JKPT Vol. 35, No. 6, December 2023
J Kor Phys Ther 2023:35(6):190-194
pISSN 1229-0475 eISSN 2287-156X

Original Article

https://doi.org/10.18857/jkpt.2023.35.6.190

Injury of the Thalamocortical Pathway Between the Mediodorsal Nuclei and the Prefrontal Cortex in a Patient with Traumatic Brain Injury

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Purpose: Traumatic brain injury (TBI) refers to brain damage caused by external forces or trauma. TBIs can vary in severity and result from accidents, falls, sports injuries, assaults, or other forms of physical trauma. The prefrontal cortex (PFC) is known have roles in various cognitive functions. We report on a patient with traumatic brain injury who showed prefrontal symptoms after injury of thalamocortical connections between mediodorsal nuclei (MD) of thalamus and PFC.

Methods: A 54-year-old, male patient suffered a TBI as a result of a heavy object falling on his head. After onset of TBI, he showed typical symptoms of prefrontal lobe injury, including personality changes, memory impairment, and general cognition problem. The thalamocortical connections between MD and PFC (ventrolateral prefrontal cortex (VLPFC), dorsolateral prefrontal cortex (DLPFC), and obrbitofrontal cortex (OFC)) were reconstructed using diffusion tensor tractography. In terms of fractional anisotropy value, the right thalamocortical connections to the OFC were significantly lower than those of control subjects.

Results: The value of mean diffusivity in the right thalamocortical connections to the DLPFC was significantly higher than that of control subjects. By contrast, both VLPFC and left OFC showed significant decrement in the tract volume of thalamocortical connections compared with that of control subjects.

Conclusion: We reported on a patient who showed cognitive and neuropsychiatric impairment due to global injury of the thalamocoritcal connections between MD and PFC following TBI.

Keywords: Diffusion tensor imaging, Traumatic brain injury, Mediodorsal nuclei, Prefrontal cortex, Cognition

INTRODUCTION

Traumatic brain injury (TBI) is a type of damage that occurs when an external force or trauma causes damage to the brain.[1,2] TBIs can vary in severity and can be caused by a wide range of events, including accidents, falls, sporting injuries, assault or other forms of physical trauma.[1-3] The effects of traumatic brain injury can range from minor to severe, temporary or permanent. Minor TBI is the least severe form of TBI.[4] Common symptoms may include short loss of consciousness, confusion, headache, dizziness, memory problems, and mood changes. Most people with mild TBI fully recover with proper rest and care.[4] Moderate TBI involves more significant effects on the brain and can lead to more significant symptoms, including longer periods of unconsciousness, memory loss, and more severe cognitive and physical impairment.[2] Rehabilitation and medical treatment are often necessary for individuals with moderate TBI.[3] Severe TBI is characterized by significant and often life-threatening effects on the brain.[5] These injuries can lead to extended periods of unconsciousness, profound cognitive and physical disabilities, and organ or permanent disabilities.[5] Rehabilitation and continuous medical care are typically required for individuals with severe TBI.

The prefrontal cortex (PFC) is implicated in various cognitive functions, including memory, attention, decision making, and motivation.[6-9] Injury of the PFC can cause frontal syndrome, such as impairment of arousal, high cognitive function, working memory, recognition memory, behavior inhibition, attention, and motivation.[6-9] These problems can be caused by injury of other parts of the brain having connectivity with the

Received November 20, 2023 **Revised** December 18, 2023
Accepted December 26, 2023
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PFC.[9] In particular, the PFC has copious connectivity with the mediodorsal nuclei (MD) of the thalamus.[10] Recently, Diffusion Tensor Imaging (DTI) has enabled the three-dimensional visualization and estimation of the thalamocortical connection between the MD and PFC in the human brain.[11] However, little is known about frontal syndrome by injury of the thalamocortical connections between the thalamic MD and the PFC.

In the current study, we report on a patient with traumatic brain injury (TBI), who showed injury of the thalamocortical connections between the thalamic MD and PFC, which was demonstrated by DTT.

METHODS

1. Subjects

A 54-year-old male patient suffered a TBI as a result of a heavy lump of metal (80-100kg) falling on his safety helmet, shoulder, and leg while at a construction site. At onset of TBI, the patient exhibited impaired alertness, with a Glasgow Coma Scale score of 8, loss of consciousness for 6 hours, and post traumatic amnesia for 2 weeks. Brain CT at onset showed subdural hematoma (SDH) in the left temporoparietooccipital lobe, and he received conservative treatment for the SDH (Figure 1A). After onset of TBI,

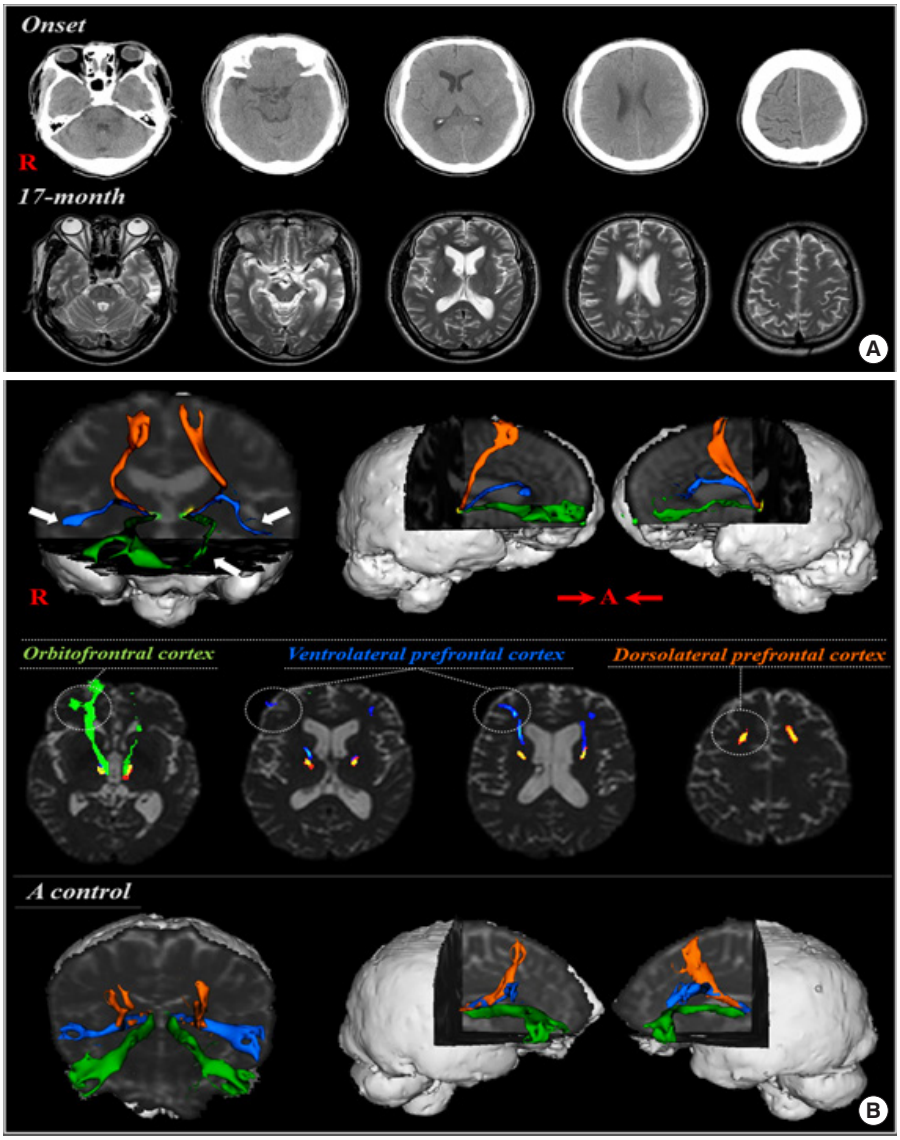

Figure 1. (A) Brain CT at onset shows subdural hematoma on the left temporoparietooccipital lobe, and brain MRI at 17 months after onset shows a leukomalactic lesion on the left temporal lobe. (B) Results of diffusion tensor tractography of the thalamocortical connections between the medial nucleus of the thalamus and the prefrontal cortex in the patient and a control subject. The integrities of the thalamocortical connections to the dorsolateral prefrontal cortex were preserved, however, the thalamocortical connection to both ventrolateral cortex and left orbitofrontal cortex are thinner than that of the control subject (arrow).

however, he showed typical symptoms of frontal lobe injury, including personality changes, memory impairment, and general cognition problem. However, brain MRI taken at 17 months after onset did not show remarkable injury on the brain except for the leukomalactic lesion in the left temporal lobe (Figure 1A). Ten age-matched control subjects (four male; mean age: 52.2 years, range: 43-62) with no neurologic disease history participated in this study. All subjects provided signed, informed consent, and the study protocol was approved by our institutional review board.

2. Clinical evaluation

Three scales were used for evaluation of cognitive function and neuropsychiatric symptoms at 17 months after onset; Korean Mini-Mental State Examination (K-MMSE), Clinical Dementia Rating (CDR), Memory Assessment Scale (MAS), and Modified Neuropsychiatric Inventory (MNI).[12-15] The patient showed severe cognitive and behavior impairment as follows: K-MMSE: 9, CDR: 1, MAS: short-term memory (68: 2%ile), verbal memory (56: < 1%ile), visual memory (91: 28%ile) and global memory (65: 1%ile), the MNI: irritability (4: 0-12), depression (12: 0-12), disinhibition (4: 0-12), and apathy (8: 0-12).

3. Diffusion tensor imaging

DTI data were acquired at 17 months after onset using a 6-channel head coil on a 1.5T Philips Gyroscan Intera (Philips, Best, The Netherlands) and single-shot echo-planar imaging. Each of the 32 non-collinear diffusion-sensitizing gradients was applied to acquire images across 67 contiguous slices that were oriented parallel to the anterior commissure-posterior commissure (AC-PC) line. Parameters of DTI: field of view (240×240mm^2); acquisition matrix (96×96); reconstructed matrix (192×192); TR (10,726ms); TE (76ms); EPI factor (49); b (1,000s/mm^2); SENSE factor (2); NEX (1); and a slice thickness (2.5mm).

4. Probabilistic fiber tracking

We used the Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (FSL v5.0; www.fmrib.ox.ac.uk/fsl) for DTI analysis. We corrected for head motion and image distortion caused by eddy currents using affine multi-scale two-dimensional registration. A seed region of interest (ROI) was set at the MD of the thalamus on a coronal plane. The ROI of thalamic MD was defined as previously studies.[10,11]

We defined the Dorsolateral Prefrontal Cortex (DLPFC) as encompassing Brodmann areas (BAs) 8, 9, and 46, and the Ventrolateral Prefrontal Cortex (VLPFC) as encompassing BAs 44, 45, and 47. We manually delineated target ROI on the coronal images for both the DLPFC and VLPFC, as previously described.[10,11] For the thalamocortical connection from the Mediodorsal Thalamus (MD) to the Orbitofrontal Cortex (OFC), we defined the OFC as encompassing BAs 47/12, 10, 11, and 13 and manually drew the target ROI on an axial image.[10,11] Thalamocortical connections between the MD and the PFC were determined by identifying fibers passing through the seed and target ROIs. We generated 5,000 samples from the seed voxel and visualized contact results, applying a threshold minimum of 1 streamline passing through each voxel for subsequent analysis. Fractional Anisotropy (FA), mean diffusivity, and tract volume in the three thalamocortical connections to each PFC were acquired.

RESULTS

Table 1 summarizes the DTI parameters for thalamocortical connections

Table 1. DTI parameters of thalamocortical connections between the medial nucleus of the thalamus and the prefrontal cortex in the patient and control subjects

	Rt hemisphere			Lt hemisphere		
	Fractional anisotropy	Mean diffusivity	Tract volume	Fractional anisotropy	Mean diffusivity	Tract volume
DLPFC	0.312	1.030**	655.000	0.348	0.812	817.000
VLPFC	0.346	0.897	285.000*	0.362	0.814	269.000*
OFC	0.268*	0.941	1,790.000	0.351	0.846	424.000*
	Control subjects (n=10)					
	Fractional anisotropy		Mean diffusivity		Track volume	
DLPFC	0.327 (0.020)		0.851 (0.058)		1,166.300 (397.717)	
VLPFC	0.323 (0.027)		0.846 (0.053)		1,198.500 (448.798)	
OFC	0.319 (0.025)		0.839 (0.056)		2,137.300 (768.090)	

DTI parameters are presented as mean (standard deviation). DLPFC: Dorsolateral prefrontal cortex, VLPFC: Ventrolateral prefrontal cortex, OFC: Orbitofrontal cortex. *: When the diffusion tensor imaging parameters were decreased two standard deviations below those of controls. **: When the diffusion tensor imaging parameters were increased two standard deviations over those of controls.

https://doi.org/10.18857/jkpt.2023.35.6.190

to each PFC in both patient and normal control subjects. Specifically, the right thalamocortical connections to the OFC exhibited a significant reduction in FA values exceeding two standard deviations from those of normal control subjects. Additionally, the mean diffusivity value in the right thalamocortical connections to the DLPFC showed an increase of more than two standard deviations compared to normal control subjects. Regarding tract volume in thalamocortical connections, both the VLPFC and the left OFC displayed a significant reduction exceeding two standard deviations from that of normal control subjects. Furthermore, the Diffusion Tensor Tractography (DTT) for the thalamocortical pathway to both the VLPFC and left OFC was observed to be thinner in the patient when compared to the right hemisphere and the DTT of control subjects, as illustrated in Figure 1B.

DISCUSSIONS

In the current study, we investigated injury of the thalamocortical connections between the thalamic MD and the PFC in a patient with TBI. According to the results of reconstructed thalamocortical connections to each PFC, the DLFPC showed significant increment of mean diffusivity value in the right hemisphere and the VLPFC showed significant decrement of tract volume in both hemispheres. In addition, the thalamocortical connection to the OFC showed significantly lower values of FA in the right hemisphere and tract volume in the left hemisphere. The FA value represents the degree of directionality of microstructures (e.g., axons, myelin, and microtubules) and the mean diffusivity value indicates the magnitude of water diffusion.[16] By contrast, the voxel volume is determined by the number of voxels contained within the neural tract.[17] Therefore, the decrement of the FA value and tract volume, and increment of mean diffusivity value of the thalamocortical connections to the PFC appeared to indicate injury of a neural tract.

The PFC plays a crucial role in various cognitive functions, such as working memory, attention, decision-making, behavior inhibition, and motivation.[6-9] Each sub-region of the PFC has a specific role in cognitive function and the known main functions of each sub-region of the PFC are as follows: the DLPFC – working memory, the VLPFC – deliberation of decision making and goal-directed behavior,[9,18-20] the OFC – recognition memory, motivation, emotional control, and inhibitory control of behavior.[7,8,21] Consequently, this patient's short-term memory and higher cognition impairment might be related to injury of the thalamocortical connections to the DLPFC and VLPFC. On the other hand, memory impairment (verbal and global memory impairment), irritability, depression, disinhibition, and diminished motivation might be caused by injury of the thalamocortical connection to the OFC.

Many previous studies have reported on the specific functional contribution of the PFC, which is concerned with cognition and behavior.[6-9] In addition, several studies demonstrated a frontal subcortical network which means universal connectivity of the PFC with other brain regions.[9-11,22] In particular, it is well known that the PFC has a significant amount of connectivity with the MD of thalamus.[10,11,22] In 2011, using DTI, Eckert et al., who reported a different connectivity of the MD and the centromedian-parafascicular complex of the thalamus with the PFC,[22] suggested that the MD of thalamus was more frequently connected to the PFC than the centromedian-parafascicular complex of the thalamus. In 2014, Jang & Yeo[11] identified thalamocortical connections and pathways between the MD of thalamus and three PFCs (DLPFC, VLPFC, and OFC) in the human brain, using DTT. However, no study has reported on the frontal syndrome by injury of thalamocortical connection between MD of thalamus and PFC. Therefore, to the best of our knowledge, this is the first DTI study demonstrating injury of the thalamocortical connection between the thalamic MD and the PFC, and its related cognitive and neuropsychiatric impairment in a patient with TBI.

CONCLUSION

In conclusion, we reported on a patient with global injury of the thalamocortical connection to the PFC who showed frontal syndrome following TBI. It appears that dementia and cognitive impairment was related to the injury of thalamocortical connections to the DLPFC and VLPFC, and decreased motivation, disinhibition, and memory impairment in this patient was related to injury of the thalamocortical connection to the OFC. Therefore, we suggest that evaluation of the thalamocortical connection to the PFC would be useful for patients with TBI. However, there are several limitations to this study that should be taken into account. First, while DTI is a powerful anatomical imaging tool that can illustrate the gross fiber architecture, it may have limitations in accurately representing complex fiber regions and crossings, potentially leading to underestimation or overestimation of fiber tracts.[23] Second, this study is constrained by its nature as a case report. Therefore, we recommend conducting larger-scale complementary studies with a more comprehensive evaluation of frontal syndrome resulting from injury to the thalamocortical connections to the PFC.

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