Diffusion tensor imaging study of pediatric patients with congenital hydrocephalus: 1-year postsurgical outcomes

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OBJECTIVE The purpose of this study was to investigate white matter (WM) structural abnormalities using diffusion tensor imaging (DTI) in children with hydrocephalus before CSF diversionary surgery (including ventriculoperitoneal shunt insertion and endoscopic third ventriculostomy) and during the course of recovery after surgery in association with neuropsychological and behavioral outcome.

METHODS This prospective study included 54 pediatric patients with congenital hydrocephalus (21 female, 33 male; age range 0.03–194.5 months) who underwent surgery and 64 normal controls (30 female, 34 male; age range 0.30–197.75 months). DTI and neurodevelopmental outcome data were collected once in the control group and 3 times (preoperatively and at 3 and 12 months postoperatively) in the patients with hydrocephalus. DTI measures, including fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) values were extracted from the genu of the corpus callosum (gCC) and the posterior limb of internal capsule (PLIC). Group analysis was performed first cross-sectionally to quantify DTI abnormalities at 3 time points by comparing the data obtained in the hydrocephalus group for each of the 3 time points to data obtained in the controls. Longitudinal comparisons were conducted pairwise between different time points in patients whose data were acquired at multiple time points. Neurodevelopmental data were collected and analyzed using the Adaptive Behavior Assessment System, Second Edition, and the Bayley Scales of Infant Development, Third Edition. Correlation analyses were performed between DTI and behavioral measures.

RESULTS Significant DTI abnormalities were found in the hydrocephalus patients in both the gCC (lower FA and higher MD, AD, and RD) and the PLIC (higher FA, lower AD and RD) before surgery. The DTI measures in the gCC remained mostly abnormal at 3 and 12 months after surgery. The DTI abnormalities in the PLIC were significant in FA and AD at 3 months after surgery but did not persist when tested at 12 months after surgery. Significant longitudinal DTI changes in the patients with hydrocephalus were found in the gCC when findings at 3 and 12 months after surgery were compared. In the PLIC, trend-level longitudinal changes were observed between preoperative findings and 3-month postoperative findings, as well as between 3- and 12-month postoperative findings. Significant correlation between DTI and developmental outcome was found at all 3 time points. Notably, a significant correlation was found between DTI in the PLIC at 3 months after surgery and developmental outcome at 12 months after surgery.

CONCLUSIONS The data showed significant WM abnormality based on DTI in both the gCC and the PLIC in patients with congenital hydrocephalus before surgery, and the abnormalities persisted in both the gCC and the PLIC at 3 months after surgery. The DTI values remained significantly abnormal in the gCC at 12 months after surgery. Longitudinal analy-

ABBREVIATIONS ABAS-II = Adaptive Behavior Assessment System, Second Edition; AD = axial diffusivity; Bayley III = Bayley Scale of Infant Development, Third Edition; CCHMC = Cincinnati Children's Hospital Medical Center; DTI = diffusion tensor imaging; FA = fractional anisotropy; FDR = false discovery rate; FOHR = frontal and occipital horn ratio; GAC = general adaptive composite; gCC = genu of corpus callosum; ICP = intracranial pressure; MD = mean diffusivity; PLIC = posterior limb of internal capsule; RD = radial diffusivity; ROI = region of interest; SLCH/WashU = St. Louis Children's Hospital and Washington University; WM = white matter.

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sis showed signs of recovery in both WM structures between different time points. Combined with the significant correlation found between DTI and neuropsychological measures, the findings of this study suggest that DTI can serve as a sensitive imaging biomarker for underlying neuroanatomical changes and postsurgical developmental outcome and even as a predictor for future outcomes.

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KEY WORDS hydrocephalus; DTI; white matter injury; postsurgery; outcome

FOR pediatric patients with hydrocephalus, CSF diversionary surgery (including ventriculoperitoneal shunt insertion and endoscopic third ventriculostomy) is the standard of care that can relieve clinical signs and symptoms of enlarged ventricles and increased intracranial pressure (ICP). Surgery has significantly reduced morbidity and mortality associated with hydrocephalus;²⁵ however, despite advances in technology, the condition remains an incurable lifelong disorder. The rapid postoperative reversal of acute clinical symptoms does not correspond to a complete reversal of structural damage in the brain. Accumulating evidence has shown that there is no significant correlation between ventricle volume and neurocognitive outcome.^{11,30} The neuroanatomical changes that occurred prior to surgery may remain or continue to progress, leading to long-term behavioral and neuropsychological deficits.³² Data from both human and animal research have suggested that extensive areas of white matter (WM) fibers connecting various functionally important cortical and subcortical regions are vulnerable targets of injury as a result of ventricular enlargement and increased ICP in hydrocephalus.^{13,14,17,20,29,33,35}

Diffusion tensor imaging (DTI) is an advanced MRI technique that uses diffusion properties of water molecules as probes to examine tissue structure, revealing characteristics of its microscopic organization. Anisotropic diffusion properties, as measured by DTI, are strongly influenced by the microstructural components of WM⁹ and provide a direct indication of the integrity of these components. Recent neuroimaging studies have shown that DTI can provide imaging biomarkers for hydrocephalus outcome.⁴³ Cross-sectional studies have shown that DTI parameters can differentiate brain structures in patients with hydrocephalus from those of controls without hydrocephalus in both human and animal studies.^{15,22,26,30,34,38,40–42,44} Initial longitudinal studies have shown variable degrees of tendency for DTI parameters to return to a normal range after surgery.^{2,6,27,36} However, there is also strong evidence from both clinical and experimental studies suggesting that the damage to brain structures suffered before CSF diversion may be irreversible.^{5,12,13,16,19,29,31,32}

Here we report the results of a prospective, longitudinal neuroimaging study combined with neuropsychological outcome assessment in pediatric patients with hydrocephalus. Data were acquired prior to CSF diversionary surgery and again at 3 and 12 months after surgery. The overall goal of this study was to establish the WM anisotropic diffusion property derived from DTI as a marker for in vivo WM damage and its course of recovery in children with hydrocephalus. These data allow us to have a better understanding of the variability in outcomes and provide a noninvasive and quantifiable means to predict

these outcomes. The following hypotheses were tested and confirmed. 1) Pediatric patients with congenital hydrocephalus have abnormal anisotropic diffusion properties in WM prior to surgery. 2) The abnormal diffusion property in WM will recover with trends toward the normal range after surgery. 3) The WM anisotropic diffusion properties correlate significantly with outcome measures.

The findings of this study provide a necessary step toward establishing DTI as a significant clinical tool in the management of patients with hydrocephalus.

Methods

Study Design and Participants

All participants were enrolled in a federally funded, multicenter, prospective, longitudinal imaging study of pediatric hydrocephalus aimed at investigating neuroimaging and neurobehavioral outcomes at baseline prior to surgical management and at 3- and 12-month postoperative follow-up assessments. Between December 2009 and June 2014, a total of 146 infants, children, and adolescents, including 74 patients who were potential candidates for surgical treatment of hydrocephalus (age range 0.03–194.49 months) and 72 infants, children, and adolescents without hydrocephalus who served as controls (age range 0.56–197.75 months), were recruited from the 2 participating hospitals, Cincinnati Children's Hospital Medical Center (CCHMC) and St. Louis Children's Hospital and Washington University (SLCH/WashU). Participants' legal guardians gave written consent when the children were enrolled into the study. Participants older than 11 years also provided oral assent. The study was conducted according to institutional review board guidelines at both institutions.

For patients in the hydrocephalus group, the inclusion criteria were as follows: age 0–18 years; referral to radiology for brain MRI for evaluation of hydrocephalus and later referral for CSF diversion surgery; hydrocephalus with ventriculomegaly; and no evidence of other medical diagnoses that would predispose him/her to adverse neurological outcomes (e.g., preterm birth with severe intraventricular hemorrhage, Dandy-Walker syndrome, stroke, or spina bifida). Of the 74 patients with hydrocephalus, 20 were excluded from the study. Of these 20 patients, 11 were excluded because they did not receive surgical treatment for hydrocephalus, and 7 were excluded because they did not meet inclusion criteria. One family withdrew consent for their child's participation in the study. One additional child was excluded after being diagnosed with neurofibromatosis Type 1. This resulted in a study population of 54 patients (21 female, 33 male; age range 0.03–194.49 months) with congenital hydrocephalus for the final data analysis. Detailed demographic information and etiology are included in Supplemental Table S1.

The participants in the control group were recruited to match the patients in the hydrocephalus group in age and sex as closely as possible. They came from 2 sources: 1) pediatric patients who were referred for clinical MRI that was evaluated as normal by clinical neuroradiologists (the inclusion criteria for participants in the control group from this source were age 0–18 years; referral to radiology for nonspecific symptoms not clearly related to a neurological disorder [e.g., headaches]; normal findings on MRI; no clinical or radiographic history of neurological or psychological disorders prior to the scan; no evidence of any neurological disorders [e.g., epilepsy, stroke]; or no suggestion of WM-related brain pathology within 3 months after the initial MRI, based on review of the patient's medical record) and 2) healthy individuals recruited from the general healthy population (the inclusion criteria for controls from this latter source were similar to those for the previously described subgroup). The MR images from these healthy controls were acquired under the research protocol on the same MRI scanners without sedation. Of the 72 control participants initially enrolled, 1 child was excluded after the diagnosis of epilepsy. Four children were excluded because of abnormal MRI findings. Two children were disqualified for having standard scores below 70 on either the Adaptive Behavior Assessment System, Second Edition (ABAS-II),²¹ or the Bayley Scales of Infant Development, Third Edition (Bayley-III).⁸ One additional child was excluded for poor image quality. This left a control population of 64 children (30 female, 34 male; age range 0.30–197.75 month) for further analysis.

Neuroimaging (MRI/DTI) and neuropsychological data were acquired in children with hydrocephalus at 3 time points: prior to the CSF diversionary surgery, 3 months after surgery, and 12 months after surgery. Neuroimaging data and neuropsychological data were acquired only once in children in the control group. Data were not acquired for some of the participants at some of the time points, most often due to the short window between diagnosis and surgery. In addition, depending on the severity of hydrocephalus, the ventricle enlargement was too severe in some patients to allow for reliable delineation of region of interest. The total numbers of participants for whom useful neuroimaging and neuropsychological outcome data were obtained are listed in Table 1.

MRI Acquisition and Preprocessing

MRI data were all acquired on 1.5-T scanners at either CCHMC (GE Signa, GE Healthcare) or SLCH/WashU (Siemens Avanto). A 15-direction diffusion-weighted spin-echo DTI sequence with single-shot echo planar imaging was used with the following specifications: FOV 240 × 240 mm, matrix 96 × 96, resolution 2.5 × 2.5 × 2.5 mm, number of slices 76, TR/TE 9400/93.2 msec, ASSET or IPAT factor 2, number of averages 2, b = 1000 sec/mm². One additional image with no diffusion weighting (b = 0) was also acquired. The MR compatibility across the 2 sites (two 1.5-T GE Signa scanners from CCHMC and one 1.5-T Siemens Avanto from SLCH) was established using both an MR phantom (fBIRN phantom) and a traveling human phantom prior to the start of the participant enrollment. The compatibility was tested annually with the

TABLE 1. Number of data sets generated for different ROIs and outcome measures at different time points

Outcome Measure	Controls	Patients w/ HCP		
		Preop	3 Mos Postop	12 Mos Postop
Neuroimaging: MRI/DTI				
gCC	64	22	28	29
Left PLIC	64	22	29	30
Neuropsych: ABAS-II				
GAC	53	26	43	28
Conceptual	53	26	43	28
Social	54	27	44	28
Practical	54	27	41	28
Motor Scale	48	23	40	23
Neuropsych: Bayley-III				
Social	33	7	27	17
Cognitive	40	6	34	19
Language	40	5	34	19
Motor	39	4	34	19

HCP = hydrocephalus.

same MR phantom and human phantom on all scanners used in the study. In addition, ACR (American College of Radiology) phantoms were also used for quality assurance within a week of each participant's scan to ensure the stability of scanner performance (Yuan et al., unpublished presentation, 2011).^{34,44}

Image processing and analysis were all performed using the DTIStudio 3.02 software.²⁸ Head motion and eddy current artifact were corrected using the automatic image registration method³⁹ embedded in the DTIStudio software.²⁸ An automatic bad slice detection method followed by additional visual inspection was used to identify signal dropout on diffusion-weighted images. DTI metrics including FA, MD, AD, and RD were calculated using the standard technique.⁷ Two regions of interest (ROIs) were examined in this study: the genu of the corpus callosum (gCC) and the posterior limb of the internal capsule (PLIC). The 2 ROIs were delineated based on the approach of Hermoye et al.,²³ as well as our previous work.^{2,40,44} It should be noted that, because shunt artifact was seen in postsurgery DTI images from many patients who were treated with adjustable valves (almost always on the right side), a bilateral DTI measurement in the PLIC was not always feasible at all 3 time points. Therefore, DTI data from the PLIC were extracted only from the left hemisphere in the present study.

Ventricle Size Assessment

Ventricle size was quantified using the frontal and occipital horn ratio (FOHR)⁴⁵ in the controls and in the participants with hydrocephalus at all 3 time points.

Neuropsychological Outcome Measures

The ABAS-II²¹ and the Bayley-III⁸ were included in the present study. Both tests were completed by pediatric neu-

ropsychologists or by psychometrists supervised by pediatric neuropsychologists at either the Division of Developmental and Behavioral Pediatrics at CCHMC or the Department of Psychology at SLCH/WashU. The ABAS-II is a caregiver report form for adaptive skills comprising an overall adaptive score, the General Adaptive Composite (GAC), and 3 subscales assessing Conceptual, Social, and Practical skills. It also includes a subtest assessing motor skills. The Bayley-III is a direct assessment tool that measures early developmental skills; it assesses Cognitive, Language, and Motor skills for patients between 0.5 and 42 months of age. The Bayley-III also includes a caregiver report measure of early social-emotional behavior.

Statistical Analysis

Developmental changes in WM and DTI measures could significantly confound the results of the present study. Therefore, all the statistical analyses of DTI measures were corrected for age. We performed a regression analysis at each ROI for every DTI measure to remove the potential confounding effect of age. The residual values of the regression, defined as the difference between the actual DTI value from the individual participant and the simulated normal DTI value at the corresponding age based on the regression, were then used to substitute for the raw DTI values in the subsequent analysis. The group differences of DTI between patients and controls were first tested cross-sectionally for data obtained before surgery, 3 months after surgery, and 12 months after surgery separately using an independent 2-tailed unpaired t-test. The false discovery rate (FDR) method was applied at each time point to correct for potential false-positive findings resulting from multiple comparisons of DTI measures and ROIs. Longitudinal comparisons of DTI abnormalities were tested for each pair of the 3 time points using a paired t-test in children with hydrocephalus who had longitudinal data at the corresponding time points. Pearson correlation analysis was performed to test the association between DTI measures and neuropsychological measures assessed at the same time and between DTI measures assessed at 3 months after surgery and neuropsychological measures assessed at 12 months after surgery. Due to the limitation in sample size in the longitudinal comparisons and correlation analyses, statistical significance was reported without correction for multiple comparisons in these analyses.

Results

Ventricle Size and Correlation With DTI and Neuropsychological Measures

The FOHR values in the control group ranged from 0.197 to 0.375 (mean $\pm$ SD] 0.310 ± 0.036). Compared with the controls, patients with hydrocephalus had significantly larger ventricles, as expressed by FOHR values, before surgery (range 0.331–0.777, mean 0.555 ± 0.102 , $p < 0.0001$) and at both 3 (range 0.339–0.687, mean 0.483 ± 0.090 , $p < 0.0001$) and 12 months after surgery (range 0.265–0.579, mean 0.400 ± 0.089 , $p < 0.0001$). No significant correlation was found between FOHR and DTI measures or FOHR and neuropsychological measures in any group or at any time point.

DTI Abnormalities in Children With Hydrocephalus

The ROI-based DTI measures in patients with hydrocephalus at the preoperative and 3- and 12-month postoperative time points are displayed in Fig. 1 (for gCC) and Fig. 2 (for PLIC). As expected, there was a developmental change in the DTI values with age in both ROIs in the control group. The regression coefficients based on exponential model fit are included in Table 2.

Quantitatively, at both the preoperative time point and the 3-month postoperative time point, DTI parameters in the gCC in patients with hydrocephalus were found to be significantly different from those of controls, characterized by lower FA ($p = 0.0008$ for both time points), higher MD ($p = 0.0004$ for both time points), higher AD ($p = 0.0095$ for the preoperative time point, $p = 0.0003$ for 3-month postoperative time point), and higher RD ($p = 0.0003$ for the preoperative time point, $p = 0.0002$ for 3-month postoperative time point). Analysis of DTI parameters in the left PLIC showed that, in comparison with controls, the patients with hydrocephalus had significantly higher FA ($p = 0.0002$ for the preoperative time point, $p = 0.0005$ for the 3-month postoperative time point), higher AD ($p = 0.0002$ for the preoperative time point, $p = 0.0003$ for the 3-month postoperative time point), and lower RD at the preoperative time point ($p = 0.0353$). With respect to the 12-month postoperative time point, the analysis of DTI parameters in the gCC showed significantly lower FA ($p = 0.0008$), higher MD ($p = 0.0004$), and higher RD ($p = 0.0003$) in patients with hydrocephalus than in controls. No significance in AD was found between patients with hydrocephalus and the controls at 12 months after surgery. In the left PLIC, no significant between-group difference was found in any of the 4 DTI measures for the 12-month postoperative time point (Figs. 3 and 4; Table 3).

Longitudinal Difference in DTI Abnormalities

To perform longitudinal comparisons, we first quantified the DTI abnormalities as the difference between the actual DTI values in children with hydrocephalus and the normal DTI value at the corresponding age based on the regression of DTI data using the control data sets. Longitudinal DTI comparisons between different time points were made for those children with hydrocephalus who had multiple MRI/DTI data sets. As shown in Table 4, no significant longitudinal change in DTI abnormality (difference between patient DTI and simulated normal DTI at the same age) was found between the preoperative and 3-month postoperative data for any of the 4 DTI parameters in the gCC ($n = 10$). Comparison of 3- and 12-month postoperative findings showed statistically significant decreases in DTI abnormalities with respect to FA ($p = 0.0417$), MD ($p = 0.0049$), and RD ($p = 0.0025$) in the gCC ($n = 19$). It should be noted that a decrease of DTI abnormalities means that the DTI values from patients with hydrocephalus become closer to the normal simulated value as shown in Fig. 5. Comparison of the preoperative and the 12-month postoperative assessment findings showed similar changes in the gCC ($n = 11$), with statistical significance in MD ($p = 0.0095$) and RD ($p = 0.0002$) and a trend toward significance in FA ($p = 0.078$). In the left

FIG. 1. Scatter plots showing the group differences in FA (A), MD (B), AD (C), and RD (D) in the gCC. Each symbol represents the DTI value extracted from the gCC from a single participant. The solid black circles, blue triangles, green triangles, and red triangles correspond to data obtained from participants in the control group, data obtained from patients before surgery, data obtained from patients 3 months after surgery, and data obtained from patients 12 months after surgery, respectively. The solid black line and the 2 dashed lines represent the results of regression analysis (the fitted curve and the two 95% prediction intervals) based on the data from the control group. m = months.

FIG. 2. Scatter plots showing the group difference of FA (A), MD (B), AD (C), and RD (D) in the left PLIC. Each symbol represents the DTI value extracted from the left PLIC from a single participant. The solid black circles, blue triangles, green triangles, and red triangles correspond to data obtained from participants in the control group, data obtained from patients before surgery, data obtained from patients 3 months after surgery, and data obtained from patients 12 months after surgery, respectively. The solid black line and the two dashed lines represent the results of regression analysis (the fitted curve and the two 95% prediction intervals) based on the data from the control group.

TABLE 2. Results of regression analysis between normal DTI measures and age using an exponential model*

Parameter	Regression Coefficients				R ² †
	a	b	c	y-Intercept	
gCC					
FA	−0.3266	0.0588	0.7677	0.4411	0.9029
MD	0.5544	0.0937	0.7820	1.3364	0.9246
AD	0.4065	0.1215	1.6482	2.0545	0.6828
RD	0.6315	0.0829	0.3506	0.9821	0.9307
Left PLIC					
FA	−0.2236	0.0748	0.5989	0.3753	0.8804
MD	0.3335	0.1816	0.7522	1.0875	0.9088
AD	0.2428	0.3218	1.3191	1.5618	0.6528
RD	0.3801	0.1414	0.4592	0.8391	0.9174

* The regression model ($Y = a \cdot \exp[-b \cdot X + c]$) fit the data in all ROIs with a significance level of $p < 0.001$.

† Exponential model fit.

PLIC, as in the gCC, no statistically significant change was found in DTI abnormality in any of the 4 DTI parameters when preoperative and 3-month postoperative values were compared. Comparison of 3- and 12-month postoperative findings showed a trend-level change in DTI abnormality for FA ($p = 0.0590$) but not for the other 3 parameters. Comparison of preoperative and 12-month postoperative findings (Fig. 6; Table 4) showed a trend-level change in DTI abnormalities for FA ($p = 0.0594$), AD ($p = 0.0650$), and RD ($p = 0.0717$).

Abnormalities in Neuropsychological Measures

The results from the present sample are summarized in Table 5. Briefly, in comparison with the controls, patients with hydrocephalus had scores that were significantly lower (or at least showed a trend toward being significantly lower) in GAC, all 3 subscale scores, and motor skills at all 3 time points, with the only exception being the Practical subscale score from the 3-month postoperative time point based on the caregiver assessment in ABAS-II tests. In the Bayley-III test, patients with hydrocephalus showed a trend toward lower scores in Social Emotional skill at both postoperative time points and had significantly lower scores in Cognitive, Language, and Motor skills at all 3 time points.

Correlation of DTI With Neuropsychological Measures at the Time of Imaging

In the control group, no significant correlation was found between any DTI measure in the gCC or the left PLIC and any neuropsychological measure in either ABAS-II or Bayley-III. Analysis of preoperative imaging in patients with hydrocephalus showed a statistically significant positive correlation between the FA residual in the gCC and the Motor Scale score in ABAS-II ($r = 0.79$, $n = 10$, $p = 0.007$; Fig. 7A). Analysis of imaging data obtained 3 months after surgery in patients with hydrocephalus showed a statistically significant positive correlation between FA residual in the gCC and GAC ($r = 0.43$, $n = 26$, $p = 0.028$; Fig. 7B), Motor Scale score ($r = 0.45$, $n = 22$, $p = 0.034$) in ABAS-II, and Language score ($r = 0.61$, $n = 19$, $p = 0.005$; Fig. 7C) in Bayley-III; RD in gCC was inversely correlated with Motor Scale score ($r = -0.44$, $n = 22$, p

FIG. 3. Cross-sectional comparisons of DTI residual in the gCC between imaging studies obtained in the controls and studies obtained in hydrocephalus patients at 3 different time points. **A:** FA. **B:** MD. **C:** AD. **D:** RD. ns = not significant.

FIG. 4. Cross-sectional comparisons of DTI residual in the left PLIC between controls and hydrocephalus patients at 3 different time points. A: FA. B: MD. C: AD. D: RD. ns = not significant.

= 0.041) in ABAS-II. Analysis of imaging data obtained 12 months after surgery in children with hydrocephalus showed a significant positive correlation between FA residual in the gCC and Motor Scale score in ABAS-II ($r = 0.57$, $n = 17$, $p = 0.018$), as well as Motor scores ($r = 0.72$, $n = 14$, $p = 0.004$; Fig. 7D) in Bayley-III.

Correlation of DTI Findings With Future Neuropsychological Outcome

The FA value in the gCC measured 3 months after surgery in children with hydrocephalus was found to have a significant positive correlation with the ABAS-II GAC ($r = 0.638$, $n = 15$, $p = 0.011$; Fig. 8A), Conceptual score ($r = 0.633$, $n = 15$, $p = 0.011$), Practical score ($r = 0.633$, $n = 15$, $p = 0.011$), and Motor Scale score ($r = 0.716$, $n = 12$, $p = 0.009$; Fig. 8B) and Bayley-III Motor score ($r = 0.842$, $n = 10$, $p = 0.002$; Fig. 8C) obtained at 12 months after surgery. The RD in gCC measured 3 months after surgery was inversely correlated with the ABAS-II Motor Scale score ($r = -0.605$, $p = 0.037$, $n = 12$) and Bayley-III Motor score ($r = -0.678$, $n = 10$, $p = 0.031$; Fig. 8D) obtained 12 months after surgery.

Discussion

The use of DTI for the noninvasive evaluation of clinical hydrocephalus was first reported by Assaf et al. in 2006.⁶ Since that time, the evaluation of WM tracts to better understand pediatric hydrocephalus has been applied both prospectively and retrospectively in human and animal studies. Significant WM abnormalities in the corpus callosum and internal capsule, i.e., decreased FA in the corpus callosum and increased FA in the internal capsule

(interpreted as disruption and compression, respectively) have been reported by our group, as well as others.^{3,6,22,40,44} Recovery after CSF diversionary surgery, with a trend toward normalization, has also been reported.^{2,6} It is interesting and worth noting that a different trend was identified when patients with benign external hydrocephalus were analyzed. Those patients also had various DTI abnormalities in initial screening MRI studies. In the patients with follow-up imaging, however, no WM abnormalities were detected, and there was no need of surgical intervention.³⁷ More recently, we reported preliminary findings suggesting a correlation between abnormal DTI values and motor deficits in a prospectively studied patient population (a subset of the patients in the present study, studied at the preoperative stage⁴⁴). Other groups have also reported that DTI parameters are sensitive in the study of hydrocephalus and suggest that DTI could serve as an important tool for quantitative assessment. Others have noted that, in comparison with ventricular size, DTI may offer a better association of WM injury and neurological deficits compared with ventricular size.^{10,30}

In the present study, DTI and neurophysiological outcomes were investigated in pediatric patients with surgically treated congenital hydrocephalus in a prospective manner, first before surgery and then at 3 and 12 months after surgery. The data collected in the present study supported the hypothesis that preoperative DTI measures were abnormal in patients with hydrocephalus in comparison with the findings in age-matched controls. These data are consistent with our previous reports, as well as those of other groups.^{2,10,20,44} In general, FA values are low in the gCC and high in the PLIC.

TABLE 3. Cross-sectional comparisons of DTI residual between controls and patients with hydrocephalus at 3 different time points

Time Point & Parameter	Mean ± SD		Difference Btwn Groups		df	t	p Value*
	Controls	Patients w/ HCP	Mean	95% CI			
Preop							
gCC							
FA	-0.0005 ± 0.0414	-0.1743 ± 0.1296	0.1738	0.1374 to 0.2102	84	9.4956	0.0008
MD	0.0006 ± 0.0709	0.3187 ± 0.2065	-0.3181	-0.3771 to -0.2590	84	10.7109	0.0004
AD	0.0000 ± 0.1111	0.1008 ± 0.2203	-0.1008	-0.1734 to 0.0281	84	2.7587	0.0095
RD	0.0008 ± 0.0687	0.4004 ± 0.2904	-0.3996	-0.4767 to -0.3225	84	10.3054	0.0003
Left PLIC							
FA	-0.0001 ± 0.0309	0.0828 ± 0.1210	-0.0829	-0.1154 to -0.0504	84	5.0694	0.0002
MD	0.0011 ± 0.0431	0.0227 ± 0.0852	-0.0228	-0.0475 to 0.0019	84	1.8368	NS
AD	-0.0000 ± 0.0624	0.1469 ± 0.1476	-0.1470	-0.1919 to -0.1020	84	6.5021	0.0002
RD	0.0004 ± 0.0436	-0.0388 ± 0.1232	0.0392	-0.0037 to 0.0747	84	2.1948	0.0353
3 mos postop							
gCC							
FA	-0.0005 ± 0.0414	-0.1948 ± 0.1041	0.1942	0.1642 to 0.2243	90	12.8527	0.0008
MD	0.0006 ± 0.0709	0.3609 ± 0.2486	-0.3602	-0.4271 to -0.2934	90	10.7034	0.0004
AD	0.0000 ± 0.1111	0.1850 ± 0.2689	-0.1850	-0.2634 to -0.1066	90	4.6881	0.0003
RD	0.0008 ± 0.0687	0.4386 ± 0.2734	-0.4380	-0.5102 to -0.3658	90	12.0531	0.0002
Left PLIC							
FA	-0.0001 ± 0.0309	0.0430 ± 0.0815	-0.0431	-0.0662 to -0.0199	91	3.7001	0.0005
MD	0.0011 ± 0.0431	0.0107 ± 0.0949	-0.0109	-0.0368 to 0.0152	91	0.8242	NS
AD	-0.0000 ± 0.0624	0.0663 ± 0.1007	-0.0663	-0.1002 to -0.0324	91	3.8833	0.0003
RD	0.0004 ± 0.0436	-0.0264 ± 0.1190	0.0267	-0.0068 to 0.0060	91	1.5850	NS
12 mos postop							
gCC							
FA	-0.0005 ± 0.0414	-0.1437 ± 0.1251	0.1432	0.1088 to 0.1777	91	8.2571	0.0008
MD	0.0006 ± 0.0709	0.1337 ± 0.1716	-0.1331	-0.1829 to -0.0083	91	5.3101	0.0004
AD	0.0000 ± 0.1111	-0.0644 ± 0.3955	0.0628	-0.0428 to 0.1684	91	1.1809	NS
RD	0.0008 ± 0.0687	0.2031 ± 0.2007	-0.2023	-0.2579 to -0.1467	91	7.2219	0.0003
Left PLIC							
FA	-0.0001 ± 0.0309	0.0089 ± 0.0958	0.0088	-0.0173 to 0.0350	92	0.6698	NS
MD	0.0011 ± 0.0431	0.0113 ± 0.0530	-0.0114	-0.0287 to 0.0058	92	1.3147	NS
AD	-0.0000 ± 0.0624	0.0137 ± 0.1531	-0.0138	-0.0578 to 0.0303	92	0.6198	NS
RD	0.0004 ± 0.0436	0.0090 ± 0.0683	-0.0087	-0.0318 to 0.0145	92	0.7444	NS

df = degrees of freedom; NS = not significant.

* p values corrected using the FDR method.

Persistence of DTI Abnormalities During the 1st Year After Surgery

It was hypothesized that there would be significant trends toward recovery in terms of DTI measures in the WM at follow-up examinations after the initial surgical procedure. However, this hypothesis was not proved to be entirely true. Qualitatively, abnormal DTI values seem to persist in many patients (Figs. 1 and 2). Cross-sectionally, the DTI findings in the corpus callosum of hydrocephalus patients demonstrated persistence of abnormalities both at 3- and 12-month follow-up compared with findings in controls. In contrast, the diffusion abnormalities in the PLIC were significant in studies performed 3 months after surgery, but the abnormalities were not appreciated at 12

months after surgery (Figs. 3 and 4). Longitudinally, the gCC DTI abnormalities in patients with hydrocephalus (difference between the hydrocephalus patients' data and the controls' data for the gCC) did not differ significantly between the preoperative and 3-month postoperative imaging studies, suggesting persistence of WM injury during the first 3 months after surgery despite the decreased ventricle size and improvement in clinical symptoms. However, a significant longitudinal difference was observed with respect to all 4 DTI measures in the gCC between the 3- and 12-month postoperative studies, with DTI values closer to normal in the 12-month postoperative assessments. Significant or trend-level differences in DTI abnormalities in the gCC between preoperative and 12-month postop-

TABLE 4. Longitudinal comparisons of DTI residual at 3 different time points in patients with hydrocephalus

Measurement	N	Mean	SD	SEM	Min	Median	Max	p Value
gCC								
3 mos postop – preop								
FA	11	–0.013	0.137	0.041	–0.237	0.016	0.197	NS
MD	11	0.064	0.324	0.098	–0.458	0.010	0.737	NS
AD	11	0.135	0.373	0.113	–0.522	0.110	0.985	NS
RD	11	0.015	0.313	0.094	–0.416	–0.041	0.623	NS
12 mos postop – 3 mos postop								
FA	18	0.050	0.096	0.023	–0.104	0.043	0.224	0.0418
MD	18	–0.228	0.300	0.071	–1.040	–0.247	0.160	0.0049
AD	18	–0.273	0.565	0.133	–2.035	–0.137	0.270	0.0565
RD	18	–0.237	0.284	0.067	–0.935	–0.224	0.186	0.0025
12 mos postop – preop								
FA	10	0.031	0.046	0.015	–0.054	0.025	0.101	0.0775
MD	10	–0.131	0.126	0.040	–0.303	–0.160	0.101	0.0095
AD	10	–0.197	0.583	0.184	–1.740	–0.086	0.388	NS
RD	10	–0.177	0.092	0.029	–0.312	–0.199	–0.029	0.0002
Left PLIC								
3 mos postop – preop								
FA	11	–0.038	0.097	0.029	–0.169	–0.051	0.174	NS
MD	11	–0.023	0.057	0.017	–0.145	–0.030	0.064	NS
AD	11	–0.098	0.144	0.043	–0.364	–0.119	0.231	0.0470
RD	11	0.005	0.067	0.020	–0.093	0.021	0.098	NS
12 mos postop – 3 mos postop								
FA	19	–0.040	0.083	0.019	–0.223	–0.028	0.117	0.0525
MD	19	–0.004	0.098	0.022	–0.353	0.023	0.094	NS
AD	19	–0.047	0.159	0.036	–0.512	–0.029	0.219	NS
RD	19	0.029	0.100	0.023	–0.251	0.030	0.207	NS
12 mos postop – preop								
FA	11	–0.096	0.150	0.045	–0.365	–0.065	0.146	0.0594
MD	11	0.013	0.063	0.019	–0.093	0.031	0.132	NS
AD	11	–0.104	0.166	0.050	–0.520	–0.067	0.072	0.0650
RD	11	0.073	0.119	0.036	–0.137	0.084	0.304	0.0717

erative imaging studies were also found, with DTI values close to the normal range at 12 months after surgery. In contrast, the DTI abnormality in the left PLIC in the patients with hydrocephalus (difference between the hydrocephalus patients' data and the controls' data for the left PLIC) appeared to resolve sooner after the surgery based on the longitudinal comparisons.

Correlation Between DTI and Neuropsychological Measures and Predictive Value of DTI for Future Outcome Measures

In the present study, we reported correlations between DTI measures and neuropsychological assessments in children with hydrocephalus. At all 3 time points, correlations were found between ABAS-II or Bayley-III in patients with hydrocephalus and their DTI results in the gCC (in general, positively with FA, negatively with RD). The direction of correlation is in line with our hypotheses—i.e.,

with a structure with abnormally lower FA and/or higher MD (or AD or RD), a patient with hydrocephalus performs better in the neuropsychological assessment when his or her DTI measure in the gCC is closer to the normal range. Although there is no direct evidence based on underlying neuroanatomy, the correlation indicates that, in addition to the persistent abnormality in DTI at both 3 and 12 months after surgery, the association between neuroanatomy and neuropsychological measures has not resolved within the time frame of this study (1 year after surgery). In addition to the correlation between outcome measures and contemporaneous DTI measures, significant correlations were also found between DTI findings obtained at 3 months after surgery and outcome measures 12 months after surgery, suggesting that behavioral and neuropsychological changes may be influenced by earlier WM changes. The predictive value of WM integrity based on DTI for future outcome has been reported frequently in populations such

FIG. 5. Longitudinal comparison of DTI residual in the gCC between 3- and 12-month postoperative assessments. A: FA. B: MD. C: AD. D: RD.

FIG. 6. Longitudinal comparison of DTI residual in the left PLIC between preoperative and 12-month postoperative assessments. A: FA. B: MD. C: AD. D: RD.

TABLE 5. Comparison of neuropsychological testing results obtained at 3 different time points in patients with hydrocephalus and results in controls*

Measure	Controls	Patients w/ HCP		
		Preop	3 Mos Postop	12 Mos Postop
ABAS-II				
GAC	101.6 ± 14.2	89.1 ± 16.9 (p = 0.0027)	94.9 ± 15.9 (p = 0.0562)	85.1 ± 18.5 (p = 0.0009)
Conceptual	104.6 ± 13.8	93.5 ± 17.3 (p = 0.0065)	99.3 ± 15.9 (p = 0.0981)	92.4 ± 17.7 (p = 0.0012)
Social	100.5 ± 15.5	91.3 ± 14.4 (p = 0.0179)	96.2 ± 15.0 (p = 0.0954)	90.3 ± 17.5 (p = 0.0097)
Practical	99.5 ± 14.4	91.9 ± 15.2 (p = 0.0384)	97.2 ± 15.6 (NS)	84.5 ± 14.2 (p = 0.0005)
Motor Scale	10.1 ± 2.9	7.9 ± 3.9 (p = 0.0085)	7.9 ± 3.1 (p = 0.0020)	6.4 ± 3.7 (p = 0.0003)
Bayley-III				
Social	103.6 ± 14.9	92.9 ± 21.0 (NS)	95.9 ± 15.6 (p = 0.0826)	93.5 ± 23.8 (p = 0.0707)
Cognitive	99.0 ± 9.8	89.2 ± 15.0 (p = 0.0434)	82.6 ± 17.2 (p = 0.0009)	84.2 ± 17.5 (p = 0.0002)
Language	98.5 ± 9.2	74.6 ± 9.1 (p = 0.0009)	85.2 ± 16.6 (p = 0.0005)	80.3 ± 16.9 (p = 0.0002)
Motor	97.4 ± 8.7	72.3 ± 15.0 (p = 0.0005)	78.9 ± 18.1 (p = 0.0003)	75.1 ± 18.7 (p = 0.0002)

* All p values corrected using FDR method. Means are presented ± SD.

as preterm infants and patients with stroke, traumatic brain injury, and hypoxic-ischemic encephalopathy.^{1,4,18,24} The findings of the current study add new value to the field, demonstrating the predictive and prognostic value of DTI performed at a time shortly after surgical treatment (i.e., 3 months after surgery) for outcomes measures assessed at a

later time (12 months after surgery). Whether this relation remains for longer-term prediction and whether DTI at 12 months after injury is a better predictor for future outcome (i.e., beyond 12 months) are yet to be tested. However, our finding shows potential value of DTI in clinical application in the management of postsurgical hydrocephalus pa-

FIG. 7. Correlation of DTI residual in the gCC with neuropsychological outcome assessed at the same time. **A:** Preoperative assessment: FA residual in the gCC versus ABAS-II Motor Scale. **B:** Three-month postoperative assessment: FA residual in the gCC versus ABAS-II GAC. **C:** Three-month postoperative assessment: FA residual in the gCC versus Bayley-III. **D:** Twelve-month postoperative assessment: FA residual in the gCC versus Bayley-III Motor.

FIG. 8. Correlation of DTI residual in the gCC at 3 months after surgery with neuropsychological outcome at 12 months after surgery. **A:** FA residual in the gCC versus ABAS-II GAC. **B:** FA residual in the gCC versus ABAS-II Motor Scale. **C:** FA residual in the gCC versus Bayley-III Motor. **D:** RD residual in gCC versus Bayley-III Motor.

tients. Correlations were found between DTI at 3 months after surgery and outcome neuropsychological measures at 12 months after surgery.

DTI may become a valuable tool for clinicians who provide long-term management for patients with hydrocephalus. The study presented here provides initial evidence that would allow the translation of noninvasively obtained radiological information to follow temporal progression of WM integrity in these patients. We generated normative WM maturation curves based on DTI for specific regions, and this can potentially be replicated in other major WM regions or tracts of interest. Creation of such curves will allow us to objectively and noninvasively evaluate patients and eventually extrapolate to future neurocognitive outcomes. When followed longitudinally, the imaging measures will serve to correlate functional outcomes the same way we currently follow head circumference measurements in infants and toddlers to predict normal development or alert us of potential impending clinical pathology.

Limitations

This study was designed as a prospective longitudinal clinical neuroimaging research project. Due to the logistical difficulty, it was often impractical to enroll and scan patients in a timely manner. Many patients who initially enrolled in the study were not tested (MRI and neuropsychological testing) at all 3 time points, which reduced the power in statistical analysis. The study was designed to

include follow-up evaluations at 3 and 12 months after surgery. We found significant DTI abnormalities before surgery and 3 months after surgery in both the gCC and the left PLIC, and the abnormalities persisted in the gCC at 12 months after surgery. However, we were not able to extrapolate findings from the present study for the trajectory of further recovery after surgery. It would be interesting to follow these surgical patients for a longer period of time to determine when or if the abnormalities (DTI and neuropsychological outcomes) observed in short-term postoperative follow-up will eventually normalize for all patients, and how the correlation between DTI findings at 3 months after surgery and behavioral outcome assessments at 12 months after surgery will evolve temporally in these young patients. A third limitation is the lack of a more comprehensive test battery due to the age range of this patient population. In a recent study, it was found that the nonverbal performance in a cohort of school-age children (6–16 years) with surgically treated hydrocephalus responded well to a short-term occupational therapy intervention targeting the visual spatial, visual attention, and visual motor deficits, which are typical domains of long-term deficits in this patient population. How we can merge the knowledge obtained from the present study, in which most patients were enrolled at 0–3 years of age, and the other reports of long-term outcome in older children remains a challenge and warrants further investigation. Longer-term follow-up of this cohort would allow addi-

tional, quantitative neuropsychological scales to be tested to measure performance relative to the performance of healthy peers.

Conclusions

This is the first prospective neuroimaging study to have systemically investigated WM abnormalities based on DTI in children with hydrocephalus before and after surgery. We found 1) significant WM abnormalities at the acute stage prior to surgery; 2) longitudinal recovery with a trend toward the normal range after surgery; 3) persistent WM abnormalities in ROIs tested at 3 months and/or 12 months after surgery; and 4) significant correlation between DTI and developmental outcome measures. These findings provide strong evidence that DTI is a sensitive imaging biomarker for WM abnormalities in pediatric patients with hydrocephalus and potentially can serve as a clinical tool for diagnosis and prognosis in the management of this patient population.

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Disclosures

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Conception and design: Yuan, Mangano, McKinstry, Holland. Acquisition of data: Powell, Phillips, Barnard, Dodd, Simpson, Mercer, Bidwell. Analysis and interpretation of data: Yuan, Mangano, Altaye, McKinstry, Shimony, Powell, Phillips, Barnard, Limbrick, Holland, Jones, Dodd. Drafting the article: Yuan, Mangano. Critically revising the article: Yuan, Mangano, Altaye, Shimony, Limbrick, Holland, Jones, Dodd. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Yuan. Statistical analysis: Yuan, Altaye. Administrative/technical/material support: Simpson, Mercer, Rajagopal, Bidwell. Study supervision: Yuan, Mangano, McKinstry, Powell, Limbrick, Jones. Data processing: Simpson, Rajagopal.

Supplemental Information

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