● IMAGING IN NEURAL REGENERATION

Injury of the Papez circuit in a patient with traumatic spinal cord injury and concomitant mild traumatic brain injury

Little is known about brain injury in concomitant mild traumatic brain injury (TBI) following traumatic spinal cord injury (TSCI). In this study, we reported on a male patient with memory impairment who showed injury of the Papez circuit following TSCI and concomitant mild TBI. A 59-year-old male underwent posterolateral fusion on T_{11}–L_2 due to an L_1 burst fracture after falling from a height of 10 meters. The patient had a T_{10} incomplete lesion (American Spinal Injury Association impairment scale C) and he complained of memory impairment, which was detected after transfer to the rehabilitation department. The patient met the criteria of mild TBI and showed memory impairment at 4 weeks after onset as follows: Wechsler Adult Intelligence Scale: 101 and the Memory Assessment Scale (global memory: 61 [1%ile >]). On 4-week diffusion tensor tractography, the entire Papez circuit including thalamocortical tract, fornix, mammillothalamic tract, and cingulum was reconstructed in both hemispheres except for the left thalamocortical tract between the anterior thalamic nuclei and cingulated gyrus, and the right mammillothalamic tract between the mammillary body and anterior thalamic nuclei, which were thinner compared with the opposite side. In this patient, injury of the Papez circuit was related to memory impairment.

Traumatic brain injury (TBI) is frequently concomitant with TSCI (Richards et al., 1988; Wei et al., 2008). However, the precise incidence of comorbidity of TBI with TSCI has not been clearly determined: the estimated prevalence of concomitant TBI in patients with TSCI is 40–60% (Davidoff et al., 1988; Richards et al., 1988; Wei et al., 2008). Because of the high incidence of comorbidity of TBI with TSCI, diagnosis of concomitant TBI has been an important topic in rehabilitation of patients with TSCI (Wei et al., 2008). Diffusion tensor tractography (DTT), which is derived from diffusion tensor imaging (DTI), has enabled diagnosis of brain injuries not detected on conventional brain MRI and has been used in diagnosis of brain injuries which were concomitant with TSCI (Wei et al., 2008). However, little is known about brain injury in concomitant mild TBI, which accounts for 70–90% of all cases of TBI, following TSCI (De Kruijk et al., 2001).

Memory impairment is a major clinical feature following mild TBI (Kurca et al., 2006). The Papez circuit, consisting of the hippocampus, fornix, mammillary body, anterior thalamic nucleus, cingulate gyrus, cingulum, and parahippocampal gyrus, is an important neural structure for memory, particularly episodic memory (Papez, 1995; Markowitsch, 1997). DTT has enabled three-dimensional reconstruction and evaluation of the entire neural tracts in the Papez circuit and many studies have reported on injury of neural structures in the Papez circuit in patients with mild TBI (Niogi et al., 2008; Lee and Jang, 2014; Yang et al., 2016). However, no study on injury of the Papez circuit in patients with concomitant mild TBI following TSCI has been reported so far.

In this study, we reported on a patient with memory impairment who showed injury of the Papez circuit was detected on DTT following TSCI and concomitant mild TBI.

A 59-year-old male who suffered an L_1 burst fracture after falling from a height of 10 meters while driving a car underwent posterolateral fusion on T_{11}–L_2 with regional autograft bone and allograft bone at the neurosurgery department of a university hospital. After 2 weeks from onset, he was transferred to the rehabilitation department of the same hospital to undergo rehabilitation. The patient had a T_{10} incomplete lesion (American Spinal Injury Association impairment scale C) and he complained of memory impairment, which was detected after transfer to the rehabilitation department. The patient met the criteria of mild TBI: loss of consciousness - 2 minutes, post-traumatic amnesia - approximately 4 minutes, Glasgow Coma Scale score - 15, and no specific lesion on conventional brain MRI performed at 4 weeks after onset (**Figure 1A**) (Alexander, 1995). The patient showed memory impairment at 4 weeks after onset: Wechsler Adult Intelligence Scale: 101 and the Memory Assessment Scale (global memory: 61 (1%ile >), short term memory: 71 (3% ile), verbal memory: 73 (4% ile), and visual memory: 66 (1% ile) (Wechsler, 1981; Williams, 1991). The study protocol was approved by the institutional review board of Yeungnam University Hospital (approval No. YUMC 2015-07-064).

DTI data were acquired at 4 weeks after onset using a 6-channel head coil on a 1.5 T 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 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 × 240 mm^2; repetition time = 10,398 ms; echo time = 72 ms; parallel imaging reduction factor = 2; b = 1,000 s/mm^2; and a slice thickness of 2.5 mm. The Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library was used to analyze DTI data with routine options (0.5 mm step lengths, 5,000 streamline samples, curvature thresholds = 0.2). Prior to the fiber tracking, eddy current correction was applied to correct the head motion effect and image distortion using FMRIB Software Library.

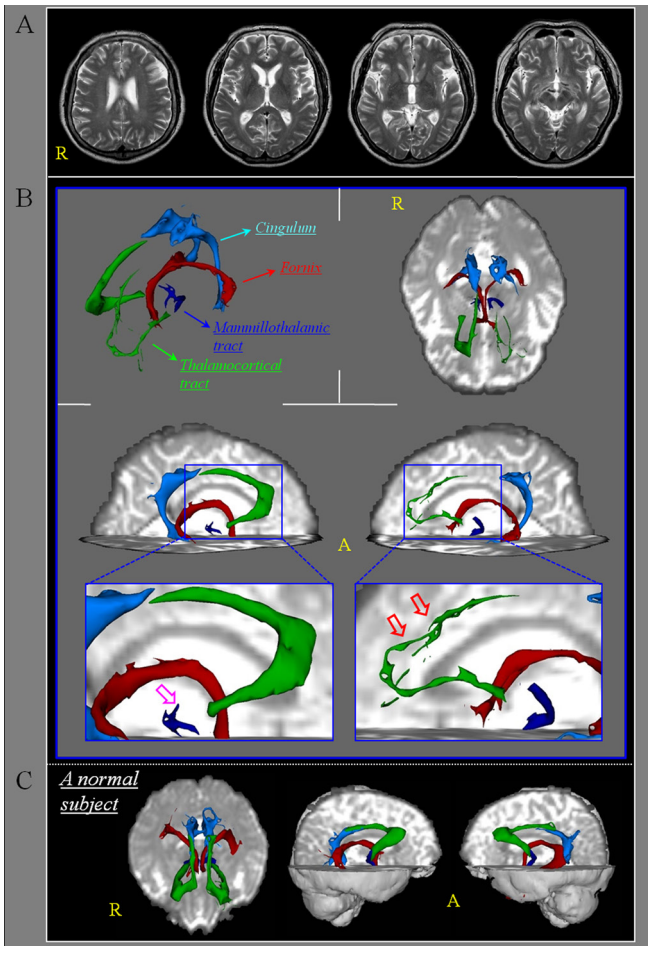

Figure 1 Brain MRI imaging and diffusion tensor tractography for a 59-year-old male patient with traumatic spinal cord injury and concomitant mild traumatic brain injury.
(A) T2-weighted brain magnetic resonance images at 4 weeks after onset show no abnormality. (B) Results of diffusion tensor tractography for each neural tract of the Papez circuit: the entire Papez circuit, including thalamocortical tract (green), cingulum (sky-blue), fornix (red), and mammillothalamic tract (blue), was well reconstructed, except for the left thalamocortical tract (red arrows) and the mammillothalamic tract (purple arrow), which were thinner compared to a normal control subject (61-year-old male). (C) Diffusion tensor tractography for the Papez circuit in a normal control subject (61-year-old male). R: Right; A: anterior.

Each neural tract of the Papez circuit was determined by selecting fibers passing through seed and target regions of interest (ROIs) as follows (Concha et al., 2005; Kwon et al., 2010; Jang and Yeo, 2013): thalamocortical tract: seed ROI - the cingulate gyrus, target ROI 1 - anterior limb of the internal capsule, target ROI 2-anterior thalamic nuclei; fornix: seed ROI - mammillary body, target ROI - crus of the fornix; mammillothalamic tract: seed ROI-anterior thalamic nucleus, target ROI 1 - portion of isolated mammillothalamic tract, target ROI 2 - mammillary body; cingulum: seed ROI - middle portion of the cingulum, target ROI - posterior portion of the cingulum.

On 4-week DTT, the entire Papez circuit including the thalamocortical tract, fornix, mammillothalamic tract, and cingulum was reconstructed in both hemispheres except for the left thalamocortical tract between the anterior thalamic nuclei and cingulated gyrus, and the right mammillothalamic tract between the mammillary body and anterior thalamic nuclei, which were thinner compared with the opposite side and a normal control subject (61-year-old male) (**Figure 1B**).

In this study, DTT findings of the neural tracts of the Papez circuit were investigated in a patient with TSCI who suffered from concomitant mild TBI. Injuries of the left thalamocortical tract were found between the anterior thalamic nuclei and cingulate gyrus and the right mammillothalamic tract between the mammillary body and anterior thalamic nuclei. Because no definite brain lesion was detected on conventional brain MRI, traumatic axonal injury was the most likely pathogenetic mechanism for the injury of the Papez circuit (Alexander, 1995; Povlishock and Christman, 1995). This patient showed severe memory impairment, even though whole cognition in terms of the Wechsler Adult Intelligence Scale was within normal range. As a result, severe memory impairment of this patient appeared to be ascribed, at least in part, to injury of the Papez circuit. Our result suggests the importance of evaluation of the Papez circuit in patients complaining of memory impairment following TSCI, particularly mild TBI which does not show a definite brain lesion on conventional MRI, like in this patient.

Since the introduction of DTI, to the best of our knowledge, only one study reported on concomitant brain injury in patients with TSCI, using DTI (Wei et al., 2008). In 2008, Wei et al. evaluated the white matter using ROI method in seven patients with definite structural brain lesions on conventional MRI and found that fractional anisotropy was reduced in the same portion (genu and splenium) of the corpus callosum. As a result, this is the first study to demonstrate neural injury concomitant with mild TBI following TSCI. However, this study is limited because it is a single case report; thus, it is suggested that further studies involving large numbers of patients should be encouraged. Limitations of DTT should also be considered in interpretation of the results: although DTT is a good anatomic imaging tool which can demonstrate gross fiber architecture, the presence of kissing fibers in regions of fiber complexity or false positive fiber trajectories may result in underestimation (Parker and Alexander, 2005).

In conclusion, injury of the Papez circuit was demonstrated in a patient with TSCI who had suffered from concomitant mild TBI, using DTT. In this patient, injury of the Papez circuit appeared to be related to memory impairment. Therefore, evaluation of the Papez circuit using DTT would be helpful in patients with concomitant mild TBI who show memory impairment following TSCI.

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