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

Sung Ho Jang1, Han Do Lee2,*

1 Department of Physical Medicine and Rehabilitation, College of Medicine, Yeungnam University, Daegu, Republic of Korea
2 Department of Physical Medicine and Rehabilitation, College of Natural Science, Ulsan College University, Ulsan, Republic of Korea

Funding: This study was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (NRF-2018R1A6A3A11043447; to HDL).

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.

Key Words: dentatorubrothalamic tract; diffusion tensor imaging; diffusion tensor tractography; fiber number; fractional anisotropy; mild traumatic brain injury; post-traumatic tremor; region of interest

Chinese Library Classification No. R445; R741

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/mm², 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.](image-url)

(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: Anterior; 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

| Parameter | 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 [8 hemispheres (14.8%) of 6 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 8 hemispheres (14.8%) of 6 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 corticopontocerebellar 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.

Author contributions: Study design and data acquisition: SHJ. Study concept and design, data acquisition and analysis, and manuscript authorization: HDL. Both authors approved the final version of this study.

Conflicts of interest: The authors report no disclosures relevant to the manuscript.

Financial support: This study was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (NRF-2018R1A6A3A11043447; to HDL).

Institutional review board statement: Approval for the study was obtained from the Institutional Review Board of Yeungnam University Hospital (YUMC-2018-09-007) on September 5, 2018.

Declaration of participant consent: The authors certify that they have obtained the appropriate participant consent forms. In the forms the participants have given their consent for their images and other clinical information to be reported in the journal. The participants understand that their names and initial will not be published and due efforts will be made to conceal their identity.

Reporting statement: This study followed the STrengthening the Reporting of Observational studies in Epidemiology (STROBE) statement.

Biostatistics statement: The statistical methods of this study were reviewed by the biostatistician of Ulsan College University, Republic of Korea.

Copyright license agreement: The Copyright License Agreement has been signed by both authors before publication.

Data sharing statement: Datasets analyzed during the current study are...
available from the corresponding author on reasonable request.

Plagiarism check: Checked twice by iThenticate.

Peer review: Peer reviewed.

Open access statement: This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-Non-Commercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

Open peer reviewer: Han Zhang, University of North Carolina at Chapel Hill, USA.

Additional file: Open peer review report 1.

References

Alexander MP (1995) Mild traumatic brain injury: pathophysiology, natural history, and clinical management. Neurology 45:1253-1260.

Assaf Y, Pasternak O (2008) Diffusion tensor imaging (DTI)-based white matter mapping in brain research: a review. J Mol Neurosci 34:51-61.

Cardoso F, Jankovic J (1995) Peripherally induced tremor and parkinsonism. Arch Neurol 52:263-270.

Cassidy JD, Carroll LJ, Peloso PM, Borg J, von Holst H, Holm L, Kraus J, Coronado VG; WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury (2004) Incidence, risk factors and prevention of mild traumatic brain injury: results of the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury: J Rehabil Med (43 Suppl):28-60.

Coenen VA, Allert N, Madler B (2011) A role of diffusion tensor imaging fiber tracking in deep brain stimulation surgery: DBS of the dentato-rubo-thalamic tract (drt) for the treatment of therapy-refractory tremor. Acta Neurochir (Wien) 153:1579-1585.

Coenen VA, Allert N, Paus S, Kronenburger M, Urbach H, Madler B (2014) Modulation of the cerebellal-thalamo-cortical network in thalamic deep brain stimulation for tremor: a diffusion tensor imaging study. Neurosurgery 75:657-670.

Jang SH, Kwon HG (2015) Injury of the dentato-rubo-thalamic tract in a patient with mild traumatic brain injury. Brain Inj 29(13-14):1725-1728.

Jang SH, Kwon HG (2017) Aggravation of an injured dentato-rubo-thalamic tract in a patient with mild traumatic brain injury: A case report. Medicine 96:e2853.

Jang SH (2018) Traumatic axonal injury in mild traumatic brain injury. In: Traumatic brain injury (Gorbunoy N, ed), pp137-154. London: InTech.

Krauss JK, Jankovic J (2002) Head injury and posttraumatic movement disorders. Neurosurgery 50:927-940.

Krauss JK, Trankle R, Kopp KH (1997) Posttraumatic movement disorders after moderate or mild head injury. Mov Disord 12:428-431.

Kwon HG, Hong JH, Hong CP, Lee DH, Ahn SH, Jang SH (2011) Dentatorubrothalamic tract in human brain: diffusion tensor tractography study. Neuoradiology 53:787-791.

Lehericy S, Grand S, Pollak P, Poupon F, Le Bas JF, Limousin P, Jedynek P, Marsault C, Agid Y, Vidailhet M (2001) Clinical characteristics and topography of lesions in movement disorders due to thalamic lesions. Neurology 57:1055-1066.

Marek M, Paus S, Allert N, Madler B, Klockgether T, Urbach H, Coenen VA (2015) Ataxia and tremor due to lesions involving cerebellar projection pathways: a DTI tractographic study in six patients. J Neurol 262:54-58.

Marx JJ, Iannetti GD, Thomke F, Fitzek S, Galeotti F, Truini A, Stoeter P, Dieterich M, Hopf HC, Cruccu G (2008) Topodiagnostic implications of hemiatasia: an MRI-based brainstem mapping analysis. Neuroimage 39:1625-1632.

Mori S, Crain BJ, Chacko VP, van Zijl PC (1999) Three-dimensional tracking of axonal projections in the brain by magnetic resonance imaging. Ann Neuro 45:265-269.

Neil JJ (2008) Diffusion imaging concepts for clinicians. J Magn Reson Imaging 27:1-7.

Povlishock JT, Christman CW (1995) The pathobiology of traumatically induced axonal injury in animals and humans: a review of current thoughts. J Neurotrauma 12:555-564.

Ruff RM, Iverson GL, Barth JT, Bush SS, Broshek DK (2009) Recommendations for diagnosing a mild traumatic brain injury: a National Academy of Neuropsychology education paper. Arch Clin Neuropsychol 24:3-10.

Schlaier J, Anthofer J, Steib K, Fellner C, Rothenfusser E, Brawanski A, Lange M (2015) Deep brain stimulation for essential tremor: targeting the dentato-rubo-thalamic tract? Neuromodulation 18:105-112

Yamada K (2009) Diffusion tensor tractography should be used with caution. Proc Natl Acad Sci U S A 106:E14.

Zasler ND, Katz DI, Zafonte RD, Arciniegas DB, Bullock MR, Kreutz JS (2012) Brain injury medicine: Principles and practice. 2nd ed. New York: Demos Medical Publishing.

P-Reviewer: Zhang H; C-Editor: Zhao M; S-Editor: Li CH; L-Editor: Song LP; T-Editor: Jia Y