Postshunt lateral ventricular volume, white matter integrity, and intellectual outcomes in spina bifida and hydrocephalus

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OBJECT No previous reports exist that have evaluated the relationships of white matter (WM) integrity with the number of shunt revisions, ventricular volume after shunting, and cognition in medically stable children who have spina bifida and hydrocephalus (SBH). The authors hypothesized that enlarged ventricles and a greater number of shunt revisions decrease WM integrity in children.

METHODS In total, 80 children (mean age 13.7 years) who had SBH underwent MRI and IQ testing. Probabilistic diffusion tractography was performed to determine mean diffusion tensor imaging (DTI) metrics along the frontal and parietal tectocortical pathways. The DTI metrics were evaluated for significant correlation with a composite IQ measure and with the total number of shunt revisions and the total lateral ventricular volume obtained through semiautomated parcellation of T1-weighted MRI scans.

RESULTS An enlargement in total lateral ventricle volume and an increase in the number of shunt revisions were both associated with higher fractional anisotropy (FA) and with lower radial diffusivity (RD) along both frontal and parietal tectocortical pathways. Children who had not undergone a shunt revision had on average a greater lateral ventricle volume and higher FA and lower RD along frontal and parietal pathways than those who had undergone multiple shunt revisions. The mean DTI metrics along parietal pathways predicted IQ scores, but intellectual ability was not significantly correlated with ventricular volume or with the number of lifetime shunt revisions.

CONCLUSIONS Significant changes in DTI metrics were observed as a function of ventricular volume. An increased lateral ventricle volume was associated with elevated FA and decreased RD. Given that the participants were medically stable at the time of the MRI examination, the results suggested that those who have enlarged ventricles show a DTI pattern consistent with axonal compression due to increased intracranial pressure (ICP) in attenuated hydrocephalus. Although limited by a cross-sectional design, the study's findings suggest that DTI metrics may serve as sensitive indicators for chronic, mild hydrocephalus in the absence of overt clinical symptoms due to increased ICP. Having enlarged ventricles and undergoing multiple shunt revisions did not affect intellectual ability in children with SBH.

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KEY WORDS hydrocephalus; diffusion tensor imaging; spina bifida; neural tube defect; congenital

FINDINGS in animal models and in humans have established that a pathological enlargement of the cerebral ventricles initiates a cascade of brain insults leading to gradual axonal degradation and demyelination. Periventricular pathways and structures, including the cor-

pus callosum, internal capsule, and fornix, as well as long periventricular projection axons controlling motor, sensory, visual, attention, and memory processes, are particularly vulnerable to the effects of ventricular expansion.¹²

In hydrocephalic rats, the extent of microstructural

ABBREVIATIONS AD = axial diffusivity; DTI = diffusion tensor imaging; FA = fractional anisotropy; ICP = intracranial pressure; RD = radial diffusivity; SBH = spina bifida and hydrocephalus; WM = white matter.

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damage to white matter (WM) regions in hydrocephalus correlates with the extent of ventricular dilation and with poorer behavioral outcomes.²⁸ The ventricular enlargement also results in increased intracranial pressure (ICP), accompanied by a restriction in cerebral blood perfusion. In turn, decreased cerebral blood flow produces further neuronal insults via hypoxic metabolism and lipid peroxidation.^{11,28} Uncontrolled hydrocephalus in children is associated with disruptions of myelination processes during development.²⁶

Research in animal models indicates that an arrested hydrocephalus produces an ongoing insult to the periventricular WM by gradually degenerating axons and by increasing myelin turnover, the extent of which correlates with larger ventricular volumes.¹³ Repeated shunt failure produces multiple episodes of ventricular enlargement and recurrent effects on cerebral WM. However, little is known about the effects of chronic hydrocephalus on the cerebral WM in humans, especially after shunt treatment. In some children, the ventricles are small or enlarged after ventricular dilation stabilizes.

Previous studies on individuals who have spina bifida and hydrocephalus (SBH) have reported a pattern of specific alterations in posterior versus anterior brain regions. These changes include malformations of the hindbrain and cerebellum that are the hallmarks of spina bifida, along with decreased WM integrity in limbic regions and impaired long-association pathways as measured by diffusion tensor imaging (DTI).^{24,25} A small longitudinal study of children having acute hydrocephalus indicated that 7 of 10 cases displayed elevated fractional anisotropy (FA) in the posterior limb of the internal capsule and decreased FA in the genu of the corpus callosum. However, these increases in FA normalized after insertion of a ventriculoperitoneal shunt.¹

In a whole-brain, voxel-wise analysis of heterogeneous hydrocephalus etiologies in a small sample of adults, the same pattern of FA variations was observed, but elevations in these DTI metrics persisted after shunting.³² Elevated FA has also been identified in the subcortical gray matter of the caudate, likely because of the elevated ICP in chronic hydrocephalus. These observations differed from those in patients who had enlarged ventricles due to neuronal atrophy and in whom the caudate FA matched that in healthy individuals. In patients with chronic hydrocephalus, caudate diffusion rapidly returns to normal immediately after shunting.²⁹

Few studies have quantified the relationship between diffusion metrics and a stabilized subacute ventricular volume in individuals who underwent shunting. The Evans ratio is a commonly used clinical indicator of ventricular dilation, but volumetric measurements of the lateral ventricles in experimental hydrocephalus models suggest that the measured extent of ventricular enlargement is 3- to 4-fold larger than that estimated with the Evans ratio.²⁷ Furthermore, few studies have investigated the consequences of numerous shunt revisions and persistently enlarged ventricles on cognitive functioning, and most (but not all) studies of children indicate no correlation of the number of shunt revisions with IQ scores.³⁵ However, these studies rarely incorporated quantitative neuroim-

aging measures, particularly DTI, which are sensitive to changes in WM integrity.

In a previous study, we showed that individuals with SBH have a lower FA along parietal (but not frontal) tectocortical pathways than normally developing individuals.³⁹ In the present study, we extended these findings by associating the integrity of these pathways with lateral ventricular volume and with clinical factors related to shunt revisions. We also assessed whether DTI metrics, ventricular volume, and shunt revisions were related to IQ scores in individuals having SBH.

We hypothesized the following: 1) among individuals who have SBH, subacute lateral ventricular volume would be correlated with WM integrity such that larger ventricles predict lower WM integrity along parietal but not frontal tectocortical pathways; 2) IQ scores would be positively associated with DTI indicators of WM integrity (that is, higher FA accompanied by lower radial diffusivity [RD] and axial diffusivity [AD] will predict higher IQ scores), while IQ scores would show no correlation with lateral ventricular volume; and 3) compared with individuals who underwent no or 1 surgical revision for SBH, individuals who underwent ≥ 2 shunt revisions would show greater decreases in DTI metrics of WM structural integrity (that is, lower FA and higher RD and AD) and enlarged lateral ventricles.

Methods

Participants

This study was approved by the committees for the protection of human subjects at The University of Houston, University of Texas Health Science Center at Houston, and at The Hospital for Sick Children, Toronto, Ontario, Canada. The study cohort comprised 80 individuals who had SBH. Because the research questions involved only variations within cases of SBH, a comparison group of healthy individuals was not included. Informed consent was obtained from the person authorized to give consent at study enrollment.

Participants who had SBH were recruited nonconsecutively through 2 clinics serving children in the Houston area: the Shriner's Hospital for Children–Houston and the Spina Bifida Clinic at Texas Children's Hospital. The data were collected from 2005 to 2010 as part of a larger study (> 300 participants) that also involved children from Ontario, Canada. The participants for whom 3-T MRI data were available were from the Houston subcohort because the Ontario site did not have a 3-T MRI scanner at the start of data collection. Children with SBH were identified as having a myelomeningocele at birth that was usually repaired surgically and treated by inserting a shunt in the 1st month of life ($n = 76$; mean age at shunt insertion 31 days). We also included 4 individuals who had SBH and arrested hydrocephalus and who did not undergo shunting. According to radiological review of MRI scans obtained for this study (see below), most of the participants were identified with normal-appearing lateral ventricles ($n = 36$), with some showing small ($n = 21$) and some showing enlarged ($n = 23$) ventricles; 31 participants showed signs of colpocephaly.

The study participants were medically stable with regard to shunt status and indicators of nonspecific illnesses. All had IQ scores above the level associated with intellectual disability (that is, standard scores > 70) because the study design required that participants be able to follow instructions. Participants were excluded if they showed signs of severe psychiatric disorders (autism and psychosis), were unable to use the upper extremities, or had kyphosis so severe that they could not undergo MRI. The demographic information of the participants in this study is shown in Table 1.

Medical Characteristics Associated With SBH

The participants' medical histories were acquired through record review supplemented with data obtained in parent interviews conducted by a research nurse. Additional information was obtained from detailed questionnaires assessing gestational, developmental, medical, and behavioral history and from an independent radiological review of MRI scans taken for this study and coded by 2 radiologists blinded to any diagnosis.

Table 2 reports the medical characteristics associated with SBH, indicating that the study cohort was similar to the larger cohort from which these participants were drawn and was representative of SBH cases.¹⁹ Most participants (n = 70) were identified with a hindbrain Chiari malformation Type II (coded by a radiologist who was blinded to the participants' medical history and group status), along with a hypoplastic or dysgenetic corpus callosum. Three cases were identified as having a Chiari malformation Type I. Four cases did not meet the criteria for a Chiari malformation (Type I or Type II) on the blind review but had milder malformations, showing varying Chiari stigmata (4 underwent shunting for aqueductal stenosis, and 3 never underwent shunting because their hydrocephalus was arrested). The remaining 3 participants did not show Chiari stigmata but were included in the study because they had lower-level spina bifida lesions (2 lumbar and 1 sacral), and all of these patients had undergone shunting for hydrocephalus due to aqueductal stenosis.

Measurement of IQ

Testing of IQ was conducted concurrently with the MRI assessment by a trained research assistant under the supervision of licensed neuropsychologists. Composite IQ scores were calculated for each participant using the short form (4 subtest) of the Stanford-Binet Intelligence Test,³⁶ with a test-retest reliability estimate (r) of 0.93–0.98 when administered to individuals age 8–23 years.

Acquisition and Processing of MRI Data

All procedures for MRI acquisition, processing, and analyses have been described in detail by Williams et al.³⁹ Briefly, T1-weighted scans were acquired on a Philips 3.0-T Intera system with the following parameters: slice thickness 1.5 mm; TR/TE 6.5–6.7/3.04–3.14 msec; flip angle 8°; square FOV 24 cm³; acquisition matrix 256 × 256; in-plane pixel dimensions (x, y) 0.94, 0.94; and NEX 2. The DTI images were acquired using a single-shot spin-echo diffusion-sensitized echo-planar imaging sequence

TABLE 1. Demographic background of the participants in this study

Variable	Individuals w/ SBH
No. of participants	80
Mean age at MRI in yrs (SD)	13.7 (4.7)
Mean SES (SD)*	33.2 (13.2)
Sex (% male)	54
Ethnicity (% of cohort)	
Hispanic	55
Non-Hispanic	45
African American	10
White	34
Other	1

SES = socioeconomic status.
* Socioeconomic status was determined as a score derived from the Hollingshead Four Factor Index of Social Status; socioeconomic data were unavailable for 1 participant.

with the balanced Icosa21-encoding scheme with the following DTI parameters: 44 slices total; square FOV 24 cm³; acquisition matrix 256 × 256; slice thickness 3 mm; TR/TE 6100/84 msec; b value 1000 sec/mm². A single nondiffusion-weighted or “low-b” image with a b value of 0 sec/mm² was also acquired as an anatomical reference volume. Each encoding was repeated twice and averaged for magnitude to increase the signal-to-noise ratio.

The T1-weighted images were processed with the semi-automated FreeSurfer image analysis suite (<http://surfer.nmr.mgh.harvard.edu/>), generating cortical labels that were nonlinearly coregistered and transformed into native DTI space to serve as tractography end point masks in subsequent analyses.^{16,17} Resulting cortical labels were subsequently extended 2 mm into adjacent WM to facilitate fiber-tracking procedures. FreeSurfer morphologically derived tissue segmentations also provided volumetric indicators of lateral ventricular volumes, which were used as predictors in subsequent statistical analyses.

The DTI data were processed with tools provided by FreeSurfer and image analysis software at the FMRIB Software Library (FSL; <http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSL>).^{6–8,22,23} Diffusion volumes were corrected for both eddy currents and motion. The diffusion tensor was then calculated for each voxel with a least-squares fit to the log of the diffusion signal. The T2-weighted low-b volume (collected as a nondiffusion-weighted anatomical reference volume within the DTI sequence), was skull stripped and served as a brain-mask for all other diffusion maps. Maps for FA, AD (λ_1), and RD ($[\lambda_2 + \lambda_3]/2$) were then isolated for further tractography processing and analysis.^{9,33,34}

Procedures for labeling midbrain seed regions and deriving DTI metrics using probabilistic tractography have been described in detail in Williams et al.³⁹ Briefly, the left and right divisions of the midbrain tectum were manually defined for each participant by a single rater (V.J.W.) blinded to the diagnosis. These definitions served as a seed region in subsequent probabilistic tractography procedures. Hand-drawn regions of interest were traced in FSL view in the axial plane of the T2-weighted low-b image col-

TABLE 2. Medical characteristics of the participants in this study

Variable	No. of Individuals (%)
Lesion level	
Above L-1 (upper lesion)	14 (18)
Below T-12 (lower lesion)	66 (82)
Chiari malformation	
None	7 (9)
Type I	3 (4)
Type II	70 (88)
Corpus callosum	
Normal	3 (4)
Hypoplastic	52 (65)
Dysgenetic	25 (31)
No. of shunt revisions*	
No shunt (arrested hydrocephalus)	4 (5)
None	9 (11)
1	22 (28)
2–4	37 (47)
≥5	7 (9)
Shunt infection†	10 (15)
Ambulatory status	
Normal	4 (5)
Independent	20 (25)
w/ support	28 (35)
Unable	28 (35)
Seizure disorder‡	
No	53 (88)
Past	5 (8)
Present	2 (3)
Radiologically coded lat ventricle size	
Normal	36 (45)
Small	21 (26)
Enlarged	23 (29)
Colpocephaly	31 (39)
Tectal beaking	
Present	51 (64)
Absent	29 (36)

* The number of shunt revisions was assessed in 79 participants.

† Shunt infection was assessed in 65 participants.

‡ Seizure disorders were assessed in 60 participants.

lected as an anatomical reference volume within the DTI sequence. By directly labeling the T2-weighted low-b image acquired in each participant's native DTI space, the label directly corresponded to the intended collicular structure. Therefore, it did not require spatial transformations relying on coregistration procedures. Evaluation with dice similarity coefficients (0.894) showed strong reliability of the manual tracings.⁴⁰

Probabilistic tractography was completed for each brain hemisphere independently with the use of either left or right collicular seed points. Two probabilistic tractography iterations were performed for each hemisphere defining connectivity from the colliculi to parietal and frontal

cortical regions, yielding 4 tracts for each participant: left tectal-frontal hemisphere, left tectal-parietal hemisphere, right tectal-frontal hemisphere, and right tectal-parietal hemisphere. The output was waytotal normalized across the participants, thresholded to remove voxels for which FA was < 0.2, and subsequently binarized to create tractography-derived masks. Fractional anisotropy, RD, and AD were derived and used as dependent variables in statistical analysis.

Statistical and Analytical Methods

All statistical analyses were performed using PASW Statistics software version 18.0.3. Experiment-wise correction for multiple comparisons was performed using the Bonferroni approach, with $\alpha < 0.02$ for the 3 main hypotheses.

Hypothesis 1: Relationship Between DTI Metrics and Ventricular Volume

To assess the associations between ventricle volume and the indices of WM integrity (that is, FA, RD, and AD), simultaneous multiple regression analyses were performed. Regression analyses were conducted per hemisphere to account for within-person variation in right and left lateral ventricular volume. To control for age-related variations in WM integrity, age was included as a covariate.

Hypothesis 2: Predicting IQ Scores With DTI Metrics and Total Lateral Ventricular Volume

To assess whether total lateral ventricular volume and the indices of WM structural integrity were predictive of IQ, simultaneous multiple regression analyses, controlling for age and socioeconomic status, were performed.

Hypothesis 3: Effect of Shunt Revisions

To examine the effect of shunt revision on IQ and the 3 DTI metrics, a univariate analysis of covariance (ANCOVA) was performed in which age was included as a covariate. To evaluate the effect of shunt revision on total lateral ventricle volume, the ANCOVA was performed with age and total brain volume (excluding CSF) as covariates. For models reaching an overall level of statistical significance, post hoc pairwise comparisons of the 4 shunt revision groups (no revision, 1 revision, 2–4 revisions, and ≥ 5 revisions) was performed using estimated marginal means accounting for the covariates.

Results

Table 3 shows the mean DTI metrics and pathway volume of the tractography-derived tectocortical tracts, as well as the mean voxel-based lateral ventricle volumes for the right and left brain hemispheres in the participants in this study.

Hypothesis 1: Relationship Between DTI Metrics and Ventricular Volume

The statistical significance of the model and of the standardized β weights for FA, RD, and AD are shown in Table 4. In an analysis controlling for the effects of age,

TABLE 3. Tractography-derived DTI metrics along frontal and parietal tectocortical pathways and lateral ventricle volume*

Variable	Measured Values
FA ($\times 10^{-6}$ mm ² /sec)	
Frontal	0.440 $\pm$ 0.078 (0.379–0.529)
Parietal	0.432 $\pm$ 0.032 (0.354–0.532)
RD ($\times 10^{-3}$ mm ² /sec)	
Frontal	593 $\pm$ 45.7 (491–722)
Parietal	632 $\pm$ 56.0 (498–871)
AD ($\times 10^{-3}$ mm ² /sec)	
Frontal	1214 $\pm$ 52.5 (1124–1410)
Parietal	1268 $\pm$ 67.1 (1150–1662)
Pathway vol (mm ³)	
Frontal	12,375 $\pm$ 2606 (6454–17,905)
Parietal	10,739 $\pm$ 2256 (5613–15,772)
Lat ventricle vol (mm ³)	
Total	33,057 $\pm$ 32,209 (5873–154,560)
Lt	18,957 $\pm$ 19,754 (2707–105,114)
Rt	14,100 $\pm$ 13,458 (2378–65,375)

* The data in this table are mean $\pm$ SD (range).

increased ventricle volume was a significant predictor of a higher FA and a lower RD along the frontal and parietal tectocortical tracts in both hemispheres.

Post Hoc Analysis of Shunt Lateralization by Hemispherical Ventricular Volume

In the present sample, the majority of participants received right-sided shunts (71%), 16% received left-sided shunts, and 8% received shunts on both sides. Four participants (5%) did not undergo shunting because their hydrocephalus was arrested. To determine whether the hemisphere in which the shunt was placed influenced left or right ventricular volume, post hoc analyses were performed on those patients undergoing only left-side ($n = 13$) or right-sided ($n = 57$) shunting. No statistically significant differences in lateral ventricle volume were observed between these groups (left-sided shunt $t_{[68]} = 1.28$, right-sided shunt $t_{[68]} = 0.26$, both $p > 0.05$).

Post Hoc Analysis of Colpocephaly and DTI Metrics

In total, 31 patients showed signs of colpocephaly. Colpocephaly did not affect the tractography results: cases of colpocephaly did not differ from those without this condition in the number of voxels in both frontal ($t_{[78]} = -0.06$, $p = 0.96$) and parietal ($t_{[78]} = -0.41$, $p = 0.67$) tectocortical pathways. Colpocephaly was associated with higher parietal FA ($t_{[51.2]} = -3.54$, $p = 0.001$), lower parietal RD ($t_{[78]} = 4.30$, $p < 0.001$), and lower parietal AD ($t_{[78]} = 2.10$, $p = 0.039$). Moreover, colpocephaly was highly correlated with total lateral ventricular volume, such that individuals having colpocephaly had significantly larger left ($t_{[33.3]} = 4.46$, $p < 0.001$), right ($t_{[36.0]} = -3.38$, $p < 0.001$), and total ($t_{[34.0]} = -4.15$, $p < 0.001$) ventricular volume. Given this relationship of colpocephaly with increased lateral ventricular volume, after controlling for lateral ventricular volume, colpocephaly did not account for any additional variance in DTI metrics.

TABLE 4. Multiple linear regression analyses predicting DTI metrics according to lateral ventricular volume and age

	Overall Model Fit		β Value	
	Adjusted R ²	F	Lateral Ventricle Vol	Age
FA				
LH frontal	0.293	17.40*	0.560*	-0.008
RH frontal	0.275	15.98*	0.510*	0.097
LH parietal	0.261	14.95*	0.502*	0.082
RH parietal	0.421	29.74*	0.638*	0.074
RD				
LH frontal	0.226	12.53*	-0.485*	-0.035
RH frontal	0.254	14.44*	-0.405*	-0.246
LH parietal	0.161	8.55*	-0.372†	-0.134
RH parietal	0.296	17.60*	-0.470*	-0.212
AD				
LH frontal	-0.013	0.48	0.064	-0.109
RH frontal	0.076	4.23	0.245	-0.266
LH parietal	0.000	0.99	-0.089	-0.110
RH parietal	0.052	3.15	0.109	-0.280

LH = left hemisphere; RH = right hemisphere.

* The F value was statistically significant at $p < 0.001$.

† The F value was statistically significant at $p < 0.01$.

Hypothesis 2: Predicting IQ Scores with DTI Metrics and Total Lateral Ventricular Volume

Table 5 shows the overall fit of the model of the relationships of IQ scores with DTI metrics and lateral ventricle volume and the calculated β weights for these 2 variables, along with those for age and socioeconomic status. The DTI metrics along the parietal pathways predicted IQ scores more reliably than the DTI metrics along the frontal pathways. Mean RD was the most significant predictor of IQ scores. In contrast, both lateral ventricular volume and age were not significant predictors of IQ in any of the models.

Hypothesis 3: Effects of Shunt Revisions

DTI Metrics and Shunt Revisions

Figure 1 shows the 3 DTI metrics along the frontal and parietal pathways in the individuals who had SBH and who underwent shunting ($n = 75$), grouped by number of shunt revisions (none, 1, 2–4, and ≥ 5 revisions).

Fractional Anisotropy

Both the number of shunt revisions and age accounted for 9.8% of the variation in FA along the frontal tectocortical pathways (adjusted $R^2 = 0.098$; $F_{[4,70]} = 3.01$, $p = 0.02$). Whereas shunt revision had a statistically significant effect on FA along the frontal pathways ($F_{[3,70]} = 4.00$, $p = 0.01$), age did not ($F_{[1,70]} = 0.44$, $p = 0.51$). Post hoc pairwise comparisons indicated that for cases of 2–4 shunt revisions, FA (adjusted for age) along the frontal pathways was significantly lower than for cases of no ($t_{[44]} = -2.57$, $p = 0.01$) or 5 or more ($t_{[42]} = -2.57$, $p = 0.01$) shunt revisions.

For the parietal pathways, number of shunt revisions

TABLE 5. Multiple linear regression analysis predicting IQ scores according to mean DTI metrics, total lateral ventricular volume, age, and socioeconomic status in individuals with SBH

Metric	Predictor Variable				Overall Model Predicting IQ Scores		
	DTI Metric β	Lat Ventricle Vol β	Age β	SES β	Adjusted R ²	F	p Value
FA							
Frontal	0.153	0.092	0.081	0.215	0.089	2.90	0.027
Parietal	0.294*	0.001	0.065	0.207	0.126	3.81	0.007
RD							
Frontal	-0.315*	0.013	0.045	0.222*	0.143	4.25	0.004
Parietal	-0.414†	-0.012	0.009	0.215*	0.200	5.87	<0.001
AD							
Frontal	-0.180	0.196	0.049	0.251*	0.106	3.30	0.015
Parietal	-0.256*	0.175	0.033	0.243*	0.139	4.15	0.004

SES = socioeconomic status.

* The β value was statistically significant at $p < 0.01$.† The β value was statistically significant at $p < 0.001$.

and age accounted both for 11.0% of the variation in FA (adjusted $R^2 = 0.110$; $F_{[4,70]} = 3.28$, $p = 0.02$). A statistically significant effect of number of shunt revisions ($F_{[3,70]} = 3.90$, $p = 0.01$), but not of age ($F_{[1,70]} = 2.71$, $p = 0.10$), was detected on FA along the parietal pathways. Post hoc pairwise comparisons indicated that for cases of 2–4 shunt revisions, FA (adjusted for age) was significantly lower along the parietal pathways than for cases of no ($t_{[44]} = -2.90$, $p < 0.01$) or 1 ($t_{[57]} = -2.74$, $p = 0.02$) shunt revision.

Radial Diffusivity

Number of shunt revisions and age both accounted for 8.6% of the variation in RD along the frontal tectocortical pathways (adjusted $R^2 = 0.086$; $F_{[4,70]} = 2.75$, $p = 0.035$). There was also a significant effect of the number of shunt revisions ($F_{[3,70]} = 2.95$, $p = 0.039$) but not of age ($F_{[1,70]} = 2.96$, $p = 0.09$) on RD along the parietal pathways. Post hoc pairwise comparisons indicated that the RD (adjusted for age) along the frontal pathways in cases of 2–4 shunt revisions was significantly higher than for cases of no shunt revisions ($t_{[44]} = 2.45$, $p = 0.016$).

The overall model predicting RD along parietal pathways according to number of shunt revisions and age did not reach statistical significance ($F_{[4,70]} = 2.16$, $p = 0.08$).

Axial Diffusivity

The shunt revision groups did not significantly differ in mean AD along the frontal ($F_{[4,70]} = 1.34$, $p = 0.27$) or the parietal ($F_{[4,70]} = 0.98$, $p = 0.43$) pathways.

IQ and Shunt Revisions.

No statistically significant differences in IQ scores were detected among the groups of patients who had no, 1, 2–4, or ≥ 5 shunt revisions ($F < 1$).

A post hoc analysis indicated that participants who had a history of shunt infection did not significantly differ from those with no infection in any of the MRI-derived variables (FA, RD, AD, and lateral ventricular volume). Assessing the effect of shunt infection on IQ scores, we found a trend toward statistical significance ($t_{[63]} = -1.87$, $p = 0.07$), suggesting that those who had shunt infections

tended to have lower IQ scores than those without this complication.

Ventricular Volume and Shunt Revisions

Figure 2 shows the variations in total lateral ventricular volume in the study participants, grouped by number of shunt revisions. Shunt revisions, age, and brain volume accounted for 12.7% of the variance in ventricular volume (adjusted $R^2 = 0.127$; $F_{[5,69]} = 3.16$, $p = 0.01$), with a statistically significant effect of shunt revision group ($F_{[3,69]} = 4.38$, $p < 0.01$) and age ($F_{[1,69]} = 4.56$, $p = 0.04$). Total brain volume was not a significant covariate ($F_{[1,69]} = 1.85$, $p = 0.18$).

Post hoc comparisons adjusted for multiple comparisons with the Bonferroni method indicated that individuals who had not undergone a shunt revision had a significantly larger lateral ventricular volume (mean adjusted for age 48,693 mm³, SEM 8826 mm³) than those who had undergone 2–4 (mean adjusted for age 21,206 mm³, SEM 4332 mm³; $t_{[44]} = 2.79$, $p < 0.01$) or ≥ 5 shunt revisions (mean adjusted for age 17,655 mm³, SEM 10,175 mm³; $t_{[14]} = 2.30$, $p = 0.02$) by the time of the scan. Individuals who underwent 1 shunt revision (mean volume adjusted for age 40,555 mm³, SEM 5700 mm³) also had greater lateral ventricular volume than those who underwent 2–4 revisions ($t_{[57]} = 2.69$; $p < 0.01$).

Discussion

In a previous study in which we compared DTI metrics in individuals who had SBH with those in normally developing individuals, we noted that SBH was associated with impaired WM integrity, indicated by decreased FA along the parietal pathways. We also observed that the 2 groups did not differ in FA along the frontal pathways.³⁹ Although our previous study did not assess the relationship between DTI metrics and ventricular volume, we hypothesized that the decrease in WM integrity was due to mechanical stretching forces during ventricular expansion in hydrocephalus. These forces spared the anterior regions but strongly affected posterior pathways. Therefore, we hypothesized that SBH results in an inverse relationship

FIG. 1. Bar graphs depicting mean DTI metrics for cases of SBH grouped by the number of shunt revisions. RD and AD metrics were multiplied by a factor of 1000. The error bars represent the 95% CI of group means.

between DTI metrics and ventricular volume (such that enlarged ventricles would predict lower WM integrity) along parietal pathways, with relatively intact frontal WM. However, we observed that SBH was associated with enlarged lateral ventricular volume and with increased FA and decreased RD along both anterior and posterior projection tracts. The lack of an anticipated anterior-posterior gradation of DTI metrics suggested global physical changes in individuals who have shunt-treated hydrocephalus. One possible explanation for this observation is that the increase in ICP is attenuated in shunt-treated hydrocephalus.

Higher FA values are generally interpreted as reflecting greater WM integrity and organization. Abnormal elevations in FA related to large ventricle volume may be damaging in the context of an existing neuropathology. In the case of enlarged ventricles, an increased FA may be due to axonal compression—a common sequelae of increased ICP in acute hydrocephalus. Although most cases in this study had undergone shunting and showed no clinical signs or symptoms of shunt malfunction or overt indicators of acute hydrocephalus, the association of large ventricles with abnormal elevations in FA suggests subclinical shunt inefficiency. Thus, our results seem more consistent with those from previous reports of individuals with SBH and a Chiari Type II malformation, who showed enlarged ventricles and a higher FA within periventricular and projection pathways than those with a normal ventricle size.³⁰ Similar patterns of changes in DTI metrics have been observed after closed head injuries accompanied by brain swelling.¹²

Fractional anisotropy is the most commonly reported DTI-derived metric in the literature. It is quantified as a scaled difference between isotropic and linear diffusion within a voxel, and reflects neuronal properties such as axon diameter, fiber density, and degree of myelination.⁵ The FA values are highly sensitive to the microstructural integrity of WM, but additional measurements of RD and AD enhance the specificity of detecting microstructural alterations and show an inverse relationship with FA.² Radial diffusivity is calculated as the average of the 2 secondary diffusion axes and is thought to approximate flow

restriction posed by membranes and myelin.^{10,33,34} Ventricular expansion resulting in an elevated ICP alters homogeneously aligned WM by increasing fiber density through mechanical axonal compression. The higher axonal density restricts diffusion of water molecules perpendicular to the fiber tract, resulting in lower RD values.⁴

Human imaging and autopsy studies have identified disruptions in myelination processes due to hydrocephalus, which result in attenuated ICP increases.^{20,21} However, hydrocephalus has also been observed to persistently alter myelin integrity through a loss of oligodendrocytes.²⁸ In animal models of hydrocephalus, partial restoration of impaired axonal connectivity to cortical regions is observed after shunt intervention.^{3,15} In a longitudinal study of children with hydrocephalus, preshunt increases in FA were observed within the internal capsule, and these changes also normalized after shunting.¹ Thus, the observed patterns in DTI metrics in the present study may stem from WM alterations similar to those found in individuals with

FIG. 2. Bar graph showing the mean total lateral ventricular volume in cases of SBH, grouped by the number of shunt revisions. The error bars represent the 95% CI of group means.

acutely enlarged ventricles due to untreated hydrocephalus.

The rate of ventricular expansion leading to overt signs of shunt malfunction is not well described in the literature but is relevant to WM disruptions observed in hydrocephalus. Elevated FA due to shunt inefficiency and a gradual expansion of ventricular volume may reflect transient alterations to WM integrity caused by axonal compression. This process is distinct from the lasting mechanical stretching forces imposed on tissue through rapid ventricular dilation often applied in animal models of hydrocephalus. Associations of DTI metrics with ventricular volume suggest subclinical gradual ventricular expansion due to shunt inefficiency before the appearance of overt behavioral symptoms and complete shunt failure in hydrocephalus. Thus, abnormal deviations in the indicators of WM integrity (that is, increased FA and decreased RD) that are significantly related to lateral ventricular volume suggest the potential for DTI metrics as clinical indicators of risk for acute hydrocephalus.

Subclinical shunt malfunction is not often encountered in a well-monitored SBH population, but the demographic characteristics of the present cohort somewhat differed from those of cohorts in previous reports. More than 50% of our participants were of Hispanic origin and from a lower socioeconomic status, representing individuals in whom medical history and care before study enrollment is variable. These participants often had limited access to routine health care, especially if they were recent immigrants. The inclusion of a large number of patients with limited prestudy clinical monitoring makes it more likely that subacute shunt malfunction and poorly managed hydrocephalus are encountered. Although the present DTI findings were most consistent with patterns identified in previous studies assessing acute hydrocephalus, ICP measurements were not available at the time of the MRI scan to verify whether an enlarged ventricular volume was associated with an increased ICP. Thus, the use of ventricular volume and DTI metrics as proxies for attenuated hydrocephalus clinically confirmed by increased ICP warrants further investigation. Nonetheless, atypical DTI metrics coinciding with enlarged ventricles may provide a useful noninvasive indicator for clinical monitoring and consideration of shunt placement or revision in SBH.

Consistent with the second hypothesis, IQ scores were predicted by the DTI metrics. However, they displayed no association with ventricular volume, despite the association between enlarged lateral ventricular volume and increased FA. The DTI metrics of the parietal pathways showed a stronger association with IQ scores than the frontal pathways. In addition, individuals with a history of shunt infection tended to have lower IQ scores than those who underwent shunting with no complications. This observation is consistent with previous studies reporting poorer cognitive performance in individuals with a history of shunt infection in SBH.¹¹ Conversely, a larger lateral ventricle size was not predictive of IQ scores. This finding supports the idea that IQ is a stable trait resistant to the transient variations of ventricular size in shunted hydrocephalus.

Ventricle instability (crudely indexed by the number of lifetime shunt revisions) did not affect IQ scores. This

finding was consistent with previous studies reporting no decreases in IQ scores with an increase in the number of shunt revisions in children with hydrocephalus.³¹ Contrary to the third hypothesis, the occurrence of multiple shunt revisions was associated with decreased FA and smaller ventricular volume (with the exception of those who had undergone ≥ 5 shunt revisions who displayed higher FA along frontal pathways than participants who had undergone 2–4 revisions).

Taken together, these findings suggest that those who had undergone a greater number of shunt revisions for SBH had a more typical lateral ventricular size and WM integrity than those undergoing fewer revisions. Given the variability of prestudy clinical monitoring in our sample, it is unclear whether participants who had undergone a greater number of shunt revisions had been more closely monitored. Finally, whether this pattern of ventricular volume and shunt revision is related to functional outcomes, such as IQ scores, remains unclear.

In clinical settings, health care professionals make variable decisions on whether to implement shunting procedures to treat hydrocephalus.¹⁴ These decisions are typically guided by weighing the risk for future damage due to ventricular enlargement against that of tissue damage, potential failure, or of infection associated with shunt insertion. Although a more conservative approach to shunt placement generally leads to more favorable outcomes, cases of asymptomatic ventricular enlargement often pose additional challenges in determining appropriate treatment.

The association of large ventricular volume and DTI metrics (that is, elevated FA and reduced RD) may support DTI metrics as useful noninvasive clinical indicators in hydrocephalus. Future longitudinal studies should further evaluate their potential as a subclinical indicator of shunt inefficiency.

Limitations

Although DTI metrics were associated with ventricular volume and IQ scores, the causal mechanisms responsible remain unclear. The specific challenges in interpreting DTI metrics have been extensively reviewed, including the limitations of partial voluming and the treatment of crossing fibers in tractography.³⁸ The procedures in this study used algorithms designed to minimize such issues, and additional postprocessing steps were also undertaken. Normalization of tracts to account for differences in seed volume and in tractability between participants was performed, along with thresholding to minimize the inclusion of periventricular voxels that may have originated from CSF.

Furthermore, although the relationship of increased FA and larger ventricular volume resembled patterns previously observed in acute hydrocephalus, the lack of quantifiable ICP data at the time of the MRI scan limits the conclusions of the present study. Future studies should incorporate longitudinal monitoring of ventricular volume and DTI metrics, which may provide further insight into additional issues related to hydrocephalus, including ventricular compliance and rate of ventricular expansion.

Finally, the IQ metric used was a composite of both

verbal and nonverbal skills because the verbal and performance subdomains were highly correlated, and a greater number of tests increased the reliability of the IQ measure. Increased lateral ventricular volume in children who have SBH and aqueductal stenosis has previously been associated with worse performance on cognitive tasks. In these cases, nonverbal measures correlated with right, and verbal measures correlated with left lateral ventricular size measured from single slices.¹⁸ This pattern was not apparent in this study.

Conclusions

The present study provides new insight into the complex relationships among variables critical for clinical management of individuals who have SBH. We observed significant changes in DTI metrics related to ventricular volume, which may be sensitive to chronic, mild hydrocephalus without overt clinical symptoms of an elevated ICP. Specifically, increased ventricle volume was associated with increased FA and decreased RD, a pattern suggestive of attenuating subclinical ventricular dilation. Although increased FA is typically interpreted as indicating intact neuronal microstructure, DTI metrics deviations, regardless of their direction, may indicate attenuated insult, which was also reported for the relationship of cortical thickness and IQ scores in SBH.³⁷ Therefore, DTI may be a useful tool in clinically managing and monitoring treated hydrocephalus.

Shunt failure is most commonly detected as an onset of adverse symptoms, so the ability to detect children at risk (or in the subclinical stages of shunt failure or inefficiency) may improve patient care. Future longitudinal studies could monitor medically stable children with a shunted hydrocephalus to assess the relationships among DTI metrics, ventricular volume, and shunt performance before the emergence of any overt clinical symptoms of shunt malfunction. Finally, our finding that enlarged ventricles and multiple shunt revisions for SBH did not appear to affect cognitive ability is an intriguing result that warrants additional investigation.

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