio region. Bile acid analysis of an affected infant's serum identified significant levels of lithocholic acid, which the authors proposed as a likely contributor to the canalicular damage seen in the liver tissue. In addition, electron microscopy of liver tissue discovered the unique coarse particulate and amorphous granular bile, later coined "Byler's bile." At the same time, Williams et al described a uniquely different form of progressive familial cholestasis. Although lithocholic acid serum levels also were elevated, the affected children's presentation, symptomatology, and bile composition, being viscid compared with the particulate coarse bile, were distinct from Byler disease.

Progressive familial intrahepatic cholestasis encompasses a growing and heterogeneous group of rare genetic cholestatic disorders defined by defects in bile acid secretion or transportation. Our understanding of the molecular pathogenesis of bile acids, mechanisms of bile acid synthesis and transportation, and genetic defects associated with progressive familial cholestatic disorders has evolved over the decades. Byler disease is now considered progressive familial intrahepatic cholestasis type 1, and, more accurately, FIC1 deficiency. A recent review highlighted the range of disease subtypes and the importance of defining the subtypes individually, and described the shortened life expectancy, debilitating symptoms, and poor health-related quality of life across the group of progressive cholestatic diseases.[1] Further work to identify and understand progressive familial cholestatic diseases is needed to manage, treat, and counsel the children and families that are affected by these disorders.

Julie B. Osborn, MD
Division of Pediatric Gastroenterology, Hepatology and Nutrition
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio

Reference

1. Ibrahim SH, Kamath BM, Loomes KM, Karpen SJ. Cholestatic liver diseases of genetic etiology: advances and controversies. Hepatology 2022;75:1627-46.

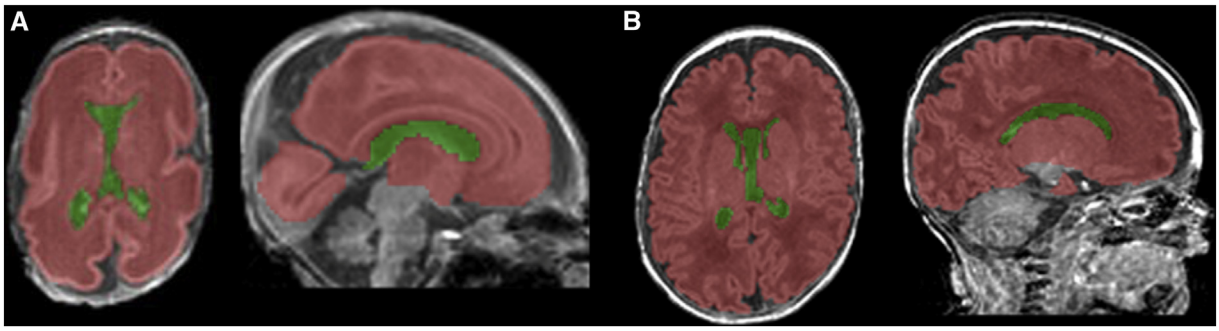

Figure 1. Segmentation of supratentorial ventricular volume (VV) and total cerebral volume (TCV) on T1-weighted MRI of a single neonate **A,** early after birth and **B,** at TEA.

Table II. FA, mean diffusivity, and radial diffusivity values of 3 ROI groups on both early life and TEA MRI

	FA, median (IQR)		Mean diffusivity, median (IQR)		Radial diffusivity, median (IQR)	
ROI groups	**Early life**	**TEA**	**Early life**	**TEA**	**Early life**	**TEA**
Superior white matter	0.12 (0.10-0.14)	0.18 (0.14-0.22)	1.84 (1.74-1.97)	1.63 (1.48-1.79)	2.02 (1.89-2.15)	2.03 (1.90-2.15)
White matter tracts	0.42 (0.33-0.48)	0.49 (0.41-0.57)	1.37 (1.28-1.52)	1.28 (1.16-1.41)	2.06 (1.91-2.22)	2.04 (1.92-2.20)
Gray matter	0.10 (0.08-0.13)	0.12 (0.10-0.14)	1.35 (1.29-1.41)	1.19 (1.12-1.25)	1.43 (1.34-1.51)	1.41 (1.33-1.50)

Table III. Associations between DTI variables with ventricular volume in each ROI group

	FA		Mean diffusivity		Axial diffusivity		Radial diffusivity	
ROI groups	β	***P***	β	***P***	β	***P***	β	***P***
Superior white matter	−0.0009	.36	0.004	.36	0.001	.67	0.005	.36
White matter tracts	−0.0008	**.02**	0.0007	**.048**	−0.0007	.32	0.001	**.02**
Gray matter	0.0003	**.01**	−0.0002	.36	0.0002	.44	−0.0004	**.048**

Independent variable: ventricular volume. Dependent variables: FA, mean diffusivity, and radial diffusivity in each ROI. Covariates: sex, PMA at scan, WMI volume, IVH grade, and total cerebral volume. *P* values are adjusted for false discovery rate. Significant *P* values are in bold type.