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Diagnostic sensitivity of traumatic axonal injury of the spinothalamic tract in patients with mild traumatic brain injury

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Abstract

Diffusion tensor tractography (DTT) can detect traumatic axonal injury (TAI) in patients whose conventional brain magnetic resonance imaging results are negative. This study investigated the diagnostic sensitivity of TAI of the spinothalamic tract (STT) in patients with a mild traumatic brain injury (TBI) suffering from central pain symptoms, using DTT.

Thirty-five patients with central pain following mild TBI and 30 healthy control subjects were recruited for this study. After DTT-based reconstruction of the STT, we analyzed the STT in terms of configuration (narrowing and/or tearing) and the DTT parameters (fractional anisotropy and tract volume).

Thirty-three (94.3%) patients had at least 1 DTT parameter value at 1 standard deviation below the control group value, and 20 (57.1%) patients had values at 2 standard deviations, below the control group value. All 35 patients showed STT abnormalities (tearing, narrowing, or both) on DTT.

A high diagnostic sensitivity of TAI of the STT in patients with mild TBI was achieved. However, the small number of subjects who visited the university hospital and the limitations of DTT should be considered when generalizing the results of this study.

Abbreviations: DTI = diffusion tensor imaging, DTT = diffusion tensor tractography, FA = fractional anisotropy, MRI = magnetic resonance imaging, ROI = region of interest, SD = standard deviation, STT = spinothalamic tract, TAI = traumatic axonal injury, TBI = traumatic brain injury, TV = tract volume, VAS = visual analogue scale.

Keywords: diffusion tensor tractography, mild traumatic brain injury, sensitivity, spinothalamic tract

1. Introduction

Traumatic brain injury (TBI) is a major cause of neurological disability in adults, and 70% to 90% TBI patients are classified as mild TBI.[1] In addition, diffusion axonal injury is the predominant mechanism of TBI caused by shearing forces by acceleration, deceleration, or rotation of the brain.[2,3] TBI causes widespread microscopic axonal damage at the border between the gray and white matter, such as the corpus callosum, brainstem, and cerebellum.[3–5] Chronic pain is a common sequela of mild TBI, with an up to 75% prevalence.[6,7] Various pathophysiologic mechanisms of chronic pain in patients with mild TBI have been suggested, with central pain caused by brain injury being a major pathophysiological mechanism.[8–18] The precise diagnosis of central pain is clinically important because its management and prognosis differ remarkably from pain attributed to other pathophysiological mechanisms.[18] In particular, diagnostic precision is important for patients with mild TBI whose conventional brain computed tomography or magnetic resonance imaging (MRI) results are negative.[19–21]

The spinothalamic tract (STT) is a sensory pathway that projects to several cortices, such as the primary somatosensory cortex, mid-cingulate cortex, and supplementary motor area via various thalamic regions, including the ventro-postero-lateral nucleus and pulvinar nucleus and it is responsible for touch, temperature, and pain.[22–24] In detail, the pulvinar nucleus connects to the sensory cortex, superior colliculus, primary visual cortex, and amygdala and is related to pain modulation.[24–26] After introducing diffusion tensor imaging (DTI), several studies using diffusion tensor tractography (DTT), which is used to reconstruct neural tract images from DTI data, have demonstrated that traumatic axonal injury (TAI) of the STT causes central pain in patients with mild TBI.[8–15] These studies focused on the prevalence of central pain caused by TAI of the STT, or they have provided a case description of patients with mild TBI.[8–15] However, there are no reports on the diagnostic sensitivity of TAI of the STT following mild TBI. This study hypothesized that DTT

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could have high diagnostic sensitivity for TAI of the STT in patients with mild TBI. Therefore, this study investigated the diagnostic sensitivity of TAI for STT in patients with mild TBI.

2. Methods

2.1. Subjects

Among 127 patients with mild TBI (September 2013–January 2017), 35 patients (male: 9, female: 26, mean age: 42.5 ± 9.8 years, range: 21–58 years) with TBI were recruited for this study. In addition, 30 healthy control subjects (male: 16, female: 14, mean age: 36.1 ± 11.0 years, range: 20–56 years) with no previous history of neurological, physical, or psychiatric illness were recruited. The following inclusion criteria were applied to patient recruitment: loss of consciousness for <30 minutes, posttraumatic amnesia for ≤24 hours, and an initial Glasgow Coma Scale score of 13 to 15[19,27]; presence of central pain characteristic of neuropathic pain: stimulation-independent pain: shooting, lancinating, burning, electric shock-like sensation, and paresthesia (crawling, itching, and tingling sensation); stimulus evoked pain: hyperalgesia or allodynia by environmental stimuli[16,28–31]; no specific lesion was observed on brain MRI (T1-weighted, T2-weighted, and fluid attenuated inversion recovery images); more than 1 month after the onset of TBI; age at the time of head trauma: >20 years-old; no radiculopathy or peripheral neuropathy on electromyography and nerve conduction study; no musculoskeletal problem (e.g., myofascial pain syndrome, complex regional pain syndrome, or heterotopic ossification); and no history of previous head trauma, neurologic or psychiatric disease. This study was conducted retrospectively and written consent was obtained from all control subjects. The study protocol was approved by the Institutional Review Board of the Yeungnam University Hospital.

Demographics, clinical data, and DTT parameters for all subjects are summarized in Table 1. The average loss of consciousness, posttraumatic amnesia, and Glasgow Coma Scale values were 4.8 ± 8.0 minutes, 7.6 ± 13.1 minutes, and 14.9 ± 0.4 units, respectively. The mechanisms of injury for TBI were as follows: motor vehicle accident, 25 patients (71.4%); pedestrian accident, 6 patients (17.1%); fall, 3 patients (8.6%); bicycle accident, 1 patient (2.9%).

2.2. Clinical evaluation

The patients' central pain was evaluated using the visual analogue scale (VAS) and the highest score was selected. The reliability and validity of the VAS have been well-established.[32] The average VAS score of the patients was 6.2 ± 1.6 (Table 1).

2.3. Diffusion tensor imaging

DTI scanning was performed at an average of 9.6 ± 8.9 months after the onset of TBI using a 1.5T Philips Gyroscan Intera (Philips, Ltd., Best, The Netherlands). Seventy contiguous slices were acquired with 32 gradients. Imaging parameters of DTI were as follows: acquisition matrix = 96 × 96; reconstructed to matrix = 192 × 192; field of view = 240 × 240 mm; repetition time = 10,398 ms; echo time = 72 ms; $b = 1000\ s/mm^2$; number of excitations = 1; and a slice thickness = 2.5 mm.

2.4. Fiber tracking

Fiber tracking was performed using the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain Diffusion Software (www.fmrib.ox.ac.uk/fsl) with the default tractography option.[33] To reconstruct the STT, the seed region of interest (ROI) was given at an isolated STT area (posterolateral to the inferior olivary nucleus and anterior to the inferior cerebellar peduncle in the medulla).[34] Two target ROIs were placed on a portion of the ventro-postero-lateral nucleus of the thalamus and on the primary somatosensory cortex on the axial images.[34] A

Table 1

Demographic, clinical data, and diffusion tensor tractography parameters of the patient and control groups.

			Patient	Control
Sex (male:female)			9:26	16:14
Mean age, yr			42.5 (9.8)	36.1 (11.0)
LOC, min			4.8 (8.0)	–
PTA, min			7.6 (13.1)	–
GCS score		13	1	–
		14	1	
		15	33	
VAS score			6.2 (1.6)	–
Mechanism of injury	Motor vehicle accident		25	–
	Bicycle accident		1	
	Pedestrian accident		6	
	Fall		3	
Mean duration to DTI (mos)			9.57 (8.86)	–
DTT parameters for STT	FA	Right	0.395 (0.040)	0.408 (0.025)
		Left	0.406 (0.032)	0.411 (0.031)
		Both	0.400 (0.036)	0.409 (0.028)
	TV	Right	1546.11 (978.22)	1667.90 (482.55)
		Left	1716.80 (987.56)	1737.53 (461.93)
		Both	1631.46 (979.53)	1702.72 (469.65)

Values represent mean (±standard deviation).

DTI = diffusion tensor imaging, DTT = diffusion tensor tractography, FA = fractional anisotropy, GCS = Glasgow Coma Scale, LOC = loss of consciousness, PTA = posttraumatic amnesia, STT = spinothalamic tract, TV = tract volume, VAS = visual analogue scale.

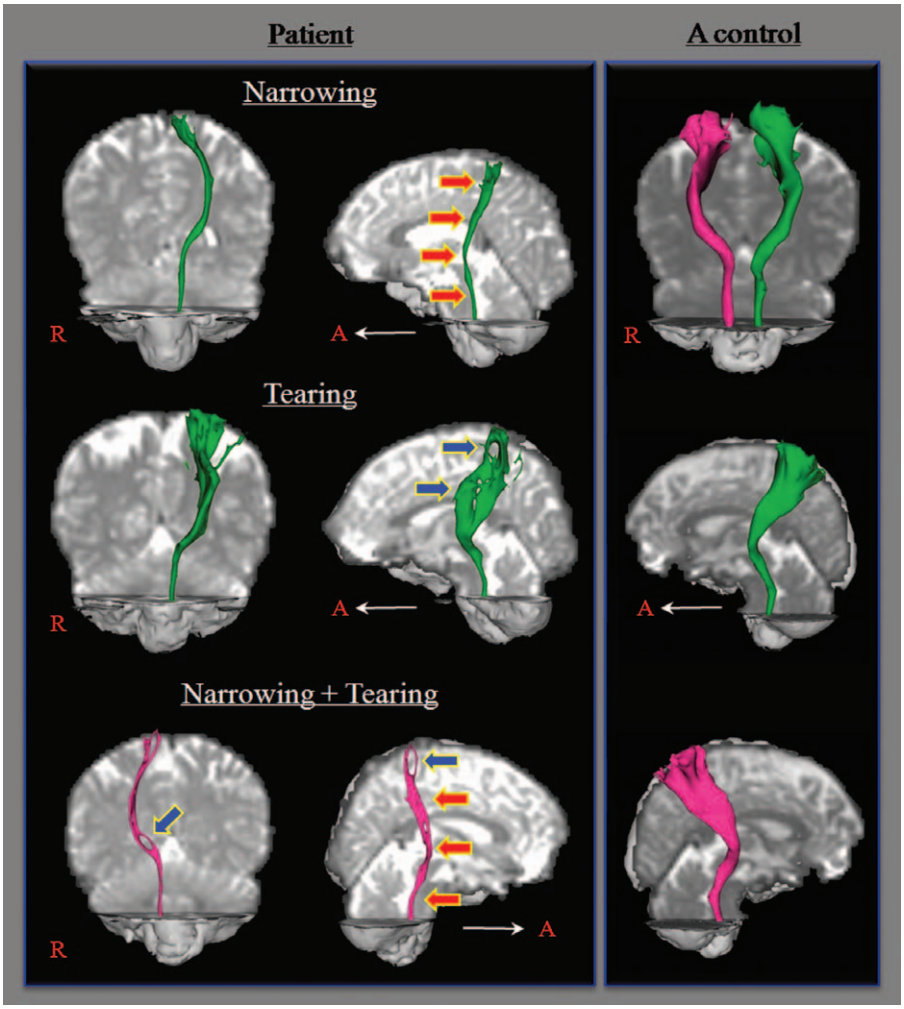

Figure 1. Results of diffusion tensor tractography for the spinothalamic tract (STT) in the patient group. Narrowing (red arrows) and tearing (blue arrows) of the STT are defined as abnormal compared with a normal control subject.

threshold of 2 streamlines was applied when obtaining the fiber tracking results. The tracking analyzer was blinded to all patient and control data, and data analyses were performed randomly. The fractional anisotropy (FA) and tract volume (TV) values for the STT were determined for both hemispheres. The observed abnormalities were classified as narrowing, tearing, or narrowing and tearing (Fig. 1).

2.5. Statistical analysis

SPSS software (SPSS for Windows, Version 15.0; SPSS Inc., Chicago) was used for statistical analysis. Before statistical analysis, we tested the normality of the DTT parameter values for the patients and controls; the data for both the patients and controls met the normality conditions. For group analysis, an independent *t* test was used to compare the FA and TV values between the patient and control groups. The null hypothesis of no difference was rejected if the *P* values were less than .05. The statistical power of the sample size was calculated using G*power 3.1 and showed a 0.5 effect size, 0.05 α error probability, and 0.64 power (1-β error probability). For individual analysis, and because the injured hemisphere in patients varied according to the injury mechanism, all patients were divided into 2 hemispheres and compared with similarly divided control groups. DTT parameter values lower than 1 or 2 standard deviations (SDs) of the control value mean were defined as indicative of an injured STT. For definition of the configuration of the STT, tearing was defined as any deficit of continuity in the entire pathway of the STT, while narrowing was defined as the thinness of the whole pathway of the STT compared to the thickness of the STT of the control subjects.

3. Results

Group-based analysis showed that the FA and TV values for the STT did not differ significantly between the patient and control groups ($P > .05$) (Table 1). Table 2 presents a summary of the results of the prevalence of STT injury based on the DTT parameters and configurations. Thirty-three patients had a DTT parameter lower than 1 SD from the mean parameter value in the control group, and 20 patients had a parameter lower than 2 SDs. In detail, the individual FA values in 21 and 7 patients, and the individual TV values of 21 and 14 patients were lower than 1 SD and 2 SDs, respectively, from the mean FA and TV values of the

Table 2

Injury of the spinothalamic tract in terms of individual values of diffusion tensor tractography parameters and configurations categories.

DTT parameters								
	Hemisphere (total: 70)				Patient (total: 35)			
	FA	TV	Both (FA + TV)	Total	FA	TV	Both (FA + TV)	Total
1 SD	25 (35.7%)	26 (37.1%)	4 (5.7%)	47 (67.1%)	21 (60.0%)	21 (60.0%)	3 (8.6%)	33 (94.3%)
2 SD	7 (10.0%)	16 (22.9%)	0	23 (32.9%)	7 (20%)	14 (40.0%)	0	20 (57.1%)

DTT configurations category	Hemisphere (total: 70)	Patient (total: 35)
Narrowing	34 (48.6%)	24 (68.6%)
Tearing	28 (40.0%)	21 (60.0%)
Narrowing + tearing	9 (12.9%)	9 (25.7%)
Total	53 (75.7%)	35 (100%)

1 SD: when the value was decreased 1 standard deviation below that of controls.
2 SD: when the value was decreased 2 standard deviations below that of controls.
DTT = diffusion tensor tractography, FA = fractional anisotropy, SD = standard deviation, TV = tract volume.

control group. Three patients had a decrease of 1 SD in both the FA and TV values compared to the control group.

Regarding the DTT configuration of the STT, 35 patients showed the STT abnormality (tearing and narrowing). Of those, 24 patients showed narrowing of the STT, and 21 patients revealed tearing of the STT. Furthermore, 9 patients revealed both tearing and narrowing of the STT.

4. Discussion

This DTT-based study investigated the diagnostic sensitivity of TAI when assessing the STT in patients with mild TBI. Thirty-five patients with central pain after mild TBI were enrolled in this study, and the following results were obtained; there is high diagnostic sensitivity for TAI of the STT, that is, 100% sensitivity for a torn or narrowed configuration of an injured STT as the individual patient denominator in the patient group. By contrast, 94.3% (1 SD decrease) and 57.1% (2 SD decrease) sensitivity were associated with the FV and TV parameters as the individual patient denominator in the patient group.

Several studies reported that an analysis of DTT parameters is better than an analysis of the DTI parameters when using an ROI-method to detect a neural injury in an individual patient.[21,35,36] Two DTT (FA and TV) and DTT-derived configurations (narrowing, tearing, or both) of the STT were analyzed. The FA value indicates the degree of directionality of water diffusion within a range of 0 (completely isotropic diffusion) to 1 (completely anisotropic diffusion).[37,38] Furthermore, the FA values indicate the white matter organization. In particular, FA indicates the degree of directionality of the white matter microstructures such as axons, myelin, and microtubules.[37,38] By contrast, TV, which reveals the number of voxels within a neural tract, indicate the number of fibers within a neural tract.[39] Therefore, changes in the DTT parameters, such as a decrease in FA or TV values, can indicate an injury to the STT. Moreover, narrowing or tearing of the STT, as visualized on DTT results, can indicate an injury to the STT. In this study, a higher sensitivity was obtained when assessing the configuration of the STT (100%) than the sensitivities (94.3% – 1 SD and 57.1% –2 SD) obtained from assessing the FA and TV parameters. Hence, configurational analysis of the STT has better diagnostic sensitivity for an STT injury than an analysis of the directionality (FA) or fiber number (TV) of a TAI in the STT of patients with mild TBI.

All subjects in the patient group suffered neuropathic pain; however, no definite brain lesions were observed on conventional brain MRI. Radiculopathy and peripheral neuropathy were also ruled out. Therefore, it appears that injury of the STT was related to the occurrence of central pain in the patient group. TAI appeared to be the most likely pathogenetic mechanism for STT injury.[5,19,21,35,40,41] After introducing DTI, many studies reported an injury to the neural tracts in patients with mild TBI.[9,21,35,42,43] However, regarding the sensitivity associated with diagnosis of TAI of a neural tract following mild TBI, a few studies reported high sensitivity (100%) of the configurational analysis of the corticoreticulospinal tract and corticospinal tract.[42,43] These results are similar to those in the above studies. Further DTT-based studies on the diagnostic sensitivity of TAI of other neural tracts should be encouraged.

Since the introduction of DTI, several studies reported an association of central pain with TAI of the STT in patients with mild TBI.[8–15] In 2015, the previous study reported central pain in 68.75% of all patients with mild TBI, injuries that had been diagnosed as STT injuries based on DTT parameters.[9] By contrast, the current study recruited new patients except for those included in Kim et al and investigated the diagnostic sensitivity of TAI in terms of DTT-based configuration and parameters for the STT in patients with mild TBI. Other studies described an association between the injury of the STT and central pain in individual patients following mild TBI.[8,10–15] The current study is the first original DTT-based study to assess the diagnostic sensitivity of TAI for the STT in patients with mild TBI. However, there are limitations to this study that should be considered. First, the study included a small number of subjects. In addition, only patients with central pain who visited the rehabilitation department of a university hospital were recruited. Therefore, among all patients with mild TBI, patients with severe clinical manifestations might have been recruited. Second, the diagnostic specificity of TAI was not estimated because the majority of the patients with mild TBI usually have some pain. Because the possibility of central pain could not be excluded in patients with other kinds of pain following mild TBI, the specificity estimation could be biased and misleading. Third, although DTT is a powerful anatomic imaging tool, which can demonstrate gross fiber architecture, it can produce both false positive and negative results caused by crossing fibers or partial volume effect.[44–46] Further studies with larger numbers of subjects and studies that include an assessment of the diagnostic

specificity of TAI of the STT should be encouraged. Moreover, studies overcoming DTT imaging limitations will be necessary.

In conclusion, the high diagnostic sensitivity of TAI of the STT was detected for assessing the STT in patients with mild TBI. The DTT for the STT is useful for diagnosing TAI in patients with central pain after mild TBI. Moreover, the DTT protocol for the STT provides reliable methods to quantify the FA and TV of the STT.

Author contributions

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