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Clinical Study

A diffusion tensor imaging study of deep gray and white matter brain maturation differences between patients with spina bifida cystica and healthy controls

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ABSTRACT

The aim of this study was to use diffusion tensor imaging (DTI) to identify differences in the maturation of deep gray matter (GM) and white matter (WM) between patients with spina bifida cystica (SBC) ($n = 29$) with normal-appearing brains on conventional MRI, and age-matched and sex-matched healthy control participants ($n = 33$). Changes in DTI metrics were calculated using a log–linear regression model. We observed increasing fractional anisotropy (FA) with age in the occipital, fornix, cingulum and middle cerebellar peduncles and decreasing FA with age in the genu and splenium of the corpus callosum (CC) and caudate nuclei in patients compared to controls. Increasing FA values in some of the WM structures probably represent faulty WM maturation, whereas decreasing FA values in the CC represents changes secondary to the affected WM fibers contributing to the CC. DTI changes in deep GM and WM in the absence of any abnormality on conventional MRI might provide the basis for cognitive decline in these patients.

1. Introduction

Central nervous system (CNS) development is a complex process that occurs over time.[1] Many neurological and neurobehavioral disorders originate during the neonatal period.[2] Spina bifida cystica (SBC) is a congenital neurodevelopmental disorder that results from incomplete closure of the neural tube during the first 3–4 weeks of gestation[3] and it is associated with congenital or developmental defects in brain macrostructure.[4] The incidence of craniospinal anomalies associated with SBC, such as hydrocephalus (46%), Chiari malformation (45%), aqueductal stenosis (15%), and corpus callosal (CC) dysgenesis (14%),[5] shows regional variation as well as differences depending on the socioeconomic status of the family.[6]

There have been only a few quantitative, conventional MRI studies of anomalous structural development of the brain in patients with SBC.[7,8] Conventional MRI provides only limited visualization of some abnormalities, such as aberrant white matter (WM) connections. Conversely, diffusion tensor imaging (DTI) provides information regarding the degree and direction of tissue water diffusion.[7] Degree of diffusion anisotropy depends on the extent to which myelin sheaths hinder water diffusion: motion parallel to axons/myelin sheaths is inhibited less than perpendicular motion, a phenomenon known as diffusion anisotropy. Two commonly used DTI metrics are fractional anisotropy (FA) and mean diffusivity (MD). FA reflects the structural integrity and degree of alignment of cellular structures within the fiber tracts. MD, the trace of the diffusion matrix, is an average measure of molecular diffusion and is affected by cellular size and integrity.[7]

Hasan et al., using DTI, reported abnormal WM development in the major association pathways of children with hydrocephalus with myelomeningocele.[9] In another study, Hasan et al. used DTI to quantify whole-brain gray matter (GM), WM and cerebrospinal fluid (CSF) volumes, and examined the results with respect to intellectual outcomes in patients with SBC.[10] A high FA indicates WM fiber integrity and myelination, which is also associated with improved functionality.[11,12] Hoeft et al., however, reported an in-

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creased FA in the superior longitudinal fasciculus in Williams's syndrome that was associated with poor visuospatial abilities.[12] A similar conclusion was reached by Herweh et al. with regard to Chiari malformation.[13]

To our knowledge, the effect of SBC on the maturation of normal-appearing deep GM and WM structures has not been reported. Thus, in the present study, we aimed to use DTI to look for differences in GM and WM maturation between patients with SBC with normal-appearing brains on conventional MRI, compared to age-matched and sex-matched healthy control participants.

2. Materials and methods

2.1. Study design

This study was performed on 29 patients with SBC (17 males and 12 females; age, 4 months to 28 years; median age, 12 years). All patients who had normal brain imaging on conventional MRI, either those with pre-operative SBC or who had undergone surgical repair for SBC were included in the study. Patients were divided into the following groups: lumbo-sacral meningomyelocele ($n = 4$), lumbo-sacral meningocele ($n = 12$), dorsal meningocele ($n = 3$), and operated-lumbar meningocele ($n = 10$). Patients with hydrocephalus or Chiari malformation were excluded from the study to overcome the confounding effect of these variables on DTI metrics. Healthy control participants (33: 22 males and 11 females; aged 9 months–29 years; median age, 11 years) were included for comparison. The inclusion criteria were: (i) a normal neurological assessment; and (ii) a clinical brain MRI study showing no visible abnormality. Informed consent to acquire MRI data was obtained from either the patients, or their parents. All studies were performed within the guidelines of the Institutional Ethics Committee.

2.2. MRI protocol

2.2.1. Conventional MRI protocol

The imaging was performed on a 1.5 Tesla MRI scanner (Signa LX, GE, Milwaukee, WI, USA) using a quadrature head coil. Axial T2-weighted fast spin-echo (SE) MRI (repetition time [TR], 6000 ms; echo time, 85 ms; number of excitations [NEX], 4), axial T1-weighted SE MRI (TR, 1000 ms; TE, 14 ms; NEX, 2) and sagittal T1-weighted MRI were acquired. A total of 36 contiguous, 3-mm-thick axial sections were acquired with a 240 mm $\times$ 240 mm field of view (FOV) and image matrix of 256 $\times$ 256 pixels.

2.2.2. Diffusion tensor imaging protocol

DTI data were acquired using a single-shot echo-planar dual SE sequence.[14] Acquisition parameters were: b-factor, 0 s/mm^2 and 1000 s/mm^2 3-mm slice thickness with no gap; 34–36 slices; a 240 $\times$ 240 mm^2 FOV; image matrix, 256 $\times$ 256 pixels; TR, 8 s; TE, 100 ms; NEX, 8. We used a rotationally invariant diffusion-encoding scheme with 10 non-collinear directions to generate the DTI data.[15] The data were processed and evaluated offline using a in-house JAVA-based program.[16]

2.2.3. DTI data post-processing

The distortion-corrected data were interpolated to attain isotropic voxels and decoded to obtain the tensor field for each voxel. The tensor field data were diagonalized using the analytical diago-

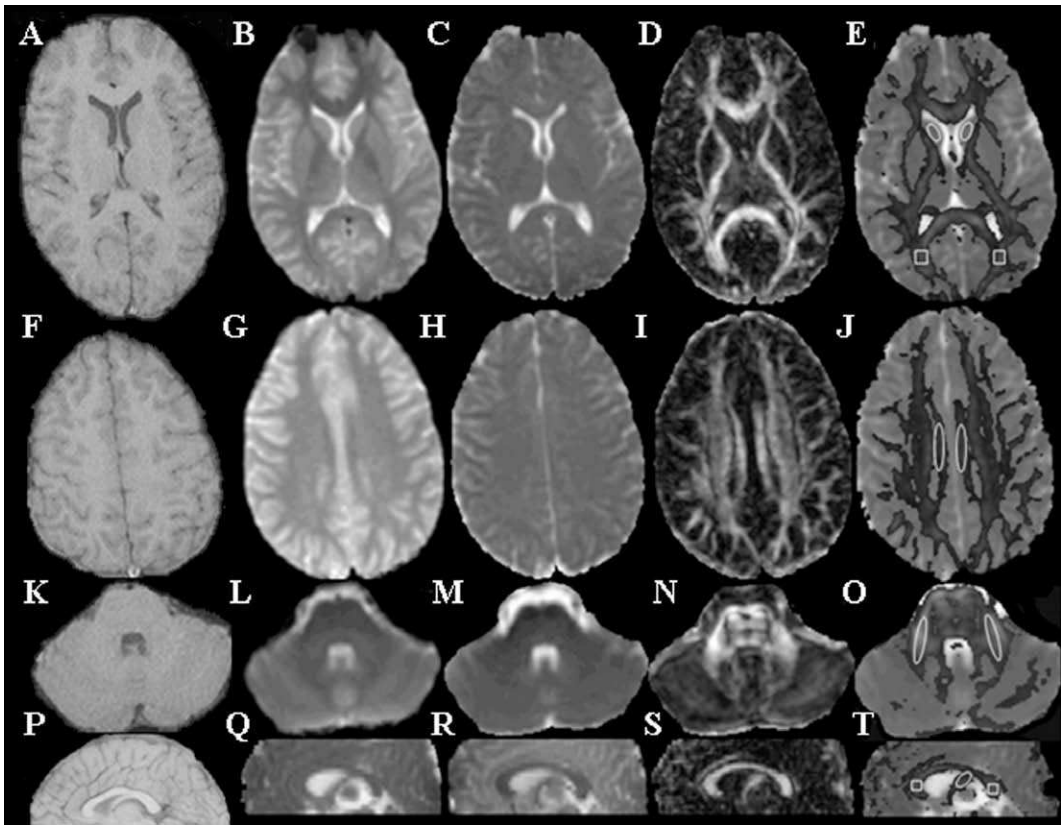

Fig. 1. The (A–O) axial and (P–T) sagittal MRI of a 15-year-old patient with spina bifida cystica showing normal-appearing cerebral and cerebellar white matter: (columns 1–5, left to right) – T1-weighted (column 1) and T2-weighted (column 2) MRI; mean diffusivity (column 3); fractional anisotropy (FA) (column 4); and FA maps (column 5). The cut-off value for the gray scale FA maps (E, J, O, T) was kept at 0.2. Images taken at (A–E) the third ventricle level, (F–J) corona radiata, (K–O) pons and (P–T) massa intermedia show the regions of interest placed on the: caudate nuclei and occipital white matter (A, F, K, P); cingulum (B, G, L, Q); middle cerebellar peduncles (C, H, M, R); genu and splenium of corpus callosum (D, I, N, S); and fornix (E, J, O, T).

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Table 1
The relationship between the fractional anisotropy (FA) values and the regression parameters in the healthy controls and patients with spina bifida cystica (SBC) in different deep gray and white matter regions of the brain, using the log–linear regression model

Brain region		FA	Regression coefficient		Model diagnostics		
		Mean ± SD	a_0	a_1	R^2	F	p value
OWM	Control	0.34 ± 0.03	0.2798	0.0230	0.597	45.92	<0.001
	Patient	0.38 ± 0.03	0.3129	0.0274	0.604	41.23	<0.001
Cing	Control	0.24 ± 0.03	0.1599	0.0310	0.623	51.33	<0.001
	Patient	0.34 ± 0.05	0.2205	0.0502	0.794	104.02	<0.001
Fornix	Control	0.36 ± 0.05	0.2136	0.0559	0.856	184.17	<0.001
	Patient	0.37 ± 0.04	0.2647	0.0445	0.893	224.68	<0.001
Genu	Control	0.54 ± 0.06	0.3748	0.0630	0.637	54.42	<0.001
	Patient	0.46 ± 0.06	0.3040	0.0652	0.711	66.47	<0.001
Splenium	Control	0.56 ± 0.06	0.4058	0.0609	0.675	64.41	<0.001
	Patient	0.54 ± 0.03	0.4529	0.0338	0.858	163.45	<0.001
MCP	Control	0.54 ± 0.06	0.0598	0.4248	0.828	120.62	<0.001
	Patient	0.60 ± 0.04	0.0285	0.5418	0.548	30.25	<0.001
CN	Control	0.15 ± 0.04	0.0434	0.0406	0.882	232.36	<0.001
	Patient	0.12 ± 0.02	0.0589	0.0249	0.888	214.36	<0.001

a_0 = constant, a_1 = regression coefficient, Cing = cingulum, CN = caudate nuclei, FA = fractional anisotropy, MCP = middle cerebellar peduncle, OWM = occipital white matter, SD = standard deviation.

nalization method to obtain the eigenvalues (λ_1, λ_2, λ_3) and the three-orthonormal eigenvectors (e_1, e_2, e_3). The tensor field data were then used to compute DTI metrics for each voxel. The FA (Equation 1) and MD (Equation 2) were calculated:

$$FA(\lambda_1,\lambda_2,\lambda_3)=\frac{1}{\sqrt{2}}\sqrt{\frac{(\lambda_1-\lambda_2)^2+(\lambda_2-\lambda_3)^2+(\lambda_1-\lambda_3)^2}{\lambda_1^2+\lambda_2^2+\lambda_3^2}} \quad (1)$$

$$MD=\frac{\lambda_1+\lambda_2+\lambda_3}{3} \quad (2)$$

Patients with SBC have deficits in learning, timing, attention, movement and memory – functions associated with both cerebellar and cerebral regions.[17] We therefore selected those brain regions with known neurocognitive deficits in these patients.[18,19] For FA and MD quantification, elliptical or rectangular regions of interest (ROI) from 2 × 2 pixels to 6 × 6 pixels were placed in the deep GM nuclei and WM (Fig. 1). The CC volume was calculated from the mid-sagittal T1-weighted images using free software for Image processing and Analysis; Image-J (Java-based) software (National Institutes of Health Image; <http://rsb.info.nih.gov/nih-image/>).

2.3. Statistical analysis

Linear, quadratic, cubic, log–linear, growth, and bi-exponential models[11] were used to describe the relationship between age and DTI indices in the deep GM and WM brain regions. For each model, regression coefficients (R^2), 95% confidence intervals and other model diagnostics were estimated. Based on the regression diagnostics, the best fit was the log–linear model (Equation 3), expressed as:

$$y=a_1\ln(x)+a_0, \quad (3)$$

where y is the estimated DTI value, x is the age, a_0 is a constant, and a_1 is the regression coefficient of the log transform of age. The results of this analysis were used to describe various relationships.

An Independent Student t-test was performed to determine the difference in CC volume between patients and controls. All computations were performed using the Statistical Package for the Social Sciences version 15 (SPSS; Chicago, IL, USA). A p value of $\leqslant 0.05$ was considered significant.

3. Results

The log–linear relationship between the age and DTI metrics in the deep GM and WM structures of the patients and controls are summarized in Tables 1 and 2.

3.1. Log–linear plots

The log–linear model had the best fit for all ROI for describing the maturation patterns through DTI metrics. We observed two different patterns in FA values (Fig. 2) with no consistent pattern in MD values between patients and controls (Fig. 3).

3.2. Regions with high FA values

We observed a rapid increase in FA values in the occipital white matter (OWM) and cingulum (Cing) up to the age of 2 years, followed by a gradual increase in FA values up to the age of 28 years (Fig. 2A, B). At all ages, the FA values were higher in the patients with SBC than in healthy control participants. In the fornix and middle cerebellar peduncles (MCP), a similar pattern of increased FA was initially observed; however, around 30 years, the FA values of the patients with SBC were similar to healthy controls (Fig. 2C, D).

3.3. Regions with low FA values

We observed a rapid increase in the FA values in the genu in both patients and controls up to the age of 2 years followed by a gradual increase. At all ages, the FA values in the genu were lower in the patients than controls (Fig. 2E). A rapid increase in the FA values in the splenium was observed in patients up to the age of 4 years and in controls up to the age of 2 years and followed by a gradual decline in the patients compared to controls. Beyond 6 years of age, the FA values in the splenium were lower in the patients than controls (Fig. 2F). In the cuadate nucleus (CN), we observed an initial increase in the FA values in patients up to the age of 2 years and in controls up to the age of 5 years followed by a gradual increase in both patients and controls. However, beyond the age of 5.5 years, the FA value in the patients was lower than in controls (Fig. 2G).

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Table 2
The relationship between mean diffusivity (MD) ($\times 10^{-3}$ mm^2/s) values and regression parameters in healthy control participants and patients with spina bifida cystica in different deep gray and white matter regions of the brain, using the log–linear regression model

Brain region		MD	Regression coefficients		Model diagnostics		
		Mean ± SD	a_0	a_1	R^2	F	p value
OWM	Control	0.76 ± 0.02	0.7199	0.0152	0.664	61.25	<0.001
	Patient	0.78 ± 0.05	0.8454	−0.0316	0.638	47.61	<0.001
Cing	Control	0.77 ± 0.04	0.6981	0.0321	0.519	33.50	<0.001
	Patient	0.75 ± 0.01	0.7346	0.0081	0.551	33.09	<0.001
Fornix	Control	0.75 ± 0.03	0.6994	0.0224	0.510	32.31	<0.001
	Patient	0.73 ± 0.02	0.7054	0.0137	0.643	48.55	<0.001
Genu	Control	0.84 ± 0.04	0.9296	−0.367	0.540	36.43	<0.001
	Patient	0.86 ± 0.09	0.9854	−0.0624	0.694	61.20	<0.001
Splenium	Control	0.82 ± 0.06	0.9707	−0.637	0.732	84.87	<0.001
	Patient	0.81 ± 0.08	0.9243	−0.0581	0.825	127.71	<0.001
MCP	Control	0.56 ± 0.08	−0.0708	0.6996	0.772	−84.81	<0.001
	Patient	0.49 ± 0.03	0.219	0.4418	0.591	36.10	<0.001
CN	Control	0.74 ± 0.04	0.6649	0.0340	0.504	31.49	<0.001
	Patient	0.75 ± 0.03	0.7849	−0.0166	0.553	33.38	<0.001

a_0 = constant, a_1 = regression coefficient, Cing = cingulum, CN = caudate nuclei, FA = fractional anisotropy, MCP = middle cerebellar peduncle, OWM = occipital white matter, SD = standard deviation.

3.4. Regional changes in MD patterns

Unlike in the FA values, we did not observe a consistent maturational pattern in the MD values. In patients, we observed an initial sharp decrease in MD values in the OWM up to the age of 2 years, followed by a decrease compared to controls (Fig. 3A). In the Cing, we observed higher MD values in patients up to the age of 3 years, which later stabilized up to 28 years of age compared to controls (Fig. 3B). In the fornix, we observed in patients and controls an initial increase in MD values up to 3–4 years of age followed by a gradually increasing pattern (Fig. 3C). In the MCP, a continuous increase in MD values was observed in patients, whereas a continuous decrease in MD values was observed in controls (Fig. 3D). In the genu and splenium, an initial decrease in the MD values was observed in both patients and controls up to the age of 2 years, followed by a sharper decrease (Fig. 3E, F). In CN, an initial sharp decrease in MD values was found in patients compared to controls up to 2 years, which was followed by a gradual decrease; however, after 10 years, MD values were lower in patients than in controls (Fig. 3G).

3.5. Volumetric assessment of CC

A significant decrease in CC volume ($p < 0.001$) was observed in patients (2029.86 ± 357.65 mm^3) compared to controls (4087.27 ± 1289.16 mm^3).

4. Discussion

This study demonstrates the potential of DTI metrics in the assessment of deep GM and WM maturation in patients with SBC with normal-appearing brains on conventional MRI. Higher FA values were observed in the OWM, fornix, Cing and MCP, while lower FA values were observed in genu of the CC in patients compared to controls at all ages. In the CN and splenium of the CC, similar FA values were observed in patients and controls during the first 4 years to 6 years of life, and thereafter, lower FA values were observed in the patients compared to controls.

Structural malformations and decrease in brain volume have been associated with poor outcomes across various neurogenetic disorders; however, little is known about microstructural changes in the CC in patients with SBC and whether these changes are associated with better or poorer outcomes.[9,10] Few reports are available on the use of DTI in SBC patients.[13,19] In this study, a significant decrease in CC volume in patients with SBC compared to controls suggests abnormal CC development, and that these volume changes are reflected by the microstructural abnormalities seen on DTI.

Reigel et al. reported developmental reorganization along with region-specific changes in deep GM and WM in SBC patients relative to controls as a result of congenital anomalies.[20] A regional variation in lobar brain volume, which possibly results from developmental reorganization, has been reported in patients with SBC.[4,8] Decrease in frontal cortical thickness with age has been reported in children with normal development,[21] whereas increased frontal cortical thickness has been reported in patients with SBC.[8]

In normal WM development, Barnea-Goraly et al. have reported increased FA values towards the periphery of the tracts in regions that are closest to the GM and WM borders without increase in WM density.[22] Previous studies on patients with various neurodevelopmental anomalies can help explain the higher FA values in OWM, Cing, fornix, and MCP in patients with SBC compared to controls in the present study.[12,23] The exact cellular mechanisms underlying the increased FA values are unknown. FA can reflect axonal integrity and organization that may not be related to myelin.[24] A packed arrangement of non-myelinated axons may adequately hinder perpendicular water diffusion and, hence, create anisotropy.[25] Thus, myelin is not necessary for fibers to have significant diffusion anisotropy.[26] However, factors such as increased myelination, microscopic deficits of axonal structures, decreased axonal diameter, and reduced volume of cortical regions, might contribute to high FA values.[27] During brain development, some axonal projections are established only transiently and are subsequently eliminated.[24] According to this theory, in patients with SBC the elimination of such transient projections in the OWM might be disturbed, which results in abnormally high FA values in these patients. This disturbance phenomenon has been studied so far in animals only; however, it is not clear if it occurs in humans and whether it accounts for gross-morphological alterations.[13]

The limbic system (i.e. fornix and Cing) is vital for declarative memory and learning.[19] Thus, abnormalities in the limbic system might correlate with emotional, memory and learning problems in patients with spina bifida myelomeningocele (SBM).[19] We observed an initial rapid increase in FA values up to the age of 2 years

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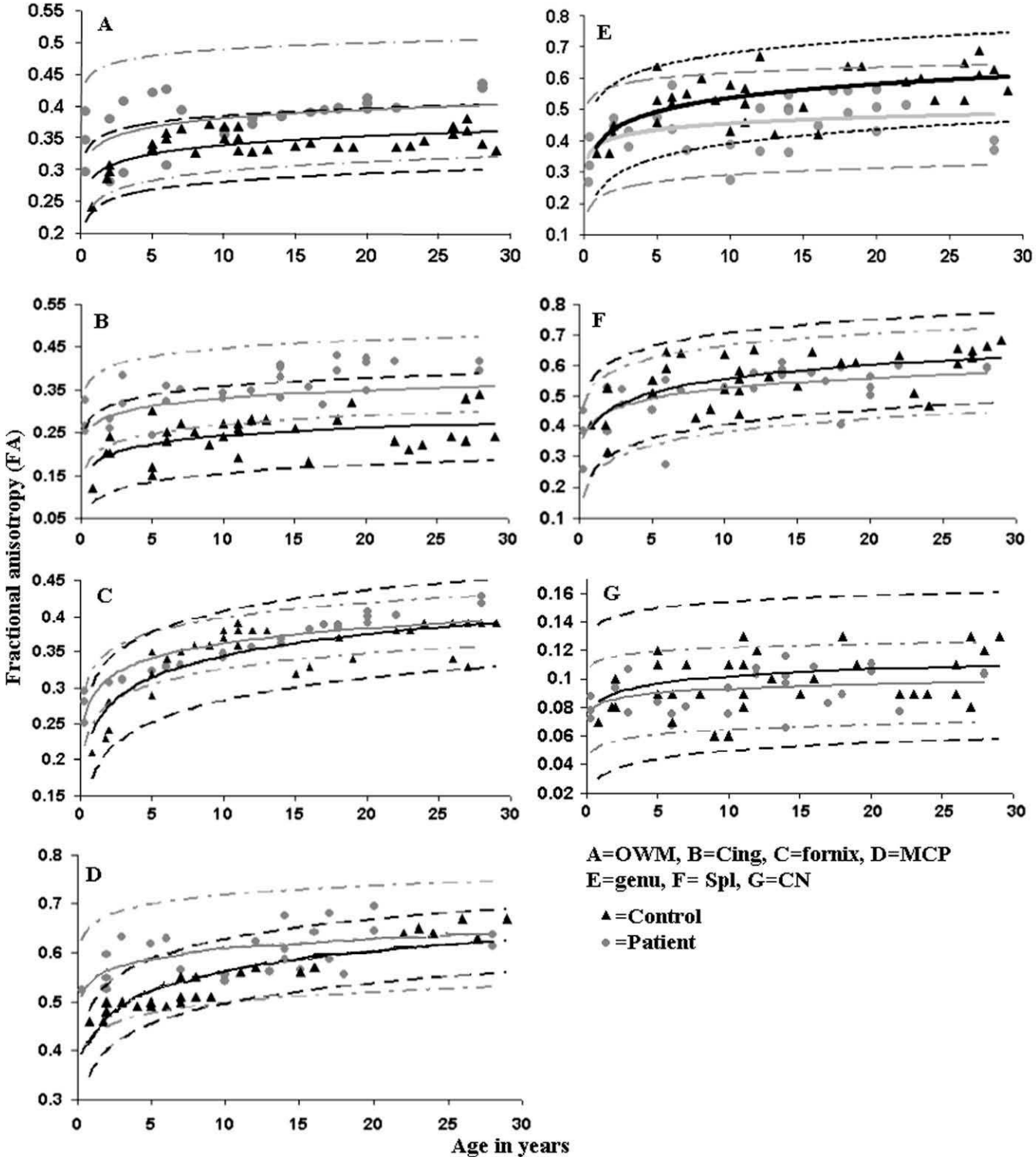

Fig. 2. The relationship between age and fractional anisotropy values in healthy control participants (black lines; solid triangles) compared to patients with spina bifida cystica (gray lines, solid gray circles) in brain deep gray and white matter regions: (A) occipital white matter; (B) cingulum; (C) fornix; (D) middle cerebellar peduncle; (E) genu; (F) splenium; and (G) caudate nuclei. Scatter plots of raw data showing lines of best fit and 95% confidence intervals (broken lines) were generated using the log–linear regression model.

followed by a progressive increase in the fornix and Cing up to 24 years, but the values were similar in Cing after the age of 24 years in patients with SBC compared to controls. The high FA values in these regions might be caused by abnormal maturational patterns of WM tracts in these patients.

There are no well-documented radiologic studies available on DTI of cerebellar WM maturation. A recent DTI study has reported increased FA values with decreased MD values with a progression up to the age of 11 years in normal cerebellar WM.[28] In a study of 1-month- to 4-month-old infants, although the MD values in MCP

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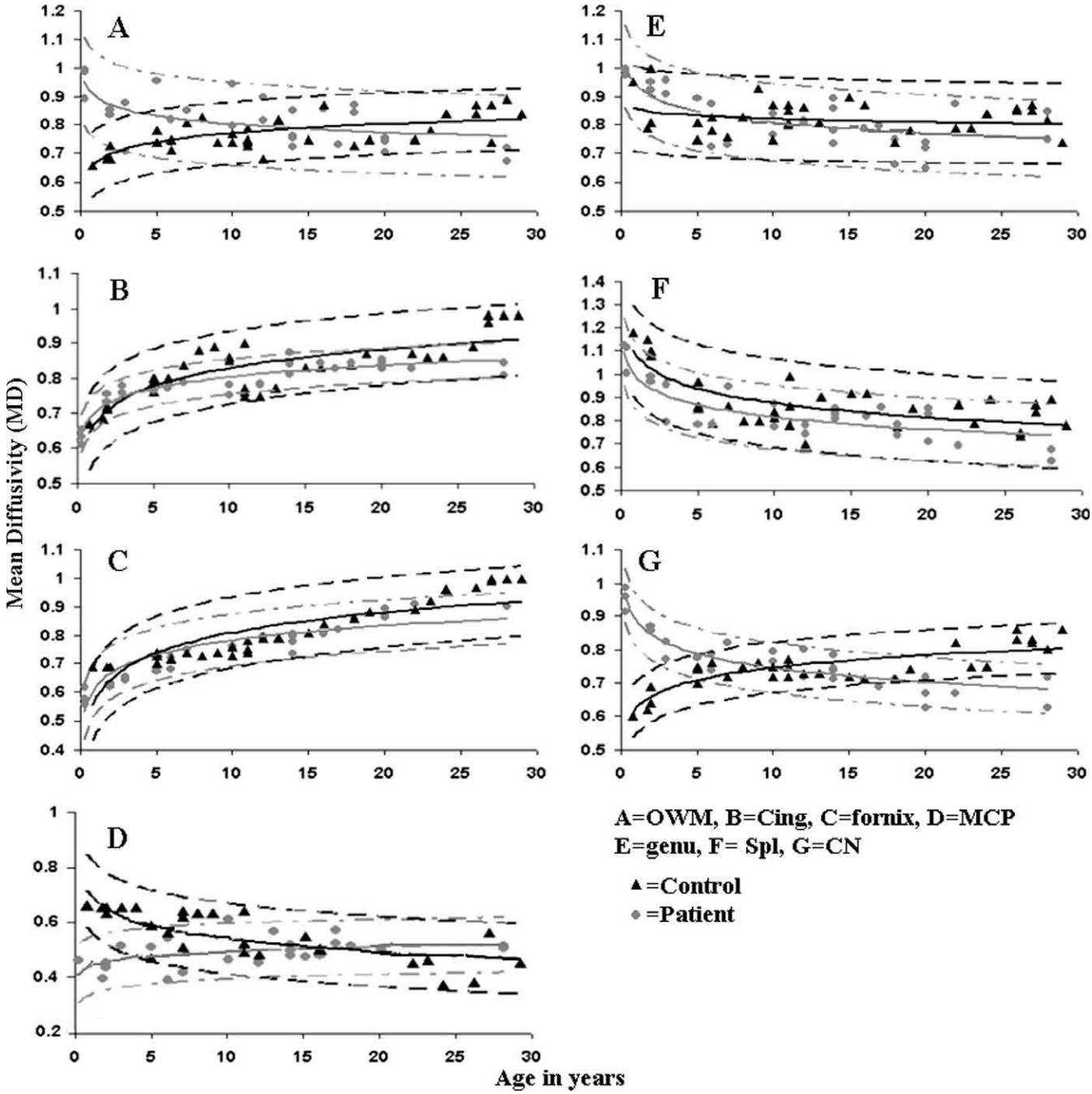

Fig. 3. The relationship between age and mean diffusivity values ($\times 10^{-3}$ mm^2/s) in healthy control participants (black lines; solid triangles) compared to patients with spina bifida cystica (gray lines, solid gray circles) in brain deep gray and white matter regions: (A) occipital white matter; (B) cingulum; (C) fornix; (D) middle cerebellar peduncle; (E) genu; (F) splenium; and (G) caudate nuclei. Scatter plots of raw data showing lines of best fit along and 95% confidence intervals (broken lines) were generated using the log–linear regression model.

were significantly decreased, there were no significant age-related changes in FA values.[29] So far, no DTI-based maturational studies in the MCP in patients with SBC have been performed. The increased FA values in the MCP could have resulted from reduced cerebellar volume, which might have compressed the WM fibers. Juranek et al. have reported anatomically defined regional patterns of thickening or thinning and have discussed their implications for reorganization and lobar reduction of brain volume in patients with SBC.[8]

During WM development, the genu and splenium have different developmental trajectories compared to other brain regions, which probably reflects a different pattern of brain maturation.[30] The posterior CC is selectively prone to injury in patients with SBM due to diffuse CNS injury sustained in life or during gestation.[31,32] Assaf et al. reported that WM compression is secondary to acute hydrocephalus, which results in reduced FA values in the genu.[33] We have observed reduced FA values in the genu and splenium in patients with SBC without hydrocephalus. Factors such as injury to the CC during development, and degenerative changes secondary to abnormal periventricular WM development, might be responsible for these reduced FA values.

Hasan et al. explained increased FA values in the CN in patients with SBM with hydrocephalus as being suggestive of delayed synaptogenesis.[9] However, increased FA values in periventricular WM

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in patients with acute hydrocephalus are due to compression of the periventricular tissue by the dilated ventricles. In the present study, we observed decreased FA values in the CN. This discrepancy in the results might be due to different patient selection between the current study and Hasan et al.[9] The FA values in the present study differ from those of Hasan et al.[9] probably because of a lack of a dilated ventricular system.

The age-dependent decline in MD parallels the rise in FA in major WM tracts.[34] Age-dependent reduction of MD reflects more than just tissue water loss. During development, other factors that influence MD include increased binding of water to macromolecules such as myelin, reduced free-water content, dendritic arborization, synaptogenesis within GM, as well as progressive myelination within WM.[35] We did not find consistent maturational patterns in MD in patients in the present study. FA and MD are theoretically independent of each other: thus, change in one metric is not always accompanied by an opposite change in the other metric.[36] This suggests that FA is a more consistent metric than MD for assessing brain maturation in patients with SBC. However, this study was limited by a lack of longitudinal imaging follow-up and cognitive assessment of these patients.

In conclusion, to our knowledge this is the first study that shows age-related maturational changes in deep GM and WM brain regions in patients with SBC who have normal-appearing brains on conventional MRI compared to healthy controls. These changes that can be observed in the deep GM and WM brain regions using DTI, but not with conventional MRI, might provide the basis for cognitive decline in patients with SBC.

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