ORIGINAL ARTICLE

Clinical correlates of cerebral diffusion tensor imaging findings in chronic traumatic spinal cord injury

EA Koskinen¹, U Hakulinen^{2,3}, AE Brander², TM Luoto¹, A Ylinen^{4,5} and JE Öhman^{1,6}

Study design: Prospective clinical case–control study.

Objectives: The aim of this study was to use diffusion tensor imaging (DTI) to assess the state of cerebral white matter tracts after spinal cord injury (SCI). The DTI metrics were evaluated in relation to neurological deficits and to the size and level of the spinal cord lesions.

Setting: Tampere University Hospital, Tampere, Finland.

Methods: Thirty-four patients ($n = 34$) with clinically complete and incomplete SCI were evaluated using the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI). DTI metrics (fractional anisotropy (FA) and apparent diffusion coefficient (ADC)) were calculated for multiple levels along the course of the corticospinal tract. The state of the spinal cord after injury was assessed using conventional magnetic resonance imaging (MRI). DTI parameters were compared with 40 orthopedically injured control subjects.

Results: Statistically significant differences in the DTI values between patients and controls were detected in the posterior area of the centrum semiovale. In this area, the FA values were lower in the patients compared with controls ($P = 0.008$). For patients with clinically complete injury, the difference was even more significant ($P = 0.0005$). Motor and sensory scores of the ISNCSCI correlated positively with FA and negatively with ADC values of the centrum semiovale. A moderate association was observed between the macroscopic changes in the spinal cord and the DTI abnormalities in the centrum semiovale.

Conclusion: In patients with chronic SCI, DTI changes can be observed in the cerebral white matter. These alterations are associated with the clinical state of the patients.

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Keywords: traumatic spinal cord injury; magnetic resonance imaging; diffusion tensor imaging; degeneration; cerebral white matter

INTRODUCTION

Spinal cord injury (SCI) causes local destruction of nervous and vascular tissue in the spinal cord, which leads to dramatic changes in motor, sensory and autonomic functions. The neuropathological cascade induced by trauma continues in the subacute phase and can exacerbate the neuronal damage at the site of the primary lesion and in the surrounding area.¹ Anterograde and retrograde degeneration proceed along the spinal white matter tracts, resulting in axonal loss and demyelination.^{2,3} This degeneration has been shown to extend cranially, even to cerebral regions.⁴ In addition, the gray matter volume of the sensorimotor cortex has been shown to decrease after SCI.^{5,6}

Diffusion tensor imaging (DTI), which is a method that measures the diffusion of water molecules in tissues, provides quantitative information about tissue microstructure. Among the parameters derived from DTI data, the apparent diffusion coefficient (ADC) or the mean diffusivity (MD) express the magnitude of the diffusion, and the fractional anisotropy (FA) describes the ease of water moving in one direction/degree of anisotropy of the diffusion.^{7,8} In nervous tissue, the orientation of fiber bundles and the axonal diameter, density and myelination have an effect on DTI metrics.^{9,10}

Numerous studies have demonstrated the ability of DTI to detect abnormalities in the spinal cord parenchyma, even in regions that are remote from the macroscopic lesions observed on conventional MRI scans. These results suggest secondary degeneration of the white matter tracts in the spinal cord.^{11–13} Previously, abnormalities in DTI values of the cerebral corticospinal tract after SCI have also been reported. However, these studies consisted of relatively small samples and primarily included subjects with complete SCI.^{5,14,15}

The purpose of this study was to quantitatively assess the state of the cerebral white matter tracts in chronic traumatic SCI using DTI in a generalizable sample of patients with both clinically complete and incomplete SCI. We also investigated the association of DTI values with clinical neurological deficit. Finally, the consequence of injury to the spinal cord was assessed using conventional MRI and the findings were correlated with cerebral DTI values.

MATERIALS AND METHODS

Study framework and statement of ethics

This study is part of the Spinal Cord Injury Series of Tampere-Retroprospective Study. The study aims to examine SCI from a multidisciplinary perspective, in a case–control setting, to enhance the clinical assessment and treatment of this

¹Department of Neuroscience and Rehabilitation, Tampere University Hospital, Tampere, Finland; ²Department of Radiology, Medical Imaging Centre of Pirkanmaa Hospital District, Tampere, Finland; ³Department of Electronics and Communications Engineering, Tampere University of Technology, Tampere, Finland; ⁴Department of Neurological Sciences, University of Helsinki, Helsinki, Finland; ⁵Department of Neurology, Helsinki University Central Hospital, Helsinki, Finland and ⁶School of Medicine, University of Tampere, Tampere, Finland

Correspondence: Dr EA Koskinen, Department of Neurosciences and Rehabilitation, Tampere University Hospital, PL 2000, Tampere 33521, Finland.

E-mail: eerika.koskinen@uta.fi

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specific patient group. The ethics approval for the study was obtained from the Ethical Committee of Pirkanmaa Hospital District, Finland. A written informed consent was obtained from each participant. We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during the course of this research.

Subjects

All consecutive patients with a chronic traumatic cervical spine injury ($n = 88$) who were admitted to either the ward or an outpatient clinic in Tampere University Hospital between 1989 and 2010 were contacted for participation in the study in 2011. The inclusion criteria were as follows: (i) age over 18 years, (ii) resident of the hospital district, (iii) clinically significant neurological findings due to a traumatic cervical spinal cord injury after 24 h of monitoring in the hospital and/or (iv) time since injury was greater than 1 year. The exclusion criteria were as follows: (i) known neurological illness other than spinal cord injury, (ii) respiratory arrest, (iii) contraindications to MRI and/or (iv) refusal to participate in the study. The final SCI population sample consisted of 34 patients. The main reason for exclusion was refusal to participate in the study ($n = 17$).

Patients with SCI were compared with an orthopedically injured control sample of 40 neurologically intact subjects. The control subjects were recruited from consecutive patients with ankle trauma from the Emergency Department of Tampere University Hospital. A total of 609 patients with ankle injury were screened for participation. The aim was to enroll five male and five female subjects into each of following age groups: (i) 18–30, (ii) 31–40, (iii) 41–50 and (iv) 51–60 years. The inclusion criteria were as follows: (i) age 18–60 years, (ii) being a resident of the University Hospital district and (iii) ankle trauma. The exclusion criteria were as follows: (i) neurological problems, (ii) psychiatric problems, (iii) history of traumatic brain injury, (iv) former neurosurgical procedure, (v) problems with hearing or vision, (vi) first language other than Finnish, (vii) contraindications to MRI and (viii) refusal to participate. In our future studies, we are planning to examine the possible confounding effects of trauma-induced psychological stress on neuropsychological performance. Therefore, orthopedic controls were used instead of healthy volunteers.

Collection of clinical data and neurological scoring

All patients with SCI were examined at an outpatient clinic in Tampere University Hospital. The collection of clinical data was performed by the first author of this study. The etiology of the spinal cord injury was classified using the International SCI Core Data Set.¹⁶ The International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) was used to evaluate and classify the neurological consequence of spinal cord injury.¹⁷ The level of disability was assessed using the motor subscale of the Functional Independence Measure.^{18,19}

The medical condition of the subjects was assessed according to the International Classification of Diseases and Related Health Problems 10th revision (ICD –10).²⁰ The Basic Pain Data Set was used to collect data from patients who suffered from neuropathic pain related to the SCI.²¹ Information on the current medication at the time of examination was classified into 17 subgroups according to the Finnish Commercial Drug Catalog (Pharmaca Fennica), which was categorized on the basis of the World Health Organization's Anatomical Therapeutic Chemical (ATC) Classification System codes.

Magnetic resonance imaging (MRI)

The MRI examinations of the brain and spinal cord were performed using a 3T MRI scanner (Siemens Trio, Siemens Medical Solutions, Erlangen, Germany). A 12-channel head coil and a 4-channel neck coil were used simultaneously.

The spinal cord series included a sagittal T2 turbo spin echo (TR 3500 ms, TE 108 ms, flip angle 160°, 1 Average, FOV 280, Matrix 288 × 384, slice/gap 3.0/0.3 mm, ETL 34), and an axial T2*-weighted multi-gradient echo combination series (TR 506 ms, TE 14 ms, flip angle 30°, 1 Average, FOV 160 mm, Matrix 256 × 256, slice/gap 3.0/0.3 mm) was acquired. The voxel size of the T2* images was 0.6 × 0.6 × 3.0 mm.

The MRI protocol of the brain included a sagittal T1-weighted series (TR 750 ms, TE 7.3 ms, slice/gap 5.0/1.5 mm, FOV 220), an axial T1 series (TR 600 ms, TE 6.8 ms, slice/gap 4.0/1.2 mm, FOV 220), an axial T2 turbo spin echo series (TR 5600 ms, TE 109 ms, flip angle 120°, slice/gap 4.0/1.2 mm, FOV 220), an axial FLAIR (TR 5500 ms, TE 87 ms, TI 1922 ms, flip angle 150°, slice/gap 4.0/1.2 mm, FOV 220), a coronal T2 turbo spin echo series (TR 5990, TE 109, flip angle 120°, FOV 220 slice/gap 3.0/0.6 mm) and an axial susceptibility-weighted (SWI) series (TR 27, TE 20, flip angle 15°, slice 1.5 mm, FOV 230). The parameters for the DTI sequence of the brain were TR 5144 ms, TE 92 ms, FOV 230, matrix 128 × 128, 3 averages, slice/gap 3.0/0.9 mm, b-factor 0 and 1000 s mm⁻² and 20 diffusion gradient orientations.

Interpretation of the imaging findings on the conventional MRI scans was performed by a neuroradiologist (AEB).

DTI analysis

DTI measurements were performed by a physicist (UH) on a workstation using the commercially available software Neuro3D (Siemens Healthcare, Malvern, PA, USA).

Circular regions of interest (ROI; 19 mm²) were manually placed on color-coded axial FA maps of the brain. The ROIs were placed at the following anatomical locations (Figure 1): (i) the cerebral peduncle, (ii) the posterior limb of the internal capsule (PLIC) (anterior and posterior), (iii) the posterior part of the corona radiata (anterior and posterior) and (iv) the centrum semiovale (anterior, center and posterior). The ROIs were placed carefully to avoid border areas, such as areas overlapping with cerebrospinal fluid spaces and neighboring tracts. The ROIs were placed bilaterally on all locations, and DTI metrics from left and right structures were averaged per level measured. Median values, mean values and s.d. for FA and ADC were calculated.

Signal-to-noise ratio (SNR) was determined according to the NEMA Standards 1–2008, including the following expression for SNR: $SNR = \frac{S}{\text{image_noise}}$, where S = signal, and image noise is estimated with Rayleigh distribution: $\text{image_noise} = \frac{s.d.}{0.66}$. The SNR measurements were used from the images of three healthy subjects. The ROI was placed on the left side of each region of the $b = 0$ s mm⁻² image.

Statistical analyses

Patients with SCI were not gender-matched or age-matched with the control subjects; therefore, the analyses were performed using linear regression adjusted for age and gender. Correlations were calculated by partial correlation, with age and gender as the controlling factors. The clinical variables used in the correlations were the ISNCSCI-derived total motor score, motor subscore for upper and lower extremities, total sensory score and single neurological level. DTI values were correlated with the most cranial level of the spinal cord lesion and with the length of the lesion assessed by conventional MRI. To correlate the single neurological level and the most cranial level of the lesion with DTI values, each vertebral level was sequentially numbered in the cranio-caudal direction. For further comparisons, the patient population was divided into two groups according to the completeness of the injury: AIS A and AIS B–E. All parameters were ranked before the analyses. Because of multiple comparisons, the statistical significance level was set at 1%. The intra-observer repeatability (intra-class correlation coefficient or ICC) and variability (coefficient of variation, or CV%) were assessed for FA and ADC values measured from healthy volunteers. The statistical analyses were performed under the guidance of a biostatistician. The SPSS program (IBM SPSS Statistics for Windows, Version 20.0, Armonk, NY, IBM Corp.) was used to perform all statistical analyses.

RESULTS

Clinical findings

Clinical characteristics of the 34 SCI patients (whole group, AIS A and AIS B–E) and 40 control subjects are shown in Table 1. Of the patients with SCI, 18 (52.9%) patients had some chronic medical problems. The most common chronic medical problem was disease of the circulatory system ($n = 9$, 26.5%) and disease of the musculoskeletal system and connective tissue ($n = 7$, 20.6%). Twenty-eight (82.4%)

Figure 1 The placement of the ROIs on the color-coded FA maps: (a) cerebral peduncle, (b) posterior limb of the internal capsule, (c) posterior part of the corona radiata and (d) centrum semiovale.

patients used some permanent medication; 15 (44.1%) patients used some pain medication; 12 (35.3%) patients used a prophylactic antibiotic; 9 (26.5%) patients used drugs for the cardiovascular system; and 13 (38.2%) patients used muscle relaxants. Thirteen (38.2%) patients with SCI suffered from neuropathic pain.

Eighteen (45.0%) of the control subjects demonstrated a diagnosed disease. Six of the patients had a disease of the circulatory system (15.0%) and 4 (10.0%) patients had disease of the musculoskeletal system and connective tissue. Thirteen (32.5%) control subjects used some permanent medication. The most prevalent group used drugs for the cardiovascular system ($n=6$, 15.0%). There were no control subjects who showed neuropathic pain.

Conventional MRI findings

Twenty-nine (85.3%) patients with clinically defined spinal cord injury had a focal post-traumatic cord lesion on either the sagittal or axial T2/T2* images. Five (17.2%) patients had two separate lesions. Five patients (14.7%) had no visible spinal cord lesions. The mean craniocaudal length of the main lesion was 18.3 mm (s.d. ± 14.4). The most cranial borders of the main lesions were located between levels C2 and C6. Spinal cord atrophy was found in 21 (61.8%) patients.

In the patients with no post-traumatic cord lesions, the average time between the SCI and MRI was 2.8 years (s.d. ± 2.2), the mean ISNCSCI motor score was 93.2 (s.d. ± 6.4) and sensory score was

192.0 (s.d. ± 28.5). In turn, in the patients with spinal cord atrophy, the time since injury was 14.3 years (s.d. ± 11.4), the ISNCSCI motor score was 50.0 (s.d. ± 31.3) and sensory score was 100.7 (s.d. ± 60.6).

Four (11.8%) patients had moderate to severe cerebral microangiopathy. One (2.9%) patient had lacunar ischemic lesions (size < 1 cm) in both cerebellar hemispheres, and one (2.9%) patient had a trigeminal schwannoma. Eleven (32.4%) SCI patients had single diffuse axonal injury (DAI) -type microhemorrhage, and three (8.8%) subjects had between two and five separate DAI lesions. Eight (23.5%) patients had an old post-traumatic parenchymal lesion, four of which were under 1 cm and four of which were 1–2 cm in diameter. Thirteen (38.2%) patients had between one and ten punctate white matter hyperintensities, and seven (20.6%) patients had more than ten punctate white matter hyperintensities. Patients with the above-mentioned abnormalities in conventional brain imaging sequences were not excluded because the abnormalities were considered ordinary for the patient and for the age groups in question and, except for microangiopathy, the abnormalities were not located in the area of ROI measurements.

None of the control subjects had significant structural abnormalities on conventional MRI scans.

Relationship between clinical variables and cerebral DTI metrics

Table 2 summarizes the measured FA and ADC values. Controls were compared with the entire group of patients with SCI and to the AIS A

Table 1 Clinical characteristics of SCI patients (entire group, AIS A and AIS B–E) and control subjects

	Controls (n = 40)	Patients (n = 34)	AIS A (n = 10)	AIS B–E (n = 24)
Age (years)	40.6 ± 12.2	57.5 ± 14.5	51.3 ± 15.7	60.1 ± 13.4
Gender (male/female)	20/20	27/7	7/3	20/4
Time since injury (mean ± s.d.)		13.9 ± 12.1	23.5 ± 13.1	9.9 ± 9.3
Median (range)		(8.8, 1.0–43.1)	(23.4, 6.4–38.2)	(6.8, 1.0–43.1)
<i>Injury etiology</i>				
Sports		6 (17.6%)	2 (20%)	4 (16.7%)
Assault		1 (2.9%)		1 (4.2%)
Transport		12 (35.3%)	5 (50%)	7 (29.2%)
Fall		13 (38.2%)	3 (30%)	10 (41.7%)
Other traumatic cause		2 (5.9%)		2 (8.3%)
<i>ASIA impairment scale (AIS)</i>				
AIS A		10 (29.4%)		
AIS B		1 (2.9%)		
AIS C		4 (11.8%)		
AIS D		18 (52.9%)		
AIS E		1 (2.9%)		
<i>ISNCSCI single neurological level</i>				
C1		2 (6.1%)		
C2		4 (12.1%)		
C3		5 (15.2%)		
C4		11 (33.3%)		
C5		5 (15.2%)		
C6		1 (3.0%)		
C7		1 (3.0%)		
C8		3 (9.1%)		
T11		1 (3.0%)		
ISNCSCI motor score (max. 100)		63.4 ± 33.8	20.4 ± 15.5	81.3 ± 20.1
ISNCSCI sensory score (max. 224)		123.5 ± 65.1	42.0 ± 16.8	160.6 ± 39.0
FIM physical subscore (max. 91)		65.8 ± 28.6	41.1 ± 28.3	76.0 ± 22.0

Abbreviations: ASIA, American Spinal Injury Association; AIS A, motor-sensory complete; AIS B, motor complete-sensory incomplete; AIS C–D, motor-sensory incomplete; AIS E, normal examination; ISNCSCI, International Standards for Neurological Classification of Spinal Cord Injury; FIM, Functional Independence Measure.

and AIS B–E subgroups. A comparison between the AIS A and AIS B–E subgroups was performed. Patients with SCI had lower FA values in the posterior ROIs of the centrum semiovale compared with the controls. In the patient group with clinically complete injury, the ADC values of the posterior centrum semiovale were higher and the FA values of the cerebral peduncle were lower than those of the healthy controls, although these differences did not reach statistical significance.

Partial correlations (age and gender as controlling factors) between cerebral DTI values and the clinical findings (ISNCSCI and MRI findings of the spinal cord lesion) are presented in Table 3. The FA values of the PLIC were moderately and positively associated with the motor score of the upper extremities and the total sensory score derived from the ISNCSCI and with the cranial level of the lesion in the conventional MRI. In the posterior part of the centrum semiovale, the FA values correlated moderately and positively and the ADC values correlated moderately and negatively with the motor and sensory scores of the ISNCSCI. In addition, the ADC values in the posterior part of the centrum semiovale were positively associated with the lesion length in the conventional MRI.

DTI values were not statistically associated with the time since injury.

SNR analysis

The mean SNR value ($\pm$ s.d.) of $b = 0 \text{ s mm}^{-2}$ images for the all regions *in vivo* measurements was 30.5 ± 3.6 (range 26.8–36.2).

Intra-observer repeatability and variability of DTI measurements

The ICC results for FA and ADC were between 0.40 and 0.88 (mean 0.67) and 0.58 and 0.85 (mean 0.72), respectively, and 75.0% of the ICCs for FA and 93.8% for ADC were over 0.6. The CV% for FA and ADC varied between 3.8% and 20.3% and 3.0% and 13.3%, respectively. The CV% values were below 10% in 37.5% of the FA and 93.7% of the ADC measurements.

DISCUSSION

The primary aim of this study was to quantitatively assess the state of cerebral white matter tracts of patients with chronic traumatic SCI by using DTI. In our study, statistically significant differences in DTI parameters between SCI patients and controls were detected only in the posterior area of the centrum semiovale, which approximately reflects the white matter in the subcortical area of the sensory-motor cortex. The associations of DTI values with clinical variables indicating SCI-related deficiencies were focused on the corresponding area. The minor findings in the cerebral peduncle and the PLIC suggest that the white matter tracts in those structures may be affected by SCI.

Few reports about the diffusion properties of the spinal cord in the chronic state of the injury have been published in the literature.^{11–13} In those studies, DTI has been shown to estimate the total lesion load in the spinal cord better than conventional MRI. FA values have been proven to diminish in areas of the intact upper spinal cord after injury. Hypothetically, diminishing FA values reflects anterograde and retrograde degeneration of the white matter tracts.³ Histologically, axonal loss, demyelination, gliosis, astrocytic scarring and an increase in the extracellular matrix are found in secondary degeneration of the white matter tracts.² From a DTI perspective, a decreased FA and an increased ADC or MD are associated with the aforementioned neuropathological changes.²²

Currently, reports studying changes in the cerebral white matter tracts after SCI in humans are relatively sparse. Yamamoto *et al.*⁴ observed histological evidence of retrograde degeneration after SCI in supraspinal areas reaching as high as the pons. In a study by Guleria *et al.*,¹⁴ alterations in DTI metrics suggesting retrograde degeneration after SCI were shown along the corticospinal tract in the medulla, pons, midbrain and PLIC. Freund *et al.*¹⁵ observed a reduction in the FA in patients with SCI in the pyramids and the PLIC. Although there were no significant differences in FA values at the level of the cerebral peduncles, axonal degeneration and demyelination-related alterations in directional diffusivities were noted. In a tractography study by Wrigley *et al.*,⁵ the corticospinal tract revealed changes in DTI metrics, which were indicative of fiber loss.

We did not find any statistically significant differences between the DTI values of patients and controls in the area of cerebral peduncles,

which simply conveys motor information. However, the FA values appeared to be lower in patients with a complete SCI compared with the controls.

The majority of connections between the motor and sensory primary and supplementary cerebral cortex and subcortical structures travel through the PLIC and the posterior part of the corona radiata.^{23,24} We did not find any significant differences in the DTI metrics between SCI patients and controls in these structures. Freund *et al.*¹⁴ and Guleria *et al.*¹⁵ showed reduced FA values but unchanged MDs in the PLIC after SCI compared with healthy subjects. Guleria *et al.*¹⁵ reported a progressive increase in the FA values in the PLIC and corona radiata up to 12 months after injury. FA values in the corona radiata were eventually higher in subjects with SCI compared with the controls. They suggested that the increase in the FA values could be related to structural alterations of compensatory subcortical regeneration. In our sample, the FA values of the PLIC were moderately related to some clinical variables and tended to increase, especially with better sensory function. It can be hypothesized that in our patient population, the white matter tracts in the PLIC may also be affected by SCI.

In our study, the significant differences in DTI values between the patients and controls were focused on the posterior ROIs of the centrum semiovale. In this area, the FA values were significantly lower in the patients, especially in the patients with complete injury, compared with the controls. The ADC of the patients with complete injury was higher than the control values, although not reaching statistical significance. The posterior ROIs were located in approximately the same area where motor corticospinal and sensory

Table 2 Diffusion tensor imaging parameters in patients with SCI and control subjects

	Controls (N = 40)		Patients (N = 34)			AIS A (n = 10)			AIS B–E (n = 24)			P-value, AIS A vs AIS B–E
	Med	Mean ± s.d.	Med	Mean ± s.d.	P-value	Med	Mean ± s.d.	P-value	Med	Mean ± s.d.	P-value	
Cerebral peduncle												
FA	0.79	0.80 ± 0.04	0.78	0.78 ± 0.06	0.175	0.74	0.74 ± 0.06	0.036*	0.78	0.79 ± 0.05	0.996	0.093
ADC	0.75	0.75 ± 0.05	0.75	0.76 ± 0.06	0.048	0.77	0.77 ± 0.07	0.156	0.75	0.75 ± 0.05	0.050	0.562
Posterior limb of the internal capsule												
Anterior FA	0.70	0.70 ± 0.04	0.70	0.70 ± 0.04	0.830	0.70	0.69 ± 0.02	0.406	0.71	0.71 ± 0.04	0.375	0.171
Anterior ADC	0.71	0.71 ± 0.03	0.69	0.70 ± 0.04	0.496	0.69	0.70 ± 0.02	0.830	0.69	0.70 ± 0.04	0.478	0.633
Posterior FA	0.71	0.70 ± 0.04	0.72	0.72 ± 0.04	0.074	0.72	0.71 ± 0.04	0.116	0.73	0.72 ± 0.04	0.083	0.855
Posterior ADC	0.71	0.71 ± 0.02	0.70	0.70 ± 0.03	0.600	0.70	0.70 ± 0.02	0.286	0.71	0.71 ± 0.03	0.788	0.575
Posterior part of the corona radiata												
Anterior FA	0.47	0.48 ± 0.07	0.48	0.48 ± 0.06	0.496	0.48	0.48 ± 0.04	0.711	0.48	0.48 ± 0.07	0.496	0.665
Anterior ADC	0.67	0.67 ± 0.05	0.71	0.72 ± 0.06	0.195	0.69	0.70 ± 0.05	0.232	0.72	0.73 ± 0.07	0.374	0.729
Posterior FA	0.53	0.53 ± 0.06	0.54	0.53 ± 0.08	0.768	0.54	0.52 ± 0.08	0.909	0.53	0.53 ± 0.08	0.832	0.805
Posterior ADC	0.71	0.72 ± 0.04	0.73	0.73 ± 0.04	0.249	0.71	0.72 ± 0.03	0.420	0.73	0.73 ± 0.05	0.494	0.704
Centrum semiovale												
Anterior FA	0.61	0.62 ± 0.06	0.57	0.57 ± 0.09	0.483	0.58	0.57 ± 0.06	0.067	0.55	0.57 ± 0.10	0.959	0.463
Anterior ADC	0.71	0.72 ± 0.04	0.73	0.74 ± 0.06	0.547	0.72	0.73 ± 0.04	0.465	0.74	0.75 ± 0.07	0.668	0.781
Central FA	0.60	0.60 ± 0.08	0.61	0.60 ± 0.07	0.270	0.60	0.59 ± 0.07	0.937	0.61	0.60 ± 0.07	0.138	0.267
Central ADC	0.72	0.72 ± 0.04	0.72	0.74 ± 0.07	0.967	0.71	0.72 ± 0.06	0.646	0.73	0.75 ± 0.07	0.531	0.597
Posterior FA	0.56	0.57 ± 0.05	0.52	0.52 ± 0.06	0.008**	0.50	0.48 ± 0.08	0.000**	0.52	0.53 ± 0.05	0.352	0.013*
Posterior ADC	0.72	0.73 ± 0.04	0.74	0.75 ± 0.06	0.465	0.76	0.78 ± 0.09	0.023*	0.73	0.74 ± 0.04	0.491	0.025*

Abbreviations: ADC, apparent diffusion coefficient; AIS, American Spinal Injury Association impairment scale; AIS A, motor-sensory complete; AIS B, motor complete; AIS C–D, motor-sensory incomplete; AIS E, normal; FA, fractional anisotropy; Med, Median.

Comparisons adjusted with age and gender by linear regression.

ADC ($\times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$).

* $P < 0.05$ in bold, ** $P < 0.01$ in bold.

Table 3 Partial correlations (age and gender as controlling factors) between cerebral DTI values and clinical findings

Brain DTI values	ISNCSCI parameters					Spinal cord MRI	
	Mtot	Mue	Mle	Stot ^a	NL	CL ^b	LL ^b
<i>Cerebral peduncle</i>							
FA	—	—	—	—	—	—	—
ADC	—	—	—	—	—	—	—
<i>PLIC</i>							
Anterior FA	—	0.414*	—	0.493**	—	0.456*	—
Anterior ADC	—	—	—	—	—	—	—
Posterior FA	—	—	—	—	—	—	—
Posterior ADC	—	—	—	—	—	—	—
<i>Corona radiata</i>							
Anterior FA	—	—	—	—	—	—	—
Anterior ADC	—	—	—	—	—	—	—
Posterior FA	—	—	—	—	—	—	—
Posterior ADC	—	—	—	—	—	—	—
<i>Centrum semiovale</i>							
Anterior FA	—	—	—	—	—	—	—
Anterior ADC	—	—	—	—	—	—	—
Central FA	—	—	—	—	0.411*	—	—
Central ADC	—	—	—	—	—	—	—
Posterior FA	0.426*	0.460**	—	0.482**	—	—	—
Posterior ADC	−0.425*	−0.505**	—	−0.554**	—	—	0.493**

Abbreviations: ADC, apparent diffusion coefficient; CL, cranial level of lesion in conventional MRI; DTI, diffusion tensor imaging; FA, fractional anisotropy; ISNCSCI, International Standards for Neurological Classification of Spinal Cord Injury; LL, lesion length; MRI, magnetic resonance imaging; Mtot, total motor score; Mue, motor score of the upper extremities; Mle, motor score of the lower extremities; NL, single neurological level; PLIC, posterior limb of internal capsule; Stot, total sensory score.

* $P < 0.05$.

** $P < 0.01$ in bold.

^a $n = 32$.

^b $n = 29$.

thalamocortical projections pass through the white matter area directly below the cortex.^{25,26}

The motor and sensory scores of the ISNCSCI were positively related to the FA values and negatively related to the ADC values in the posterior part of the centrum semiovale. These findings suggest that the clinical state of the patient tends to be better with higher FA values and lower ADC values. Recently, the relationship between spinal DTI values and ISNCSCI scores has been reported in chronic SCI patients.^{12,27} To the best of our knowledge, this is the first study concerning cerebral sensory-motor white matter tracts in which the association of DTI values to the neurological deficit of patients with SCI has been demonstrated.

In our study, no statistically significant correlation was found between DTI values and time since injury. This finding is in agreement with previous studies.^{5,15}

There was a moderate association between macroscopic post-traumatic changes in the spinal cord and microstructural changes in the centrum semiovale. An increase in ADC in the posterior part of the centrum semiovale was positively correlated with the craniocaudal length of the spinal cord lesion. Only Freund *et al.*¹⁵ have previously demonstrated a relationship between the peripheral macrostructural effects of SCI and the cerebral DTI values. In their study, one of the directional diffusivities, the radial diffusivity, in the right cerebral peduncle correlated negatively with the cross-sectional area of the spinal cord after injury.

Strength of our study was that the patient sample included SCI patients with a wide range of neurological deficits and disabilities.

This design provided us the possibility to examine DTI findings in relation to the completeness of the SCI. Our study sample was substantially larger than in previous studies, and a detailed data collection was performed.

Taking into account the repeatability of the measurements, the vast majority of the ICCs for FA and ADC were over 0.6 indicating at least substantial agreement.²⁸ In turn, the SNR was very well above 20 in all regions, which is considered to enable the measurement of reliable DTI values.²⁹

Despite the detailed data collection and design, our study has several considerable limitations. To best of our knowledge, the patients with known neurological diseases, which could potentially have a confounding effect on cerebral DTI values, were excluded. However, some patients were injured over thirty years ago. Thus, the clinical information collected from the medical records of these patients cannot be considered as accurate as in the more modern records. For example, there is a high probability that our patient population includes subjects with undiagnosed TBI. In the literature, up to 70% of patients with traumatic SCI have been reported to have concomitant TBI,³⁰ and mild TBI has also been shown to cause DTI changes in the white matter.³¹ Our sample includes few subjects with moderate to severe microangiopathy, which could also have an effect on DTI values. Another weakness was that the SCI patients and controls were not age- or gender- matched. The possible confounding effects of age and gender³² were addressed with statistical methods. Lastly, the ROI method that we used did not allow us to separate the motor and sensory tracts. The measurements could represent different

white matter tracts in individual subjects, complicating the interpretation of the results. The small circular ROIs represent only a small sample of the larger tracts, and it is possible that the pathological changes were outside of the measurement area.

CONCLUSION

Patients with chronic SCI have considerable DTI changes in the posterior area of the centrum semiovale. Cerebral microstructural changes detected by DTI are linked to the completeness of the injury and reflect the motor and sensory scores measured by the ISNCSCI. Macroscopic lesions in the spinal cord, visualized on conventional MRI, are associated with DTI abnormalities in the centrum semiovale.

DATA ARCHIVING

There were no data to deposit.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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