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Original Research

Injury of the Spinothalamic Tract Following Whiplash Injury: A Diffusion Tensor Tractography Study

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Abstract

Objectives: Using diffusion tensor tractography (DTT), we demonstrated the spinothalamic tract (STT) injury in patients with central pain following whiplash injury. Our primary hypothesis is that fractional anisotropy (FA) and tract volume (TV) of the STT in injured people differ from non-injured people. Our secondary hypothesis is that the direction of the collision results in a different type of injury. **Methods**: Nineteen central pain patients following whiplash injury and 19 normal control subjects were recruited. The STT was reconstructed by the DTT, the FA and TV of the STT were measured. In addition, different characteristics of the STT injury according to the collision direction were investigated. **Results**: The FA value did not differ significantly between the patient and control groups ($p > 0.05$). However, the significantly lower value of the TV was observed in patient group than the control group ($p < 0.05$). The onset of central pain was significantly delayed (13.5 days) in patients who were involved in a frontal collision, compared to patients with rear-end collision (0.6 days) ($p < 0.05$). In contrast, the Visual Analogue Scale was higher in the patients with rear-end collision ($p < 0.05$). **Conclusions**: We found the STT injury mild traumatic brain injury (TBI) who suffered central pain after whiplash injury, using DTT. In addition, we demonstrated different characteristics of the STT injury according to the collision direction. We believe that injury of the STT would be usefully detected by DTT following whiplash injury.

Keywords: diffusion tensor imaging; spinothalamic tract; mild traumatic axonal injury; whiplash injury

1. Introduction

Whiplash injury is caused by sudden acceleration-deceleration, to the above cervical level such as head and neck [1–14]. The patient with whiplash injury suffers varied symptoms, including some suggesting brain injury such as posttraumatic headache, posttraumatic concussion syndrome and posttraumatic chronic pain [2–10]. Example studies of symptoms indicating brain injury in whiplash injury patients describe changes of perfusion or blood flow in functional neuroimaging studies, increased gray matter density in voxel-based morphometry study and axonal injury in brain dissection study for post-mortem brain [12–14].

Pain is a common and cardinal symptom in patients with whiplash injury [1,15]. Although neck pain due to sprain is the most common pain following whiplash injury, a significant portion of patients with whiplash show neuropathic pain: 34% of patients have neuropathic pain component following acute whiplash [1,16,17]. Possible mechanisms for neuropathic pain include central hypersensitivity, increased activity in brain areas of pain and additional cortical areas, maladaptive neuroplasticity and cortical reorganization, structural brain change, alterations in neurochemistry, and disruption of the brain default mode network [1,12–14,16,18–20].

Since development of diffusion tensor imaging (DTI), a few studies using diffusion tensor tractography (DTT), reported injuries of the corticospinal tract, corticoreticulospinal tract (CRT), dentatorubrothalamic tract (DRTT), ascending reticular activating system (ARAS), auditory radiation (AR), and spinothalamic tract (STT) following whiplash injury [21–27]. However, all of these studies were case reports, and only one case study reported specifically an injury of the STT [21–27].

In this study, we demonstrated the STT injury in central pain patients following whiplash injury, using DTT. Our primary hypothesis is that fractional anisotropy (FA) and tract volume (TV) of the STT in injured people differ from non-injured people. Our secondary hypothesis is that the direction of the collision results in a different type of injury.

2. Materials and Methods

2.1 Subjects

Nineteen patients (man: 11, women: 8, mean-age: 44.7 ± 12.6 years, range: 18~61 year-old) and 19 healthy control subjects (man: 9, women: 10, mean-age: 41.1 ± 11.3 year-old, range: 20~58 year-old) with no history of neurological, physical, or psychiatric illness were recruited for this study. The inclusion criteria were (1) LOC for <30

Table 1. Information of subjects, clinical and diffusion tensor tractography parameter data of each group.

		Patient group	Control group	*p*-value
Sex (male:female)		11:8	9:10	0.52
Mean age, year		44.7 (12.6)	41.1 (11.3)	0.75
LOC, minutes		1.1 (2.0)	-	
PTA, minutes		5.0 (13.5)	-	
GCS score		15.0 (0.0)	-	
VAS score		5.1 (1.1)	-	
Mean duration to DTI (months)		9.25 (13.9)	-	
Location of central pain	Head	18 (94.7%)		
	Trunk	9 (47.4%)		
	Arm and Leg	15 (78.9%)		

Values represent mean (± standard deviation), LOC, loss of consciousness; PTA, post-traumatic amnesia; GCS, Glasgow Coma Scale; VAS, Visual Analogue Scale; DTI, diffusion tensor imaging; DTT, diffusion tensor tractography; FA, fractional anisotropy; TV, tract volume.

minutes, PTA for $\leq$24 hours, and initial GCS score of 13–15 [28], (2) presence of central pain characteristic of neuropathic pain: stimulation-independent pain, and paraesthesia; stimulus evoked pain [29–31], (3) no specific lesion observed on brain MRI, (4) more than one month after onset of traumatic brain injury (TBI), (5) the time of head trauma: over18 year-old, (6) no radiculopathy or peripheral neuropathy on electromyography (EMG) and nerve conduction study, (7) no peripheral neurogenic or musculoskeletal problem, (8) the patient with frontal or rear-end car collision (flexion-hyperextension injury of the head and neck without direct head injury to the front or side window or seat), and (9) no history of head trauma, neurologic or psychiatric disease. The data were collected retrospectively. The study protocol was approved by the IRB of a Yeungnam university hospital (YUMC-2021-03-014). Demographic and clinical data are summarized in Table 1. No significant difference was observed in age and sex between the patient and control groups ($p > 0.05$).

2.2 Clinical Evaluation

Central pain was selected highest score using Visual Analogue Scale (VAS). The reliability and validity of the VAS are well-established [31]. The average VAS score was 6.2 $\pm$ 1.6. We defined primary and secondary axonal injuries by the onset timing of the central pain after the onset of head trauma: primary axonal injury, less than one hour after onset; secondary axonal injury, at least four hours after onset [32].

2.3 Diffusion Tensor Imaging

DTI scanning was performed at an average of 9.3 $\pm$ 13.8 months after onset of TBI using a six-channel head coil on a 1.5T Philips Gyroscan Intera (Philips, Ltd., Best, The Netherlands). For each of the 32 non-collinear diffusion sensitizing gradients, we acquired 70 contiguous slices parallel to the anterior commissure-posterior commissure line.

Table 2. Diffusion tensor tractography parameters of the each groups.

			Patient group	Control group	*p*-value
DTT Parameters	FA	Right	0.39 (0.06)	0.41 (0.03)	0.41
		Left	0.41 (0.06)	0.43 (0.04)	0.44
	TV	Right	908.32 (458.82)	1800.83 (617.34)	0.01*
		Left	982.42 (651.59)	1896.28 (795.27)	0.01*

Values represent mean (± standard deviation), DTT, diffusion tensor tractography; FA, fractional anisotropy; TV, tract volume.
*: significant difference of track volume of spinothalamic tract between patient and control group, $p < 0.05$.

2.4 Fiber Tracking

Fiber tracking was performed by FMRIB Software Library (FSL, https://www.fmrib.ox.ac.uk/datasets/techrep/tr04ss2/tr04ss2/node19.html) with the default tractography option [33]. Head motion effect and image distortion due to eddy current were corrected by affine multi-scale two-dimensional registration. For reconstruction of the STT, the regions of interest (ROIs) of the STTs were placed. A seed ROI was placed on the posterolateral medulla on an axial slice [33]. Two target regions of interest were placed on the portion of the ventro-postero-lateral nucleus of the thalamus and primary somatosensory cortex on the axial images [34]. A threshold of two streamlines was applied for the results of fiber tracking. The values of fractional anisotropy (FA) and tract volume (TV) of the STT were measured in both hemispheres.

2.5 Statistical Analysis

SPSS software (SPSS for Windows, Version 15.0. SPSS Inc., Chicago, IL, USA) was used for statistical analysis. An independent *t*-test was used to compare FA and TV between the patient and control groups. Regarding the value of FA, there was no significant differences were observed ($p > 0.05$), in detail, average and standard deviation

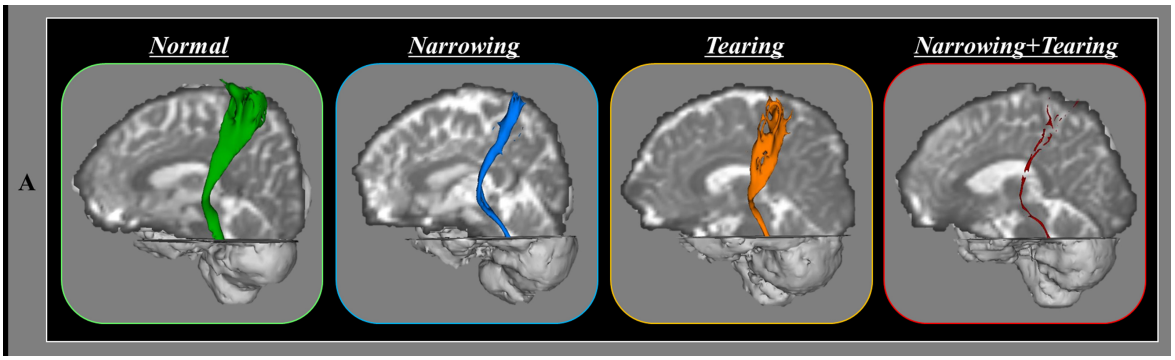

Fig. 1. Examples of injury of the spinothalamic tract on diffusion tensor tractography.

Table 3. Results by collision direction.

	Frontal collision	Rear-end collision	*p*-value
Duration to pain onset (days)	13.5	0.6	0.01*
Primary injury	0/6 (0%)	7/13 (53.8%)	
Secondary injury	6/6 (100%)	6/13 (46.2%)	
VAS	4.2	5.5	0.02*

VAS, visual analogue scale.

*: significant difference of the visual analogue scale between frontal collision and rear collision, $p < 0.05$.

were 0.39 (0.06) for right (RT), and 0.41 (0.06) for LT in the patient group. In control group, average and standard deviation were 0.41 (0.03) for RT, and 0.43 (0.04) for left (LT). Regarding the value of TV, there was significant differences were observed ($p < 0.05$). In detail, average and standard deviation were 908.32 (458.82) for RT, and 982.42 (651.59) for LT in the patient group. In control group, average and standard deviation were 1800.83 (617.34) for RT, and 1896.28 (795.27) for LT.

3. Results

The result of DTT parameters of the STT between the patient and control groups is shown in Table 2. The FA value did not differ significantly between the patient and control groups ($p > 0.05$). However, the TV value in the patient group was significantly lower than the control group ($p < 0.05$).

In this study, the patient with frontal or rear-end car collision was registered. The onset of central pain was significantly delayed (13.5 days) in patients who were involved in a frontal collision, compared to patients in a rear-end collision (0.6 days) ($p < 0.05$). All patients with frontal collision suffered secondary axonal injury, but only 46.2% of patients in a rear-end collision did. The Visual Analogue Scale was higher in the patients with rear-end collision ($p < 0.05$) (Table 3).

4. Discussion

In this study, we demonstrated the STT injury using DTT parameters in patients with central pain following whiplash injury and found the following results (Fig. 1, Tables 1,2,3). First, TV of the STT in the patient group was lower than the control group; however, FA value did not differ. Second, patients in a frontal collision (13.5 days) showed delayed onset of central pain more than the patients in a rear-end collision (0.6 days). All patients in a frontal collision suffered secondary axonal injury, but approximately half of patients in a rear-end collision did.

Result of DTT parameters, FA and TV are most commonly used to evaluate the condition of a neural tract with brain injury. FA value indicates water diffusion directionality degree, and the white matter organization [35]. In detail, it indicates the degree of directionality of white matter microstructures such as axon, myelin, and microtubule [35]. TV indicates the included number of voxels in a neural tract, suggests fiber numbers of a neural tract [36]. Therefore, the decrease of TV without change of FA value in the patient group appeared to indicate injury of the STT. Because the conventional brain MRI, electromyography, and nerve conduction studies in the patient group were normal, traumatic axonal injury (TAI) was the most likely pathogenic mechanism for injuries of the STT [37–40].

The primary axonal injury indicates that the axons are damaged by shear or strain injury at the time of injury that lead to disconnection or malfunction of neuron's interconnection [41]. In contrast, the secondary axonal injury refers to a condition in which axons were not damaged at the time of injury (evolve over a period of time from hours to days after the primary brain injury), but undergo axonal injury caused by the sequential process of cellular, chemical, or tissue such as decreased axoplasmic transport, continued

axonal swelling, and subsequent ~ ultimate disconnection that lead to increased mortality [38,41]. Central pain onset was delayed in the patients in a frontal collision (13.5 days) compared with patients in a rear-end collision (0.6 days). Considering the definition of the primary and secondary axonal injury, the patients in a frontal collision had secondary injuries (the onset duration of the central pain was more than four hours after whiplash injury) much more than the patients in a rear-end collision. In detail, usually, we could not take a defensive physical position when the accident occurs rear-end collision and it may result the direct injury (primary injury). However, when the accident occurs frontal collision, the occupant could take a defensive physical position. Although it prevents direct injury (primary injury), but due to the acceleration-deceleration force, the brain shaking is unavoidable. We assume that this may results secondary injury. Therefore, these results suggest that TAIs in the patients in a frontal collision were mainly attributed to the secondary injury than the patients in a rear-end collision [38,41].

We think that the higher risk of secondary injury in the patients in a frontal collision might be related to time to protect their body when colliding in front rather than the rear.

TAI is demonstrably associated with whiplash injury [19–24]. Before introduction of DTI, a few studies reported on TAI following whiplash injury in the post-mortem brain dissection study [19,20]. In 1982, Gennarelli *et al*. [19] applied artificial whiplash force to 45 monkeys, and 26 of 45 monkeys suffered brain injury, with 18 of those 26 monkeys revealed to have diffuse axonal injury on post-mortem brain dissection. In 1998, Shannon *et al*. [20] reported that axonal injury was detected on post-mortem brain dissection in 14 children with shaken baby syndrome. After introduction of DTI, several studies using DTT demonstrated TAI following whiplash injury in patients with mild TBI [21–27]. In 2019, Jang and Seo reported on two patient with mild TBI who showed injury of STT with central pain following whiplash injury [23]. From 2015 to 2019, Jang *et al*. [21–27] reported several manuscripts of TAI using DTT in the patient (suffering tremor, ataxia, hypersomnia, impaired motor function, tinnitus and neural pain) with neural tract injury such as DRTT, ARAS, Corticospinal tract (CST), CRT, AR and STT after whiplash injury. Therefore, to the best of our knowledge, this is the first original study to demonstrate the STT injury in large number of patients after whiplash injury.

However, some limitation of this study should be considered. First, this study included a small number of subjects. In addition, we recruited patients who visited the rehabilitation department of a university hospital, therefore, it is possible that severe clinical manifestation mild TBI patients would be recruited. Second, although DTT is a powerful anatomic imaging technique that can demonstrate gross fiber architecture, it can produce both false positive and negative results due to crossing fiber or partial volume effect [42,43].

5. Conclusions

In this study, we found injury of the STT in patients with mild TBI who suffered central pain after whiplash injury, using DTT. In addition, we demonstrated different characteristics of the STT injury according to the collision direction. We believe that DTT would be a useful technique for detection of injury of the STT following whiplash injury and can be recommended for patients who complain of brain symptoms after whiplash injury.

Availability of Data and Materials

All data generated or analysed during this study are included in this published article.

Author Contributions

SHJ—Project administration, Writing – original draft. KK—Data curation, Methodology. YSS—Formal analysis, Methodology, Writing – review & editing.

Ethics Approval and Consent to Participate

All subjects gave their informed consent for inclusion before they participated in the study. The protocol was approved by the Yeungnam University Hospital Institutional Review Board (approval number: YUMC 2021-03-014).

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Conflict of Interest

The authors declare no conflict of interest.

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