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Differences in corpus callosum injury between cerebral concussion and diffuse axonal injury

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Abstract

Background: We investigated differences in corpus callosum (CC) injuries between patients with concussion and those with diffuse axonal injury (DAI) by using diffusion tensor tractography (DTT).

Methods: Twenty-nine patients with concussion, 21 patients with DAI, and 25 control subjects were recruited. We reconstructed the whole CC and 5 regions of the CC after applying Hofer classification (I, II, III, IV, and V). The whole CC and each region of the CC were analyzed to measure DTT parameters (fractional anisotropy [FA], apparent diffusion coefficient [ADC], and fiber number [FN]).

Results: In the whole CC, significant differences were observed in all DTT parameters between the concussion and control groups and the DAI and control groups ($P < .05$). Among the 5 regions of the CC, significant differences were observed in FA and ADC between the concussion and control groups and the DAI and control groups ($P < .05$). Significant differences in FN were observed in CC regions I and II (connected with the prefrontal lobe and secondary motor area) between the concussion and control groups, in CC regions I, II, III, and IV (connected with the frontoparietal lobes) between the DAI and control groups, and in CC regions III, IV (connected with the motor-sensory cortex) between the concussion and DAI groups ($P < .05$).

Conclusion: It was observed that both concussion and DAI patients showed diffuse neural injuries in the whole CC and all 5 regions of the CC. Neural FN results revealed that concussion patients appeared to be specifically injured in the anterior part of the CC connected with the frontal lobe, whereas DAI patients were injured in more diffuse regions connected with whole frontoparietal lobes.

Abbreviations: ADC = apparent diffusion coefficient, ANOVA = analysis of variance, CC = corpus callosum, DAI = diffuse axonal injury, DTI = diffusion tensor imaging, DTT = diffusion tensor tractography, FA = fractional anisotropy, FN = fiber number, LOC = loss of consciousness, MRI = magnetic resonance imaging, TBI = traumatic brain injury.

Keywords: cerebral concussion, corpus callosum, diffuse axonal injury, diffusion tensor tractography, traumatic brain injury

1. Introduction

Cerebral concussion is defined as a transient, temporary, and neurological dysfunction resulting from head injury with temporary loss of brain function.[1] In detail, it is a temporary, reversible neurological deficiency caused by trauma that results in temporary loss of consciousness (LOC) for <6 hours.[2] Diffuse axonal injury (DAI) is a widespread axonal injury caused by the stretching and/or shearing of white matter fibers in the brain, due to the shearing forces associated with acceleration, deceleration, or rotation of the brain.[3–5] It is clinically characterized by prolonged (>6 hours) LOC.[2] Although the classification of concussion and DAI has been based on the duration of LOC, recent many studies have reported on neural injuries in patients with concussion and DAI that were not detected via conventional brain magnetic resonance imaging (MRI).[6–10]

The corpus callosum (CC), which links the left and right cerebral hemispheres, is the largest commissural white matter bundle in the brain.[11–13] A CC injury is a serious concern in traumatic brain injury (TBI) because of the important role of the CC in the inter-hemispheric transfer of cognitive function, working memory, bimanual coordination, and motor function, etc.[14–16] In addition, it is one of the more vulnerable neural structures in the brain after TBI due to its midline location and the high possibility of secondary injury due to elevated intracranial pressure.[9,11,12] However, conventional brain MRI is not sufficiently sensitive to detect CC injury following concussion or DAI.[9,11,16–22]

The introduction of diffusion tensor tractography (DTT), which is derived from diffusion tensor imaging (DTI) results, has enabled three-dimensional reconstruction and assessment of the CC in the human brain. Many studies using DTT have demonstrated CC injuries in patients with various TBI types.[9,11,16–22] However, only a few studies have demonstrated CC injury in concussion or DAI.[9,16–18,21] In addition, little is known about differences in CC injuries between patients with concussion and those with DAI.[11,19,20] In this DTT-based study,

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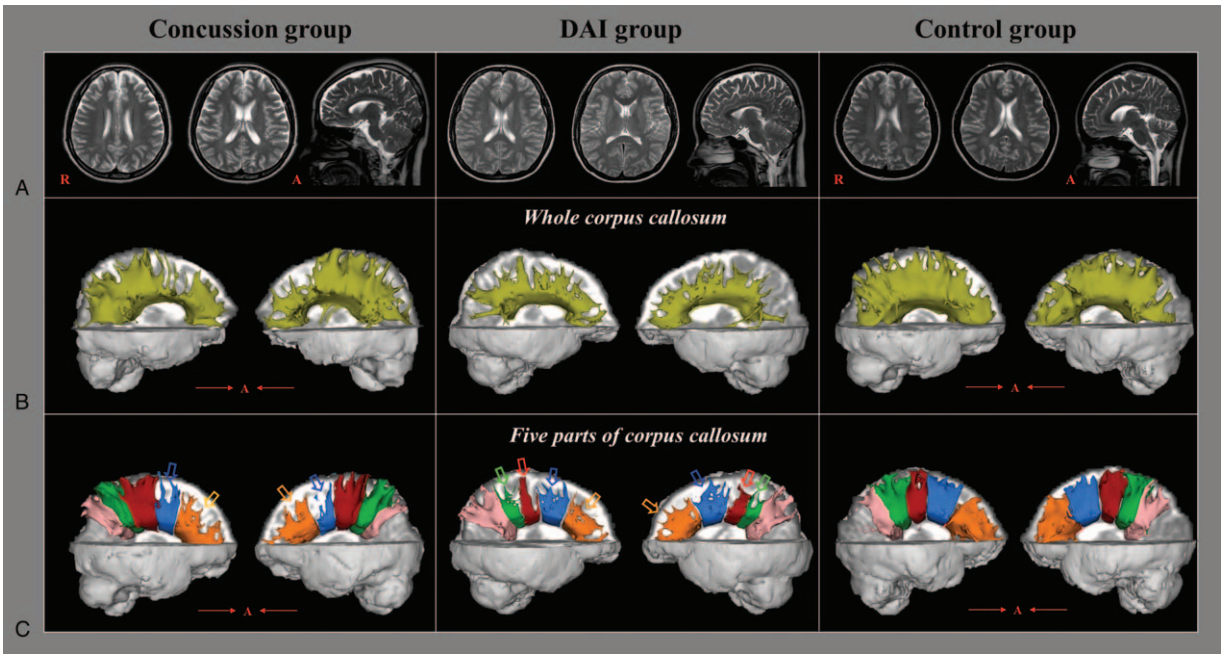

Figure 1. Brain images of a representative patient of each group. (A) T2-weighted brain magnetic resonance images show no abnormality in patients with concussion (43-year-old man, 4 months after onset), diffuse axonal injury (DAI; 47-year-old man, 6 months after onset), and control subject (49-year-old man). (B) Result of diffusion tensor tractography (DTT) for the whole corpus callosum (CC). Decreased tract volume of the whole CC is observed in both concussion and DAI patients. (C) Results of DTT for the 5 regions of the CC. Decreased tract volume is observed at regions I (orange arrow) and II (blue arrow) of the CC in the concussion patient, and at regions I (orange arrow), II (blue arrow), III (red arrow), and IV (green arrow) of the CC in the DAI patient.

we investigated differences in CC injuries between patients with concussion and those with DAI (Fig. 1).

2. Methods

2.1. Subjects

Fifty consecutive patients (24 men, 28 women; mean age 42.91 ± 16.16 years, range 19–65 years) with traumatic brain injury (TBI) who had visited the rehabilitation department of a university hospital and 25 right-handed normal subjects (11 men, 14 women; mean age 39.17 ± 11.64 years, range 21–61 years) were recruited for this study. Patients were recruited consecutively according to the following inclusion criteria: (1) age at the time of head trauma: 19–65 years; (2) no history of previous head trauma, neurologic, or psychiatric disease; (3) >1 month after onset of TBI; (4) no specific brain lesions except for DAI lesion (petechial white matter microhemorrhage or focal areas of gliotic scarring) on conventional MRI.[4,23] The study was conducted retrospectively, and the study protocol was approved by the Institutional Review Board of a university hospital.

The patients with TBI that met the inclusion criteria were classified according to LOC: 29 (58.0%) of the 50 patients (12 men, 17 women; mean age 45.43 ± 11.01 years) belonged to concussion group (i.e., LOC for <6 hours) and 21 (42.0%) of the 50 patients (12 men, 11 women; mean age 40.27 ± 20.14 years) belonged in the DAI group (i.e., LOC for >6 hours).[2]

2.2. Diffusion tensor imaging

DTI data were acquired at an average of 9.13 ± 6.41 months after the onset of TBI by using a 1.5 T Philips Gyroscan Intera (Hoffman-LaRoche, Best, Netherlands) with 32 non-collinear diffusion sensitizing gradients by performing single-shot echo-planar imaging. For each of the 32 non-collinear diffusion sensitizing gradients, 67 contiguous slices were acquired parallel to the anterior commissure–posterior commissure line. Imaging parameters were as follows: acquisition matrix = 96 × 96; reconstructed matrix = 192 × 192; field of view = 221 mm × 221 mm; repetition time = 10,726 ms; Echo time = 76 ms; parallel imaging reduction factor (SENSE factor) = 2; echo-planar imaging factor = 49; $b = 1000\ s/mm^2$; number of excitations = 1; and slice thickness = 2.5 mm with no gap (acquired voxel size 1.25 mm × 1.25 mm × 2.5 mm). The Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (www.fmrib.ox.ac.uk/fsl) was used for analysis of DTI data. Affine multi-scale two-dimensional registration was used for correction of head motion effect and image distortion due to eddy current. FMRIB Diffusion software with the routines option (0.5 mm step lengths, 5000 streamline samples, curvature thresholds = 0.2) was used for fiber tracking.[24]

2.3. Diffusion tensor tractography for reconstruction of corpus callosum

For analysis of the whole CC, the region of interest (ROI) was placed on the CC. In addition, 5 parts of the CC were reconstructed by selecting ROIs based on Hofer classification.[14] The CC regions are as follows: region I—the most anterior segment covers the first sixth of the CC and contains fibers projecting into the prefrontal region; region II—the remaining anterior half of the CC containing fibers projecting to premotor and supplementary motor cortical areas; region III—the posterior half of the CC minus the posterior third, comprising fibers projecting into the primary motor cortex; region IV—the

Table 1

Demographic data of patients with concussion or diffuse axonal injury.

Variables	Concussion group	DAI group
Patients, n (%)	29 (58.0%)	21 (42.0%)
Age, y	45.43 (11.01)	40.27 (20.14)
Sex, male/female	12/17	12/11
Duration to DTI, mo	7.87 (5.86)	10.39 (6.96)
LOC, min/d	8.05 (5.30) (min)	4.56 (5.08) (d)

Values represent mean (±standard deviation). DAI = diffuse axonal injury, DTI = diffusion tensor imaging, LOC = loss of consciousness.

posterior one-third of the CC minus the posterior one-fourth, including primary sensory fibers; region V—the posterior one-fourth of the CC, including temporal and occipital fibers.[14] Fractional anisotropy (FA), apparent diffusion coefficient (ADC), and fiber number (FN) values for the whole CC and the 5 CC regions were obtained.

2.4. Statistical analysis

SPSS software (v. 18.0; SPSS, Chicago, IL) was used for data analysis. One-way analysis of variance (ANOVA) was performed for determination of significant differences in the whole CC and the 5 CC regions for each of the DTT parameters (i.e., FA, ADC, and FN) between the concussion, DAI, and control groups. When using ANOVA, if a significant difference was detected among the 3 groups, a least significant difference post-hoc test was performed to determine significance of differences in the DTT parameters among the 3 groups. Statistical significance was accepted for P values of $<.05$.

3. Results

Demographic data of the concussion and DAI groups are summarized in Table 1. A summary of the comparison of DTT parameters of the whole CC among the 3 study groups is presented in Table 2. Significant differences were observed in all 3 DTT parameters (FA, ADC, and FN) between the concussion and control groups and between the DAI and control groups ($P < .05$). However, there was no significant difference in any of the DTT parameters between the concussion and DAI groups ($P > .05$).

Table 2

Comparison of diffusion tensor tractography parameters for the entire corpus callosum.

	Concussion group	DAI group	Control group
FA	0.41 ± 0.09	0.39 ± 0.08	0.49 ± 0.04
ADC	1.11 ± 0.29	1.16 ± 0.30	0.89 ± 0.06
FN	11080 ± 2909	9815 ± 2674	13085 ± 1760
	FA	**ADC**	**FN**
P-value			
Concussion vs Control	0.00*	0.00*	0.03*
DAI vs Control	0.00*	0.00*	0.01*
Concussion vs DAI	0.29	0.43	0.67

ADC = apparent diffusion coefficient, DAI = diffuse axonal injury, FA = fractional anisotropy, FN = fiber number. ±Standard deviation.
* $P < .05$.

The DTT parameter results for the 5 CC regions in the 3 study groups are shown in Table 3. Significant differences were observed in FA and ADC values in all 5 CC regions between the concussion and control groups and between the DAI and control groups ($P < .05$). However, no significant difference was detected in FA and ADC values in all 5 CC regions between the concussion and DAI groups ($P > .05$). Neural FN values were significantly different in regions I and II between the concussion and control groups, in regions I, II, III, and IV between the DAI and control groups, and in regions III and IV between the concussion and DAI groups ($P < .05$). However, there were no other significant differences in the other regions among the 3 groups ($P > .05$).

4. Discussion

In the current study, by using DTT, we investigated differences in CC injuries by evaluating the whole CC as well as 5 regions of the CC in patients with concussion and DAI. The following results were obtained: regarding the whole CC: decrements in FA and FN values and an increment in ADC were observed in the concussion and DAI groups, respectively, compared with the control group and there was no significant difference in DTT parameters between the concussion and DAI groups; regarding the 5 regions of the CC: in the concussion group, FA decrements, and ADC increments were detected in all 5 regions of the CC compared with the control group, whereas FN decrements were observed in only CC regions I and II compared with the control group; in the DAI group, FA decrements and ADC increments were observed in all 5 regions of the CC compared with the control group, and a FN decrement was observed in regions I, II, III, and IV compared with the control group; and in the comparison between the concussion and DAI groups, FN decrements were found only in regions III and IV in the DAI group compared with the concussion group, with no other significant differences in the other CC regions or other DTT parameters.

FA parameter, which indicates the degree of directionality of water diffusion, represents the degree of directionality and integrity of white matter microstructures, such as axons, myelin, and microtubules, whereas ADC value indicates the magnitude of water diffusion.[25,26] In contrast, FN indicates the existing number of voxels within a neural tract.[25] There were decrements of FA and FN with increments of ADC in the whole CC in the concussion and DAI groups, and decrements of FA with increments of ADC in the all 5 regions of the CC, results that indicate neural injuries of the whole CC and of the 5 regions of the CC, respectively. These results suggest that the CC underwent diffuse injury with the neural injury in the concussion group ascribed to traumatic axonal injury because no specific lesion was observed on conventional brain MRI of these patients.[10,27] However, results indicating no significant difference between the concussion and DAI groups suggest that the injury severity was not different between the concussion and DAI groups. These results are similar to those in a previous study which demonstrated that measurement of DTT parameters for an entire neural tract, especially a large tract such as the uncinate fasciculus, can lead to false negative results because the axonal lesion may be focal or minor compared with the large whole neural tract.[28]

In contrast, decrements of FN in regions I and II in the concussion group, and in regions I, II, III, and IV in the DAI group compared with the control group indicate that the decrement of neural FNs in these regions of the CC than controls. In addition, FN decrements only in regions III and IV in the DAI group indicate a specific decrement of neural FNs in these areas in the

Table 3

Comparison of diffusion tensor tractography parameters for the 5 regions of the corpus callosum.

DTT parameters	R I	R II	R III	R IV	R V
Concussion group					
FA	0.35 (0.08)	0.35 (0.10)	0.35 (0.12)	0.37 (0.09)	0.42 (0.08)
ADC	0.94 (0.12)	1.11 (0.29)	1.16 (0.36)	1.19 (0.38)	1.17 (0.28)
FN	5781 (1138)	3572 (618)	2600 (466)	2775 (874)	4825 (1369)
DAI group					
FA	0.35 (0.06)	0.35 (0.08)	0.35 (0.09)	0.36 (0.07)	0.41 (0.05)
ADC	0.96 (0.11)	1.09 (0.30)	1.17 (0.36)	1.26 (0.41)	1.19 (0.20)
FN	5826 (1613)	3421 (1021)	2119 (688)	2261 (1036)	4502 (1881)
Control group					
FA	0.42 (0.02)	0.43 (0.02)	0.45 (0.02)	0.45 (0.02)	0.49 (0.02)
ADC	0.83 (0.03)	0.89 (0.05)	0.90 (0.05)	0.93 (0.10)	0.91 (0.08)
FN	6704 (964)	4089 (534)	2743 (413)	3186 (725)	5050 (901)

P-value	R I	R II	R III	R IV	R V
FA					
Concussion versus Control	0.00*	0.00*	0.00*	0.00*	0.00*
DAI versus Control	0.00*	0.00*	0.00*	0.00*	0.00*
Concussion versus DAI	0.81	0.92	0.95	0.61	0.92
ADC					
Concussion versus Control	0.00*	0.00*	0.00*	0.00*	0.00*
DAI versus Control	0.00*	0.00*	0.00*	0.00*	0.00*
Concussion versus DAI	0.81	0.56	0.87	0.64	0.98
FN					
Concussion versus Control	0.04*	0.03*	0.04*	0.04*	0.68
DAI versus Control	0.00*	0.00*	0.15	0.17	0.49
Concussion versus DAI	0.24	0.34	0.03*	0.04*	0.77

ADC = apparent diffusion coefficient, DAI = diffuse axonal injury, DTT = diffusion tensor tractography, FA = fractional anisotropy, FN = fiber number, *R* = region. Bracketed numbers: ±standard deviation.
* $P < 0.05$.

DAI group but not in the concussion group. Taken together, the results lead us we conclude that the whole CC and all 5 regions of the CC were injured. However, in terms of the neural FN, the concussion group exhibited specific injuries in the anterior portion of the CC (regions I and II), which is connected with the prefrontal lobe and the secondary motor area, while, in the DAI group, the injuries were in a more diffuse area (regions I, II, III, and IV) connected with the frontoparietal lobes. These results appear to be consistent with those of previous studies showing that concussion patients exhibit clinical features mainly related with prefrontal injury, whereas DAI patients exhibit motor-sensory symptoms as well as prefrontal symptoms.[29–34] According to many previous studies of clinical features of TBI, patients with concussion have been reported to main problems of consciousness was associated with prefrontal injury. However, there have been reports about problems of various clinical symptoms such as motor and sensory as well as problem of consciouness in patients with DAI.[29–35] In addition, in 2011, Browne et al,[36] reported on injury of the mechanism about the DAI. They found that both planes of rotational injury resulted in DAI, characterized by widely disseminated multi-focal axonal pathology throughout the white matter, extending from the frontal lobe to the wide base of white matter such as brainstem and cerebellum.

Many previous studies have reported on CC injury in patients with TBI.[9,11,16–22] Generally, CC injury was reported in concussion or mild TBI patients.[16,21] In 2015, Dean et al[21] investigated differences in white matter changes related to CC injury between 16 patients with mild TBI and 9 patients with post-concussion. They found that injury of splenium of the CC was more associated with post-concussion than with mild TBI. In 2015, Kim et al[16] demonstrated that CC injuries in 14 patients (74%) were located in the anterior two-thirds of the CC (CC regions I, II, III), while CC injuries in 1 patient (5%) and 4 patients (21%) were located in region IV and region V, respectively, among 19 patients with mild TBI. In addition, CC injury has been reported in patients with DAI.[9,17,18] In 2009, Kumar et al[18] demonstrated CC injury of the genu and splenium in 16 patients with chronic DAI. In 2010, Chang and Jang[17] investigated CC injuries by dividing the CC into 6 subdivisions in 20 patients with DAI and found all 6 CC subdivisions showed injury. In 2017, Ljungqvist et al[9] demonstrated that CC injury could be detected at 6 months after onset, and such injury was aggravated until 12 months after onset in 15 patients with DAI. Moreover, differences in the regions of CC injuries were demonstrated to be associated with TBI severity.[11,19,20] In 2008, Rutgers et al[11] reported injury of the genu of the CC showed in 24 patients with mild TBI, and injury of the genu and splenium of the CC in 15 patients with moderate and severe TBI. In 2012, Kasahara et al[19] investigated differences in CC injuries between 10 patients with mild TBI and 5 patients with DAI and found injuries in the body and splenium of the CC in patients with DAI but no CC injury in patients with mild TBI. In 2016, Arenth et al[20] investigated white matter integrity by reconstructing the CC in 12 patients with mild, moderate, or severe TBI. They demonstrated that the CC injuries in the genu and splenium of the CC were related to the severity of TBI. To the best of our knowledge, this is the first study to investigate differences in CC injury between concussion and DAI.

However, some limitations of this study should be considered. First, DTT can produce false negative results throughout the white matter of the brain due to crossing fibers or a partial volume effect. Second, this study was conducted retrospectively, so we were unable to investigate possible correlations of injuries in the 5 CC regions with clinical features. Further prospective studies to clarify this potential association and the rehabilitation effect of the CC alterations should be encouraged. Third, since patients were recruited from those who visited the rehabilitation department of a university hospital, there was a possibility that patients with severe clinical manifestations might be included in this study, as compared with a more general population of patients with TBI. In addition, we recruited consecutively patients with TBI. As a result, the patient groups recruited in this study showed a wide range of ages (range 19–65 years).

In conclusion, we investigated the differences in CC injuries between concussion and DAI patients. The results showed that both concussion and DAI patients exhibit diffuse neural injuries in the whole CC and in all 5 regions of the CC. However, in terms of neural FNs, the concussion patients appeared to be specifically injured in the anterior part of the CC, which is connected with the prefrontal lobe and secondary motor area, whereas the injuries in the DAI patients were in a more diffuse CC area connected with entire frontoparietal lobes.

Author contributions

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