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Original Research

Cerebellar Peduncle Injuries in Patients with Mild Traumatic Brain Injury

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Abstract

Background: The cerebellum is connected to the brain stem by three pairs of cerebellar peduncles (CPs)—superior (SCP), middle (MCP), and inferior (ICP)—which carry proprioceptive information to regulate movement and maintain balance and posture. Injury or damage to the CPs caused by tumors, infarcts, or traumatic brain injuries (TBI) results in poor coordination and balance problems. Current data on CP-related injuries and their effect on balance control are sparse and restricted to a few case studies. There have been no studies to date that have investigated CP injuries in a large sample of patients with balance problems following a mild TBI. Hence, we investigated CP-related injuries in patients with balance problems following mild TBI using diffusion tensor tractography (DTT). **Methods**: Twenty-one patients with TBI and 21 normal subjects were recruited for this study. Balance was evaluated using the Balance Error Scoring System (BESS). Three DTT-related parameters—fractional anisotropy (FA), apparent diffusion coefficient (ADC), and fiber number (FN) of the CPs—were measured. **Results**: The FN values of the SCP and ICP in the patient group were significantly lower than those in the control group ($p < 0.05$). No significant differences in the FA, ADC, and FN values of the MCP were observed between the patient and control groups ($p > 0.05$). **Conclusions**: Using DTT, we demonstrated injuries to the SCP and ICP in mild TBI patients with balance problems. Our results suggest that DTT could be a useful tool for detecting injuries to the CPs that may not be identified on conventional brain magnetic resonance imaging in mild TBI patients.

Keywords: balance; cerebellar peduncles; cerebellum; diffusion tensor tractography; mild traumatic brain injury

1. Introduction

The cerebellum plays a crucial role in the regulation of movement and maintenance of balance and posture. In addition to its well-defined role in motor coordination, there is increasing evidence that the cerebellum contributes to several cognitive features and emotional control [1–3]. The three cerebellar peduncles (CPs), which connect the cerebellum to the brain stem and cerebrum, are involved in motor control and carry somatosensory information, such as that involved with proprioception (the body's ability to sense movement, action, and location), and vestibular information (the sense of balance and information about body position) [1–3]. The superior cerebellar peduncles (SCPs) are paired (afferent and efferent) tracts that connect the cerebellum to the mid-brain containing the red nucleus and the ventrolateral thalamus involved in motor control and continue to the cerebral cortex via the thalamocortical pathway [4]. They carry vestibular information and proprioceptive inputs for motor control [4]. The middle cerebellar peduncle (MCP) contains only the afferent tract connecting the pontine nucleus to the cerebellum and is associated with higher cognitive and motor-sensory functions, thereby modulating skilled movements [4]. The inferior cerebellar peduncle (ICP) has four afferent tracts and one efferent tract connecting the spinal cord to the cerebellum [4]. It integrates somatosensory information, including the proprioceptive and motor vestibular inputs for balance and posture maintenance [4], for motor control, such as motor coordination, balance control, and gait, and other types of skilled movements [1–5]. Injuries to the CPs caused by tumors, infarcts, and traumatic brain injury (TBI) can result in loss of motor control [5–14].

Traumatic brain injury is a broad term that describes a vast array of injuries from focal to diffuse and is a major cause of functional disabilities such as motor weakness, imbalance [15,16]. Studies have reported that TBIs to the medial lemniscus and cerebellum are associated with poor balance [17–22]. Caeyenberghs *et al*. (2012) [19] demonstrated that lower connectivity between the cerebellum and parietal gyrus was significantly correlated with poor balance in young patients with traumatic axonal injury (TAI). In terms of severity, TBI is classified into three types: mild, moderate, and severe [23]. Mild TBI accounts for 70–85% of all TBIs [23,24]. While loss of balance and stability is a common physical symptom following mild TBI, it is difficult to detect the lesion using conventional brain computed tomography (CT) and magnetic resonance imaging (MRI) [25,26]. However, diffusion tensor imaging (DTI) makes it possible to probe microscopic or small injuries that are invisible in two-dimensional images by measuring the directional coherence of water diffusion in white matter [27].

Furthermore, diffusion tensor tractography (DTT), derived from DTI, has the advantage of using three dimensions to visualize and evaluate specific neural tracts by measuring the quantitative indices of fractional anisotropy (FA), apparent diffusion coefficient (ADC), and fiber number (FN) [28,29]. Thus, many studies have used DTT to evaluate neural tract injuries following mild TBI [30–32]. Specifically, injuries to several neural tracts, including the corticobulbar tract, fornix, and spinothalamic tract following mild TBI, have been reported using DTT [30–32]. However, there is very little data on CP-related injuries in mild TBI, barring one case study on an injury to the ICP [13]. To date, no study has investigated a large sample of patients with balance problems following a mild TBI for injuries to the three CPs. This study hypothesized that injury to CPs and mild TBI could be the cause of balance problems in these patients.

Thus, we used DTT to investigate injuries to the three CPs in patients with balance problems following mild TBI.

2. Materials and Methods

2.1 Subjects

We recruited twenty-one patients (male: 10, female: 11, mean age: 42.4 ± 9.6 years, range: 28~58 years) with mild TBI and 21 normal healthy subjects (male: 10, female: 11, mean age: 40.5 ± 9.2 years, range: 27~57 years) with no previous history of neurological, physical, or psychiatric illnesses were recruited as controls for this study (Table 1). Patients were recruited according to the following inclusion criteria: (1) loss of consciousness for <30 minutes, post-traumatic amnesia for ≤24 hours, and initial Glasgow Coma Scale score of 13–15 [24], (2) absence of a specific lesion on a brain MRI (T1-weighted, T2-weighted, and fluid attenuated inversion recovery images), (3) complaints of balance or gait disturbance after the onset of head trauma, and (4) no history of previous head trauma, neurological, or psychiatric disease. The patients and control subjects provided signed, informed consent, and the study protocol was approved by our institutional review board (approval number: YUMC 2021-03-014).

2.2 Clinical Evaluation

Balance was evaluated using the Balance Error Scoring System (BESS), a reliable and valid tool for assessing postural stability [33]. Three different stances (double-leg [hands on the hips and feet together], one-leg [standing on the non-dominant leg with hands on hips], and tandem stances [non-dominant foot behind the dominant foot]) were tested twice, once on a firm surface and once on balance foam for a total of six trials. The order of the clinical tests was randomized between subjects and sessions, with each test lasting 20 seconds. Subjects were instructed to maintain balance, make any necessary adjustments, and return to the testing position as quickly as possible. Performance was scored by the addition of 1 error point for each error committed, and the range of scores was 0–60 (lower scores indicate better balance and fewer errors). The average BESS score in the patient group (20.7 ± 5.8) was significantly different to that in the control group (10.6 ± 4.3).

Table 1. Demographic and clinical data of the patient and control groups.

	Patient group	Control group	*p*-value
Sex (male:female)	10:11	10:11	1.000
Mean age, years	42.4 (9.6)	40.5 (9.2)	0.373
LOC, minutes	5.14 (6.97)		
PTA, minutes	14.62 (21.67)		
GCS score	14.86 (0.48)		
Mean duration to DTI, months	5.4 (3.9)		
BESS score	20.7 (5.8)	10.6 (4.3)	0.000*

Values represent mean (± standard deviation); LOC, loss of consciousness; PTA, post-traumatic amnesia; GCS, Glasgow Coma Scale; DTI, diffusion tensor imaging; BESS, balance error scoring system.

*Significant difference between patient and control groups, $p < 0.05$.

2.3 Diffusion Tensor Imaging

Diffusion tension imaging data were acquired 5.4 ± 3.9 months after the onset of mild TBI using a 6-channel head coil on a 1.5T Philips Gyroscan Intera (Philips, Ltd, Best, the Netherlands) with single-shot echo-planar imaging. For each of the 32 non-collinear diffusion-sensitizing gradients, 70 contiguous slices parallel to the anterior commissure-posterior commissure line were acquired. The imaging parameters were as follows: acquisition matrix = 96 × 96; reconstructed matrix = 192 × 192; field of view = 240 × 240 mm^2; repetition time (TR) = 10,398 ms; echo time (TE) = 72 ms; parallel imaging reduction factor = 2; echo planar imaging (EPI) factor = 59; b = 1000 s/mm^2; and slice thickness = 2.5 mm (acquired voxel size = 2.5 × 2.5 × 2.5 mm^3). Prior to the fiber tracking, an eddy current correction was applied to correct the head motion effect and image distortion using the functional magnetic resonance imaging of the brain (FMRIB) Software Library [34]. DTI-Studio software (Center of Magnetic Resonance Microimaging, Johns Hopkins Medical Institute, Baltimore, MD, USA) based on deterministic tracking was used for the reconstruction of the three CPs [35,36]. For the SCP, regions were defined as follows: region of interest (ROI) 1—the junction of the SCP between the upper pons and cerebellum; ROI 2—between the lateral wall of the fourth ventricle and the ICP at the fourth ventricle level on the color map. For the MCP: ROI 1—the anterior junction of the MCP between the pons and cerebellum, and the posterior; ROI 2—junction of the MCP between the pons and cerebellum on the color map. For the ICP: ROI 1—restiform body; ROI 2—the caudal part of the SCP on the axial view at the upper pons level on the color map. Fiber tracking was started at the center of a seed voxel with an FA >0.2 and ended at a

Table 2. Results of diffusion tensor tractography parameters values of three cerebellar peduncles of the patient and control groups.

		Patient group			Control group		
		FA	ADC	FN	FA	ADC	FN
SCP	Right	0.48 (0.03)	0.84 (0.06)	1086.38 (574.94)	0.48 (0.02)	0.82 (0.03)	1456.41 (519.43)
	Left	0.49 (0.03)	0.81 (0.04)	1121.10 (620.93)	0.50 (0.03)	0.80 (0.03)	1603.36 (546.23)
	Both	0.49 (0.03)	0.82 (0.05)	1103.74* (591.30)	0.49 (0.03)	0.81 (0.03)	1529.89 (531.98)
MCP	Right	0.51 (0.02)	0.79 (0.03)	4879.43 (1243.08)	0.51 (0.01)	0.80 (0.03)	4606.55 (1193.04)
	Left	0.51 (0.02)	0.80 (0.03)	4902.76 (1105.38)	0.52 (0.01)	0.80 (0.03)	4774.23 (922.01)
	Both	0.51 (0.02)	0.79 (0.03)	4891.10 (1161.87)	0.51 (0.01)	0.80 (0.03)	4690.39 (1057.11)
ICP	Right	0.48 (0.03)	0.84 (0.04)	279.57 (83.13)	0.48 (0.02)	0.85 (0.03)	326.32 (64.39)
	Left	0.48 (0.03)	0.86 (0.06)	239.29 (102.18)	0.47 (0.03)	0.86 (0.03)	319.59 (76.36)
	Both	0.48 (0.03)	0.85 (0.05)	259.43* (94.23)	0.48 (0.03)	0.85 (0.03)	322.95 (69.89)

Values represent mean (± standard deviation); FA, fractional anisotropy; ADC, apparent diffusion coefficient; FN, fiber number; SCP, superior cerebellar peduncle; MCP, middle cerebellar peduncle; ICP, inferior cerebellar peduncle.
*Significant differences between patient and control groups, $p < 0.05$.

voxel with an FA of <0.2 and a tract turning-angle of <60 degrees. The FA, ADC, and FN parameters of the CPs were measured.

2.4 Statistical Analysis

SPSS software (SPSS for Windows, Version 15.0; SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. Levene's Test for equality of variances was used to assess the meeting of the statistical assumption of homogeneity of variance between the patient and control groups, and equal variance was met. An independent *t*-test was used to compare the BESS score and DTT parameters (FA, ADC, and FN values) between the patient and control groups. The null hypothesis of no difference was rejected if the p-values were less than 0.05. The statistical power of the sample size was calculated using G*Power 3.1 (Version 9.4, Heinrich Heine University Düsseldorf, Düsseldorf, North Rhine-Westphalia, Germany) and showed a 0.5 effect size, 0.05 α error probability, and 0.34 power (1-β error probability).

3. Results

Thinning of both SCPs and discontinuation of both ICPs were observed in the patient group when compared with the control group (Fig. 1). A summary of the results of the CP-related DTI parameters measured in the patient and control groups is shown in Table 2. The FN values of the SCP and ICP in the patient group were significantly lower than the values in the control group ($p < 0.05$). In contrast, there were no significant differences in the FA and ADC values of the SCP and ICP between the patient and control groups ($p > 0.05$). No significant differences were observed between the patient and control groups in the FA, ADC, and FN values of the MCP ($p > 0.05$).

4. Discussion

In the current study, injuries to the three CPs were investigated using DTT in patients with balance problems following mild TBI. The patient group showed injuries to the SCP and ICP (as observed by a decrease in the FN value) compared with the control group. However, based on the FN values, the MCPs in the patient group did not appear to be injured. This could be attributed to the more robust anatomical characteristics of the MCP, with large or thick fibers relative to the SCP and ICP [4]. In addition, the junction areas between the brain stem and the cerebellum involving the SCP and ICP are probably the most vulnerable to injuries [6]. Among the commonly assessed DTT parameters, the FA, ADC, and FN have been widely used to detect injuries of the neural tracts [27,37]. The FA value measures the directionality of diffusion and reflects fiber density and axonal diameter, ranging from 0 to 1 [37]. The ADC value is an index of the rate of diffusion averaged over all directions [37]. The FN value indicates the volume of the neural tract based on the number of voxels within the neural tract [37]. Thus, a decrease in the FA or FN or an increase in the ADC represents injuries of the neural tract [27,37]. As the patients did not show any specific lesions on conventional MRIs, we believe the decrease in the FN of the SCP and ICP in the patient group could be at least partly ascribed to balance problems.

Several DTI-based studies have reported damage to CPs in patients with brain injuries caused by tumors, multiple sclerosis, and infarcts [5–8]. Hong *et al.* (2009) [6] investigated the CPs in six patients with gait and balance problems and found injuries to the SCP and ICP at the junction area between the brain stem and cerebellum following a diffuse axonal injury. In 2015, Drijkoningen *et al.* [7] demonstrated that improvements in balance were associated with recovery of the injured ICP in 19 patients with moderate to severe TBI. In 2020, Gera *et al.* [5] reported that SCP and ICP injuries were related to posture sway in 29 patients

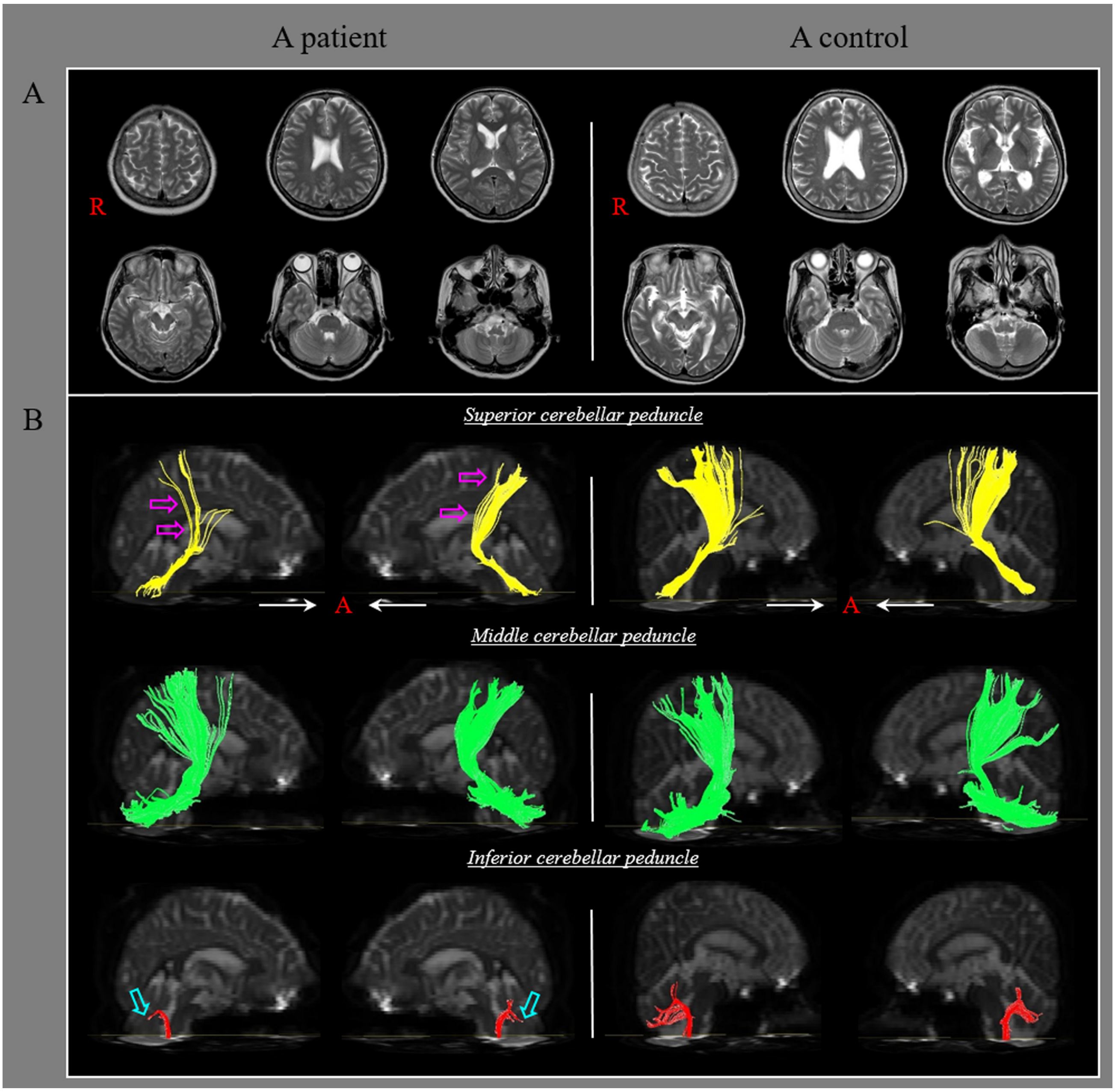

Fig. 1. Results of brain magnetic resonance (MR) images and diffusion tensor tractography of the three cerebellar peduncles. (A) T2-weighted brain MR images show no abnormalities in a patient and a control. (B) Results of diffusion tensor tractography of the three cerebellar peduncles in a patient and a control. Compared with the control, thinning (purple arrows) of both superior cerebellar peduncles and discontinuation (sky-blue arrows) of both inferior cerebellar peduncles are seen in the patient.

with multiple sclerosis. They asserted that the SCP contributed to the control of the standing posture with visual information, and that the ICP contributed to the control of standing balance regardless of visual information. Kim *et al*. (2021) [8] demonstrated that an injured ICP showed a moderate correlation with gait function in 27 patients with hemorrhagic stroke. All the studies indicated that injuries to the SCP and ICP were associated with balance or gait problems in patients with brain injuries. The results of our study agree with the results of these earlier studies.

Few DTT-based studies have reported CP injury in patients with balance problems [9–14]. Yamada *et al*. (2003) [9] demonstrated that the forward-leaning posture and inability to walk in a patient with a lateral medullary infarct were ascribed to an injury of the ICP. In 2010, Hong and Jang described injuries to the three CPs that were involved with poor balance in six patients with cerebellar infarcts [10]. Kwon and Jang (2012) [11] found injuries of various neural tracts, including the corticospinal tract, fornix, and ICP, in a patient with gait disturbance following a diffuse axonal injury. Subsequently, Kim *et al*. (2014) [12]

found that an injured SCP affected the gait and balance in a patient with a tumor. They also reported that the recovery of the SCP mainly contributed to an improvement of the balance and gait function after 3 months. In 2019, Kim *et al*. [14] demonstrated that decreased axial diffusivity in the left ICP positively correlated with poor balance control in 15 patients with mild to moderate TBI. One case study in three patients with mild TBI investigated the injury to the ICP and demonstrated that the gait and balance problems could be ascribed to a decrease in the FN of the ICP [13]. In all these studies, injuries to the SCP and ICP were related to balance problems, as was seen in our study. In addition, because the functions of the SCP and ICP are to carry and integrate vestibular and proprioception information, the balance problems in our patients appeared to be ascribed to injuries to the SCP and ICP. To the best of our knowledge, this is the first study to demonstrate injuries to both the SCP and ICP using DTT in a large number of patients with mild TBI. However, some limitations of this study should be considered [38,39]. First, we recruited patients who had been admitted for rehabilitation at a university hospital. Therefore, it is possible that among all the patients with mild TBI, we only recruited chronic patients with severe clinical manifestations. Second, the fiber tracking technique is operator dependent. Third, DTT could lead to both false-positive and false-negative results throughout the white matter of the brain because of complex fiber configurations such as crossing or kissing fiber and partial volume effects.

5. Conclusions

Using DTT, we demonstrated that the balance problems in patients with mild TBI could be attributed to injuries to the SCP and ICP. Our results suggest that DTT could be useful in detecting injuries to CPs that may not be detected on conventional brain MRI in patients with mild TBI.

Availability of Data and Materials

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

Author Contributions

SHJ: study concept and design, manuscript development, writing, and critical revision of the manuscript for intellectual content. HGK: study concept, funding, design, data analysis, and critical revision of the manuscript for intellectual content. Both authors contributed to editorial changes in the manuscript. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The patients and control subjects provided signed, informed consent, and the study protocol was approved by 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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