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Ataxia due to injury of the cortico-ponto-cerebellar tract in patients with mild traumatic brain injury

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Abstract

Introduction: The cortico-ponto-cerebellar tract (CPCT) is involved in coordination of movement; injury of the CPCT can therefore be accompanied by ataxia. In this study, using diffusion tensor tractography (DTT), we investigated injury of the CPCT in patients with mild traumatic brain injury (TBI).

Methods: We recruited 45 consecutive patients with ataxia following mild TBI and 20 normal control subjects. The score of assessment and rating of ataxia (SARA) was used to evaluate of ataxia. The patients were classified into 2 groups based on the SARA; patient group A had with post-traumatic ataxia and patient group B had without post-traumatic ataxia. The fractional anisotropy (FA) value and fiber number (FN) of the CPCT was measured.

Results: Significant differences were observed in the FA and FN values of the CPCT between patient group A and the control group and between patient groups A and B ($P < .05$). In addition, a significant difference was observed in the FA value only of the CPCT between patient group B and the control group ($P < .05$). However, no significant difference was observed in the FN value of the CPCT between patient group B and the control group ($P > .05$).

Conclusion: By using DTT, injury of the CPCT was demonstrated in patients who showed ataxia following mild TBI. These results suggest that DTT would be useful for evaluation of the CPCT in patients with ataxia after mTBI because mTBI usually does not show any abnormalities on conventional brain MRI.

Abbreviations: CPCT = cortico-ponto-cerebellar tract, DTI = diffusion tensor imaging, DTT = diffusion tensor tractography, FA = fractional anisotropy.

Keywords: ataxia, cortico-ponto-cerebellar tract, diffusion tensor imaging, diffusion tensor tractography, mild traumatic brain injury

1. Introduction

Ataxia is a neurological dysfunction that results in a lack of voluntary coordination of muscle movements that can include gait abnormality, speech changes and abnormalities in eye movements.[1] It can be caused by interruption of the sensory input to the cerebellum, pathology of the cerebellar cortex resulting in incorrect execution of cortical signals, or by a combination of both.[2,3] Elucidation of the pathophysiological mechanism of ataxia after traumatic brain injury (TBI) involving cerebellar injury would be important in terms of rehabilitation as cerebellar injury could cause dysfunction of fine motor activity and gait.[4] However, this pathophysiological mechanism has not been clearly elucidated.

The cortico-ponto-cerebellar tract (CPCT) is a major neural circuit in the cerebellum involved in movement coordination with the dentate-rubro-thalamic tract.[5,6] Because of its involvement in movement coordination, injury of the CPCT can be accompanied by ataxia.[7–10] Since the introduction of diffusion tensor imaging (DTI), several studies have demonstrated injury of the CPCT in a few brain pathologies.[7,9,10] Regarding TBI, little is known about the association of ataxia with injury of the CPCT in large numbers of patients although 1 case study has been reported.[10]

In the current study, we used diffusion tensor tractography (DTT) to investigate injury of the CPCT in patients with mild TBI.

2. Method

2.1. Subjects

Forty five consecutive patients with mild TBI (16 males; 29 females, mean age 51.11 ± 11.82 years, range 23–68) and 20 age- and sex-matched healthy control subjects (7 males; 13 females,

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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mean age 42.71 ± 10.82 years, range 25–65) were recruited for the study. The American Congress of Rehabilitation Medicine defined a patient with mild TBI is a person who has had a traumatically induced physiological disruption of brain function as manifested by at least 1 of the following;

1. any period of loss of consciousness,
2. any loss of memory for events immediately before or after the accident,
3. any alteration in mental state at the time of the accident,
4. focal neurologic deficit that may or may not transient; but where the severity of the injury does not exceed as following; loss of consciousness of approximately 30 minutes or less, after 30 minutes, an initial Glasgow Coma Scale Score of 13 to 15, and post-traumatic amnesia not greater than 24 hour.[11–13]

Patients were recruited consecutively according to the following inclusion criteria including the above definition of mild TBI:

1. loss of consciousness for <30 minutes, post-traumatic amnesia for ≤24 hours, and an initial Glasgow Coma Scale score of 13 to 15.[12,13];
2. no specific lesion was observed on brain MRI (T1-weighted, T2-weighted and Fluid attenuated inversion recovery images),
3. more than 1 month after onset of TBI to rule out the effect of the secondary traumatic axonal injury following mTBI[14–17];
4. age range 20 to 70 years, and
5. no history of previous head trauma or neurologic or psychiatric disease. The study protocol was approved by the institutional review board of the university hospital.

2.2. Evaluation of ataxia

The score of assessment and rating of ataxia (SARA) was used to evaluate ataxia in the patient group.[18,19] This scale consists of 8 items related to gait (0–8 points), stance (0–6 points), sitting (0–4 points), speech disturbance (0–6 points), finger-chase test (0–4 points), nose-finger test (0–4 points), fast alternating hand movement (0–4 points) and heel-shin test (0–4 points). Once each of the 8 categories was assessed, the total was calculated to determine the severity of ataxia. The cumulative score of these eight categories can range from 0 (no ataxia) to 40 (most severe ataxia). Both the reliability and validity of SARA are well established.[18] The patients were classified into 2 groups based on the SARA:

1. patient group A – with post-traumatic ataxia (range of SARA scores: 2–17);
2. patient group B – without post-traumatic ataxia (no ataxia). Evaluators of clinical data were blinded to DTT data, and analyzers of DTT were also blinded to the clinical data.

Table 1 summarizes the demographic and clinical characteristics of the patients. Eighteen patients (6 males; 12 females; mean age 48.14 ± 12.98 years; range 23–68 years) belonged to group A, and 27 patients belonged to group B (10 males; 17 females; mean age 44.52 ± 11.19 years; range 26–60 years).

2.3. Diffusion tensor imaging and tractography

DTI data were acquired an average of 8.13 ± 9.08 months after the onset of TBI using a 1.5 T Philips Gyroscan Intera system (Philips Ltd, Best, Netherlands) equipped with a Synergy-L Sensitivity Encoding (SENSE) head coil and using a single-shot, spin-echo planar imaging pulse sequence. For each of the 32 noncollinear diffusion sensitizing gradients, 60 contiguous slices were acquired parallel to the anterior commissure-posterior commissure line. Imaging parameters were as follows: acquisition matrix = 96 × 96, reconstructed to matrix = 192 × 192, field of view = 240 mm × 240 mm, TR = 10,398 ms, TE = 72 ms, parallel imaging reduction factor (SENSE factor) = 2, EPI factor = 59 and b = 1000 s/mm^2, NEX = 1, thickness = 2.5 mm. Fiber tracking was performed by applying the fiber assignment continuous tracking algorithm within the Philips DTI task card software (Philips Extended MR Work Space 2.6.3). Each DTI replication was intra-registered to the baseline (b0) images to correct for residual eddy-current image distortions and head motion effects by using a diffusion registration package (Philips Medical Systems). For reconstruction of the CPCT, a seed region of interest was given at the primary sensorimotor cortex on the axial image and 2 target region of interest were placed at the anterior portion of pons on the axial image and the contralateral middle cerebellar peduncle on the coronal image.[20] A threshold of 10 streamlines was applied to the results of fiber tracking for assessment of the CPCT. Values of fractional anisotropy (FA) and fiber number (FN) of the reconstructed CPCT were determined for both hemispheres in each subject.

2.4. Statistical analysis

Statistical analyses were performed using SPSS software (v. 20.0; SPSS, Chicago, IL). One-way analysis of variance was performed for determination of significant differences for each DTT parameters (FA and FN values) between patient group A, B and control group, a least significant difference post-hoc test was performed to determine significance of differences in DTT parameters among the 3 groups. Statistical significance was accepted for P value of <.05.

3. Results

A summary of results for DTT parameters of the patient and control groups is shown in Table 2. Significant differences were

Table 1

Demographic data for the patient and control groups.

	Patient group A (with post-traumatic ataxia)	Patient group B (without post-traumatic ataxia)	Control group
Age, y	48.14 (± 12.98)	44.52 (± 11.19)	42.71 (± 10.82)
Patients (male/female)	18 (6/12)	27 (10/17)	20 (8/12)
Duration from onset	6.31 (± 6.53)	4.18 (±5.93)	–
SARA	7.62 (± 4.78)	0	–

SARA = score of assessment and rating of ataxia. Values represent mean ± standard deviation values.

Table 2

Comparison of diffusion tensor tractography parameters of the cortico-ponto-cerebellar tract between the patient groups and the control group.

	Fractional anisotropy	Fiber number
Patient group A (n = 18)	0.45 (± 0.03)	1193.15 (± 807.55)
Patient group B (n = 27)	0.44 (± 0.02)	1552.84 (± 718.94)
Control group (n = 20)	0.49 (± 0.04)	1676.28 (± 849.16)
P value(by LSD)		
Patient group A – Patient group B	0.04*	0.03*
Patient group A – Control group	0.01*	0.01*
Patient group B – Control group	0.00*	0.67
P-value(by Bonferroni correction method)		
Patient group A – Patient group B	0.17	0.10
Patient group A – Control group	0.07	0.04*
Patient group B – Control group	0.00*	1.00

Values represent mean ± standard deviation values.
* Indicates $P < .05$ on *t*-test analysis.

observed in the FA and FN values of the CPCT between patient group A (Fig. 1A) and the control group (Fig. 1C), and between patient groups A and B (Fig. 1B) ($p < 0.05$). In addition, a significant difference was observed in the FA value of the CPCT between patient group B and the control group ($P < .05$). However, no significant difference was observed in the FN value of the CPCT between patient group B and the control group ($P > .05$).

4. Discussion

In the current study, we used DTT to evaluate the CPCT in patients who suffered ataxia following mild TBI. Our results are summarized as follows: the values for FA and FN of the CPCT were decreased in patient group A compared with patient group B and the control group. However, only the FA value of the CPCT was decreased in patient group B compared with the control group. The FA value indicates the degree of directionality of water diffusion; in contrast, the FN value suggests the existing number of voxels within a neural tract. Therefore, the decrement of FA and/or FN values in patient group A or B seem to indicate injury of the CPCT.[21–23] The decrements of both the FA and FN values in patient group A and the decrement of only the FA value in patient group B compared with the control group indicate more severe injury of the CPCT in patient group A than in patient group B. In other words, patients who exhibited ataxia (group A) had more severe injury of the CPCT than patients who did not show ataxia (group B). Regarding the milder injury of patient group B, the results appeared to be ascribed to a kind of asymptomatic axonal injury that was previously reported by Povlishock et al[24] In 1983, Povlishock et al demonstrated mild axonal injury of the corticospinal tract in the brains of cats with minor head injury such as a concussion that did not present with symptoms of a corticospinal tract injury.[24]

Since the introduction of DTI, several studies have demonstrated that CPCT injury is associated with ataxia.[7,9,10] In 2007, Kitamura et al detected axonal injury of the CPCT projection in 18 patients with adult-onset ataxic neurodegenerative disease.[7] They also found increased apparent diffusion coefficient values and decreased FA values of the ventral and central portions of the pons, middle cerebellar peduncle, and internal capsules using DTI.[7] In 2016, using DTT, Jang et al demonstrated injury of the CPCT in a patient who showed severe truncal ataxia following bilateral tegmental pontine hemorrhage.[9] Recently, Jang and Kwon reported on a patient who showed mild truncal ataxia (SARA score: 8 points) due to injury of the CPCT following mTBI.[10]

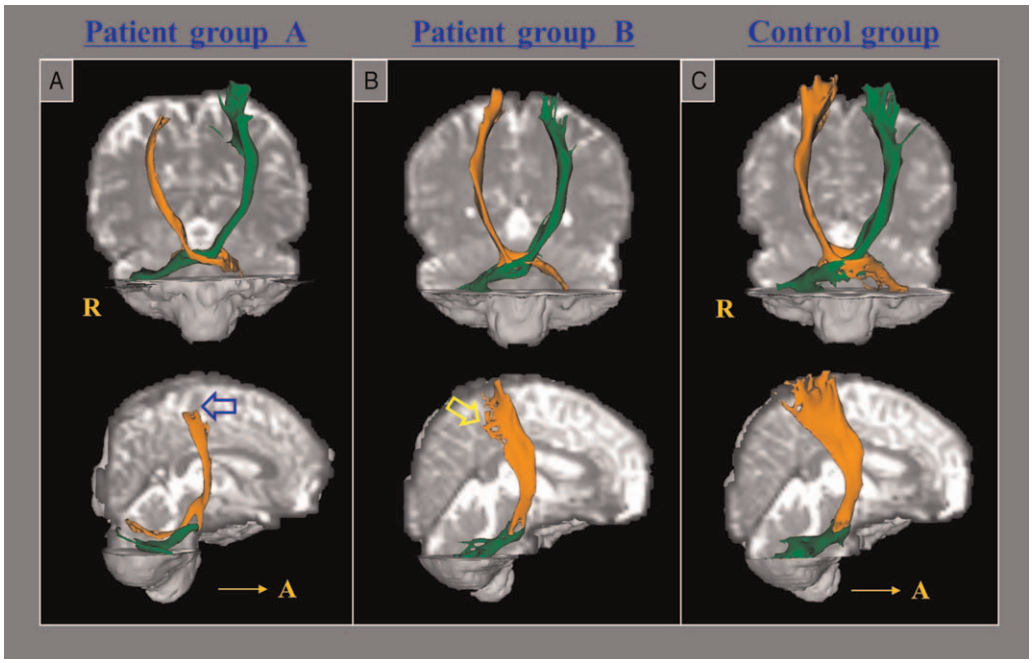

Figure 1. Diffusion tensor tractography for the cortico-ponto-cerebellar tract (CPCT). (A) a representative subject (49-year-old female) of patient group A who showed ataxia (injury of the CPCT; blue arrow), (B) a representative patient (45-year-old female) of patient group B who did not show ataxia (injury of the CPCT; yellow arrow). (C) A representative subject (44-year-old female) of the control group.

To the best of our knowledge, the current study is the first to investigate CPCT injuries in a series of consecutive patients who experienced ataxia after TBI. However, the limitations of this study should be considered. First, DTT could lead to both false positives and negatives throughout the white matter of the brain due to multiple fiber directions in a voxel or partial volume effects. Second, other neural structures that might be related to ataxia, such as the basal ganglia, the cortico-ponto-cerebellar tract, the dentate-rubro-thalamic tract and the cerebellar peduncle, were not examined because the main purpose of this study was to describe CPCT injury in patients with mild TBI. Last, because this study was conducted retrospectively, we were not able to examine the detailed clinical evaluation data for the CPCT injury.[24] Further prospective studies to clarify this potential association and the clinical data of ataxia with injury of CPCT should be encouraged.

In conclusion, injury of the CPCT was demonstrated in patients who showed ataxia following mild TBI. The results of this study suggest that DTT for the CPCT would be useful for evaluation of patients with ataxia after mTBI because mTBI usually does not show any abnormalities on conventional brain MRI. In addition, patients with mTBI cause several neural injury, but among them, patients with ataxia following mTBI can be caused by several neural injuries. CPCT is known as the neural pathway most related to ataxia, but it is insufficient to explain everything about ataxia. However, according to our results, it can be explained that patients with ataxia following mTBI are accompanied by impairment of CPCT.

Author contributions

Methodology: HanDo Lee.
Writing – original draft: HanDo Lee.
Writing – review & editing: SungHo Jang.

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