RESEARCH ARTICLE

Injury of the dentatorubrothalamic tract in patients with post-traumatic tremor following mild traumatic brain injury: a case-control study

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Abstract

Post-traumatic movement disorder is one of the sequelae of traumatic brain injury. The dentatorubrothalamic tract (DRTT) is reported to be involved in the control of movement. Therefore, injury of the DRTT can be accompanied by abnormal movements, including ataxia, tremor, or dystonia. We investigated DRTT injuries in 27 patients who showed post-traumatic tremor in at least one of four extremities following mild traumatic brain injury. We classified DRTT injuries based on diffusion tensor tractography parameters and configuration: type A: the DRTT showed narrowing, type B: the DRTT showed partial tearing, and type C: the DRTT showed discontinuation. Fractional anisotropy and fiber number of the DRTT were significantly decreased in patients compared with the healthy controls. Based on our DRTT injury classification, among the 54 hemispheres of the 27 patients, type A injury occurred in 22 hemispheres (40.7%) of 17 patients, type B injury was present in 15 hemispheres (27.7%) of 10 patients, and type C injury was observed in 8 hemispheres (14.8%) of 6 patients. Our results suggest that diffusion tensor tractography-based evaluation of the DRTT would be useful when determining cause of post-traumatic tremor in patients with mild traumatic brain injury. The study protocol was approved by the Institutional Review Board of Yeungnam University Hospital (YUMC-2018-09-007) on September 5, 2018.

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Introduction

Post-traumatic movement disorder is one of the sequelae of traumatic brain injury (TBI) (Zasler et al., 2012). Previous studies have demonstrated that approximately 10% patients showed abnormal movements after TBI (Krauss et al., 1997; Zasler et al., 2012). Tremor, an involuntary muscle contraction and relaxation vibration often observed in parkinsonism, is a major abnormal movement pattern in patients with post-traumatic movement disorder (Cardoso and Jankovic, 1995; Krauss et al., 1997; Krauss and Jankovic, 2002; Zasler et al., 2012). Post-traumatic tremor usually affects the entire body, but especially affects the upper extremities following TBI (Cardoso and Jankovic, 1995; Krauss and Jankovic, 2002). As a result, the presence of post-traumatic tremor following TBI can disturb a patient's daily living activities. Therefore, elucidation of the pathophysiologic mechanism associated with post-traumatic tremor is important. However, little has been reported on this topic.

The dentatorubrothalamic tract (DRTT) is reported to be involved in the control of movement. Therefore, injury of the DRTT can be accompanied by abnormal movements, including ataxia, tremor, or dystonia (Lehericy et al., 2001; Marx et al., 2008). Introduction of diffusion tensor tractography (DTT) has enabled three-dimensional reconstruction of the DRTT (Mori et al., 1999; Assaf and Pasternak, 2008). Several studies using DTT have demonstrated injury of the DRTT in a few pathologies including brain tumor, stroke, and TBI (Coenen et al., 2011, 2014; Jang and Kwon, 2015, 2017; Marek et al., 2015; Schlaier et al., 2015). Using DTT, only two case studies have reported on DRTT injury after TBI (Jang and Kwon, 2015, 2017). We hypothesized that tremor could be associated with DRTT injury in patients with mild TBI, which comprises more than 70% of TBI cases (Cassidy et al., 2004).

In the current study, we used DTT to investigate DRTT injuries in patients who exhibited post-traumatic tremor following mild TBI.

Subjects and Methods

Subjects

Twenty-seven patients (11 males, 16 females, mean age 47.34 ± 11.64 years, range 21–65 years) with TBI and 20 healthy control subjects (8 males, 12 females, mean age 40.57 ± 9.46 years, range 21–63 years) were recruited for this study. Patients were recruited according to the following criteria: (1) loss of consciousness for < 30 minutes, post-traumatic

amnesia for ≤ 24 hours, and an initial Glasgow Coma Scale score of 13–15 (Alexander, 1995); (2) more than 1 month after onset of TBI; (3) age range between 21–65 years; (4) post-traumatic tremor in at least one of four extremities; (5) no brain lesion on conventional magnetic resonance image; and (6) no history of previous head trauma or neurologic or psychiatric disease (Ruff et al., 2009). This study was conducted retrospectively, and the study protocol was approved by the Institutional Review Board of Yeungnam University Hospital (YUMC-2018-09-007) on September 5, 2018. The participants provided signed informed consent.

DTI acquisition and analysis

DTI data were acquired at an average of 5.42 ± 6.12 months after the onset of TBI by using a 1.5 T Philips Gyroscan Intera system (Philips, Amsterdam, the Netherlands). Imaging parameters were as follows: acquisition matrix = 96 × 96, reconstructed to matrix = 192 × 192, field of view = 240 mm × 240 mm, repetition time (TR) = 10,398 ms, echo time (TE) = 72 ms, parallel imaging reduction factor (SENSE factor) = 2, echo-planar imaging (EPI) factor = 59 and b = 1000 s/mm^2, number of excitations (NEX) = 1, thickness = 2.5 mm. Fiber tracking was performed using probabilistic tractography and applied in the default tractography option in the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain Diffusion Software (5000 streamline samples, 0.5 mm step lengths, curvature thresholds = 0.2) (Yamada, 2009). This fiber-tracking method was used to calculate and generate 5000 streamline samples from seed regions of interest (ROI) with reflection of both dominant and non-dominant orientation of diffusion in each voxel. For reconstruction of the DRTT, a seed ROI was given at the dentate nucleus behind the floor of the fourth ventricle. Two target ROIs were given at the junction of the superior cerebellar peduncle between the upper pons and cerebellum and the contralateral red nucleus of the upper midbrain (Kwon et al., 2011).

The width and length of each ROI was measured for reconstruction of the DRTT according to the previous study of definition of ROI areas of the DRTT (Kwon et al., 2011). Each ROI was calculated as an individual pixel unit and converted to millimeters by averaging ROI width and length across all patients and normal subjects as follows: 1) seed ROI – width: 11.25 ± 1.25 mm and length: 6.66 ± 0.72 mm, 2) target ROI 1 – width: 5.41 ± 0.72 mm and length: 7.08 ± 1.90, and 3) target ROI 2 – width: 5.83 ± 1.44 mm and length: 7.51 ± 1.25 mm. A threshold of 2 streamlines was applied to the results of fiber tracking for assessment of the DRTT. For measurement of intra- and inter-observer, random analyses of the DTT parameters and ROI sizes were performed by two evaluations (HDL and SJL) who were blinded to the other evaluator's data. The consistency rate of analyses with three tract turning angles by two evaluators was identical for 94 hemispheres of patient (54 hemispheres of 27 subjects) and control (40 hemispheres of 20 subjects) groups (93.61%). Two sets of analyses made by one analyzer (Han Do Lee) acquired identical results from 94 hemispheres of patient (54 hemispheres of 27 subjects) and control (40 hemispheres of 20 subjects) groups (100%). We classified the DRTT injury based on DTT parameters and DTT reconstruction configuration as follows, type A: the integrity of the DRTT was preserved between the dentate nucleus and the thalamus, however, the FN of the DRTT was lower than two standard deviations from the mean of the normal subjects; type B: the integrity of the DRTT was preserved, however, partial tearing was observed more than one portion of the entire DRTT. We defined partial tearing as a partial or isolated defect in the reconstructed DRTT; and type C: the DRTT showed discontinuation more than one portion of the entire DRTT (**Figure 1**).

Statistical analysis

Statistical analyses were performed using SPSS 18.0 software (SPSS, Chicago, IL, USA). Independent-samples t-tests were performed to compare the DTT parameters [fractional an-

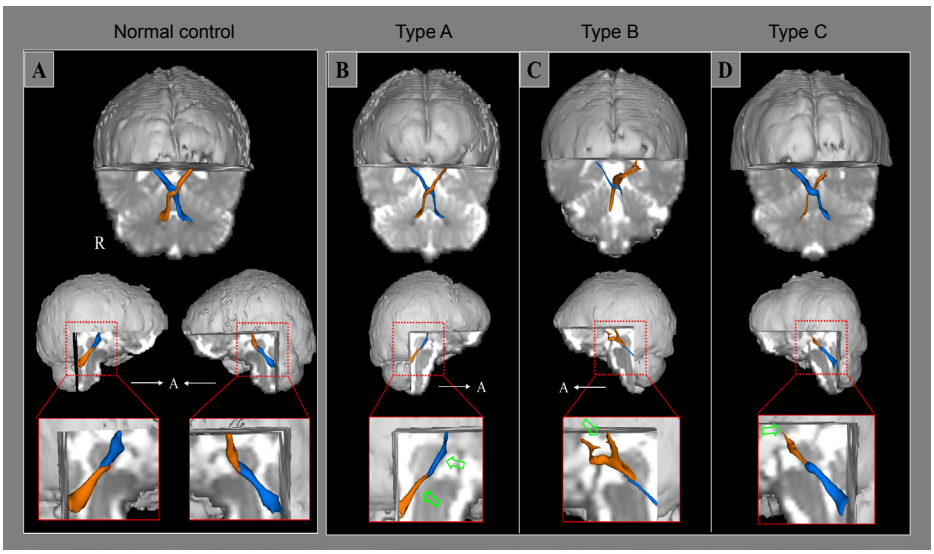

Figure 1 DTTs for patients with TBI and a healthy control subject.
(A) A normal control subject (52-year-old female). Blue color of the neural tract means the left DRTT, and orange color of the neural tract means the right DRTT. (B) Type A injury – The DRTTs show narrowing, although tract integrity was preserved from the dentate nucleus to the thalamus (green arrows) (59-year-old female). (C) Type B injury – Tearing of more than one portion of the entire DRTT was observed, although tract integrity was preserved (green arrow) (45-year-old female). (D) Type C injury – The DRTTs show tract discontinuation more than one portion of the entire DRTT (green arrow) (51-year-old female). We classified DRTT injuries based on diffusion tensor tractography parameters and configuration. A: Auterior; DRTT: dentatorubrothalamic tract; DTT: diffusion tensor tractography; R: right; TBI: traumatic brain injury.

isotropy (FA); apparent diffusion coefficient (ADC), and FN (fiber number)] in the patient and control groups. *P*-value was considered statistically significant.

Results

A summary of results for DTT parameters of the patient and control groups is shown in **Table 1**. DRTT FA and FN values were significantly decreased in the patient group compared with the control group ($P < 0.05$). In contrast, there was no significant difference in ADC of the DRTT between the patients and control groups ($P > 0.05$).

According to the configurational classification of the DRTT injury based on DTT parameters and DTT configuration, the 54 hemispheres of the 27 patients were classified as follows: type A injury in 22 hemispheres (40.7%) of 17 patients, type B injury in 15 hemispheres (27.7%) of 10 patients, and type C injury in 8 hemispheres (14.8%) of 6 patients.

Table 1 Comparison of diffusion tensor tractography parameters between the patient and control groups

	Patient group (n = 27)	Control group (n = 20)	*P*-value
FA	0.41±0.04*	0.45±0.06	0.01
ADC	0.89±0.19	0.87±0.13	0.61
FN	365.51±305.84*	629.68±340.35	0.00

ADC: Apparent diffusion coefficient (indicating the magnitude of water diffusion); FA: fractional anisotropy (indicating the degree of directionality of water diffusion); FN: fiber number (the number of voxels within a neural tract). Values are expressed by the mean ± SD. *$P < 0.05$, *vs*. control group (independent-samples *t*-test).

Discussion

We investigated injury of the DRTT in patients who showed post-traumatic tremor following mild TBI. 1) The FA and FN values for the DRTT in the patient group were lower than those of the control group. 2) The characteristics of DRTT injury within the patient group included: a) narrowing of the DRTT with integrity preserved [22 hemispheres (40.7%) of 17 patients], b) partial tearing of the DRTT [15 hemispheres (27.0%) of 10 patients], and c) DRTT discontinuation [eight hemispheres (14.8%) of six patients].

The DTT parameter, FA, indicates the degree of directionality of water diffusion, representing the degree of directionality and the integrity of white matter microstructures (Neil, 2008). In contrast, the FN indicates the number of voxels within a neural tract (Neil, 2008). Our results revealed decrements in the FA and FN values in the patient group, indicating injury of the DRTT.

Regarding the characteristics of DRTT injury in patients from the patient group, we observed narrowing of the DRTT with integrity preserved in 22 hemispheres (40.7%) of 17 patients. In addition, partial tearing and discontinuation of the DRTT were observed in 15 hemispheres (27.0%) of 10 patients and eight hemispheres (14.8%) of six patients, respectively. These results appear to indicate the evidence of traumatic axonal injuries of the patients' DRTT following mild TBI even though conventional brain MRI did not show abnormalities in any of the patients (Alexander, 1995; Povlishock and Christman, 1995; Jang, 2018).

Since the introduction of DTT, only two case studies have reported on DRTT injury associated with post-traumatic tremor in patients with mild TBI (Jang and Kwon, 2015, 2017). In 2015, Jang and Kwon reported a patient who showed post-traumatic tremor because narrowing of the left DRTT in patients with mild TBI (Jang and Kwon, 2015). In 2017, Jang and Kwon reported a patient who showed tremor aggravation because of aggravation of DRTT injury (Jang and Kwon, 2017). As a result, to the best of our knowledge, the current study is the first original study to investigate DRTT injury in a large number of patients with mild TBI who showed post-traumatic tremor. However, limitations of this study should be considered. First, because this study was conducted retrospectively, we were not able to examine the specific clinical evaluation for the DRTT injury. In addition, we could not investigate correlation between DTT parameters and tremor. The clinical data was unavailable because this study was performed retrospectively. Second, other neural structures that might be related with tremor presence, such as the basal ganglia and the cortiocopontocerebellar tract, were not examined because the main purpose of this study was to describe DRTT injury in patients with mild TBI.

In conclusion, we have used DTT to demonstrate the presence of DRTT injury in patients who exhibit post-traumatic tremor following mild TBI. Our results suggest that evaluation of the DRTT would be useful when determining the cause of post-traumatic tremor following mild TBI.

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