IMAGING IN NEURAL REGENERATION

Appearance of a neural bypass between injured cingulum and brainstem cholinergic nuclei of a patient with traumatic brain injury on follow-up diffusion tensor tractography images

The human brain is known to contain a maximum of eight cholinergic nuclei: the basal forebrain region: the medial septal nucleus (Ch 1), the vertical nucleus of the diagonal band (Ch 2), the horizontal limb of the diagonal band (Ch 3), and the nucleus basalis of Meynert (Ch 4); the brainstem: the pedunculopontine nucleus (Ch 5), the laterodorsal tegmental nucleus (Ch 6), and the parabigeminal nucleus (Ch 8); and the thalamus: the medial habenular nucleus (Ch 7) (Nieuwenhuys et al., 2008; Naidich and Duvernoy, 2009). The cingulum is the neural tract extending from the orbitofrontal cortex to the medial temporal lobe (Mufson and Pandya, 1984). The cingulum plays an important role in memory because it is a passage of the medial cholinergic pathway, which provides cholinergic innervations to the cerebral cortex after originating from Ch 1 and Ch 2 as well as Ch 4 (mainly) (Selden et al., 1998; Nieuwenhuys et al., 2008; Hong and Jang, 2010).

Diffusion tensor tractography (DTT), which is derived from diffusion tensor imaging (DTI), enables three-dimensional visualization and estimation of the cingulum (Concha et al., 2005). As a result, many DTI studies have reported on injury of the cingulum following brain injury (Kraus et al., 2007; Sugiyama et al., 2009; Wu et al., 2010). On the contrary, several studies have reported on the mechanism for recovery of an injured cingulum: recovery of an injured cingulum and neural bypass between an injured cingulum and brainstem cholinergic nuclei (Yeo et al., 2012; Seo and Jang, 2013, 2014; Yoo et al., 2014), however, this recovery mechanism has not been clearly elucidated so far (Yeo et al., 2012; Seo and Jang, 2014; Yoo et al., 2014).

In the current study, we report on a patient with traumatic brain injury in whom a neural bypass was found between an injured cingulum and brainstem cholinergic nuclei on follow-up DTTs.

A 13-year-old male suffered from head trauma resulting from a pedestrian car accident. The patient lost consciousness for 2 months and experienced post-traumatic amnesia for 4 months from the time of the accident. The patient's Glasgow Coma Scale score was 5 on the day of head trauma. He received conservative management under the diagnosis of intraventricular hemorrhage in the lateral ventricle and diffuse axonal injury. The patient underwent rehabilitative management beginning at 1 month after onset. No specific lesion was observed on brain MRI (T1-weighted, T2-weighted, and Fluid attenuated inversion recovery [FLAIR] images) performed at 5 months after onset (**Figure 1A**). The patient showed memory impairment at 5 months after onset: Wechsler Adult Intelligence Scale: 43, and the Memory Assessment Scale (MAS, global memory: 62 [1%ile], short term memory: 76 [6%ile], verbal memory: 69 [2%ile], and visual memory: 60 [1%ile>]) (Wechsler, 1981; Williams, 1991). However, his short-term memory impairment had recovered to normal range at 12 months after onset: Wechsler Adult Intelligence Scale: 43, and the Memory Assessment Scale (MAS, global memory: 64 [1%ile], short term memory: 91 [28%ile], verbal memory: 61 [1%ile>], and visual memory: 87 [19%ile]) (Wechsler, 1981; Williams, 1991). Five age-matched control subjects (five male; mean age: 15.3 years, range: 11–17) with no history of neurologic disease were recruited for comparison of the configuration of the fornix.

DTIs were acquired twice, at 5 months and 12 months after onset, using a 1.5 T Philips Gyroscan Intera system (Philips, Ltd, Best, The Netherlands) equipped with a Synergy-L Sensitivity Encoding (SENSE) head coil using a single-shot, spin-echo planar imaging pulse sequence. For each of the 32 non-collinear diffusion sensitizing gradients, we acquired 60 contiguous slices 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, repetition time = 10,398 ms, echo time = 72 ms, parallel imaging reduction factor (SENSE factor) = 2, echo planar imaging factor = 59 and b = 1,000 s/mm^2, number of excitations = 1, thickness = 2.5 mm. Eddy current-induced image distortions were removed using affine multi-scale two-dimensional registration at the Oxford Centre for Functional Magnetic Resonance Imaging of Brain (FMRIB) Software Library (FSL; www.fmrib.ox.ac.uk/fsl). DTI-Studio software (CMRM, Johns Hopkins Medical Institute, Baltimore, MD, USA) was used for evaluation of the CST. The CST was reconstructed using fibers passing through two regions of interest (ROIs) on the color map. The cingulums were reconstructed using fibers passing through two ROIs on the color map (green color: middle and posterior portion of the cingulum). Termination criteria were fractional anisotropy (FA) < 0.15 and an angle change > 70°.

DTTs of the cingulum in control subjects originated from the basal forebrain and extended posteriorly along and over the corpus callosum. On both 5-month and 12-month DTTs of the patient, discontinuations were observed in both anterior cingulums. On 5-month DTT of the patient and control subjects, we did not observe any neural bypass between injured cingulum and brainstem cholinergic nuclei. However, on 12-month DTT, a neural bypass was observed between the right injured cingulum and right brainstem cholinergic nuclei (Ch 6 and 8) (**Figure 1A**).

Discussion

In the current study, we observed a neural bypass between

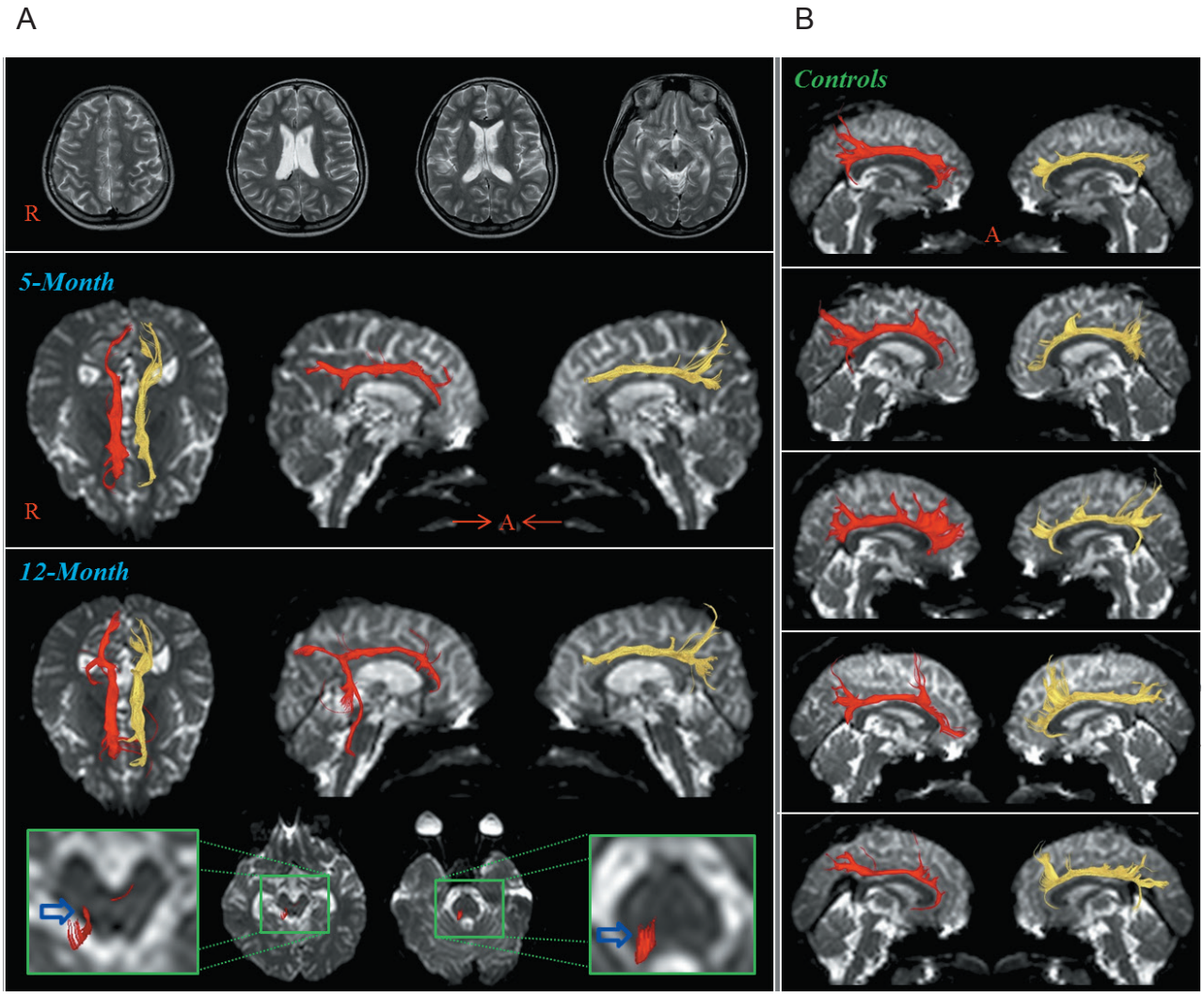

Figure 1 Conventional magnetic resonance (MR) images and diffusion tensor tractography (DTT) images of a 13-year-old male patient with traumatic brain injury.
(A) T2-weighted MR images showed no specific lesions. On both 5-month and 12-month DTT images, discontinuations were observed in both anterior cingulums (yellow: left, red: right). On 5-month DTT, we did not observe any neural bypass between injured cingulum and brainstem cholinergic nuclei. However, on 12-month DTT images, a neural bypass (blue arrows) was observed between the right injured cingulum and right brainstem cholinergic nuclei (Ch 6 and 8: blue arrows). (B) No neural bypass was observed between injured cingulum and brainstem cholinergic nuclei in five age-matched control subjects. R: Right; A; anterior.

the right injured cingulum, and the right brainstem nuclei (Ch 6 and 8) on 12-month DTT, in a patient with traumatic brain injury. This kind of neural bypass was not observed in any of five age-matched normal subjects or on 5-month DTT of the patient. Both 5-month and 12-month DTTs of the patient showed discontinuations in both anterior cingulums. It appears that the pathophysiological mechanism of both cingulums was traumatic axonal injury because conventional brain MRI did not show any specific lesion in any brain region. Discontinuation of both anterior cingulums indicates blockage of cholinergic innervation from the basal forebrain to the cerebral cortex. The patient showed significant recovery of short-term memory on MAS, from 76 to 91, even though other cognition on IQ and total memory did not show significant change with the appearance of the neural bypass on 12-month DTT. Short-term memory means the ability to store new information over seconds to minutes in the cerebral cortex (Harding and Beech, 1996; Gazzaniga et al., 2009). Considering that cortical cholinergic activity appears to be related to short-term memory formation, recovery of short-term memory in this patient appears to have been attributed to the presence of cholinergic innervation to the cerebral cortex through the neural bypass instead of the injured anterior cingulum (Miranda et al., 2003). As a result, the neural bypass between injured cingulum and brainstem cholinergic nuclei appears to compensate for injury of both anterior cingulums in obtaining cholinergic innervations. Our finding appears to be in agreement with that of a previous study demonstrating that patients in whom a neural bypass was found between injured cingulum and brainstem cholinergic nuclei showed better short-term memory (Yoo et al., 2014).

Since introduction of DTI, a few studies have reported on a neural bypass between the injured cingulum and brainstem cholinergic nuclei (Yeo et al., 2012; Seo and Jang, 2014; Yoo et al., 2014). In 2012, Yeo et al (2012) reported on a patient with discontinuations in both anterior cingulums following TBI in whom a neural bypass was found between the left injured cingulum and left Ch 5. Subsequently, Seo and Jang (2014) reported on a patient in whom a neural bypass was found between an injured cingulum and brainstem cholinergic nuclei (Ch 5 and 6) in the brainstem on DTT following an aneurysmal subarachnoid hemorrhage. In a recent study, using DTT, Yoo et al. (2014) investigated the relation between cognition and the neural bypass between injured cingulum and brainstem cholinergic nuclei in chronic patients with traumatic brain injury. According to their findings, patients who had a neural bypass showed better short-term memory than patients who did not have such a neural bypass.

In conclusion, we report on a patient with traumatic brain injury in whom a neural bypass was found between the injured cingulum and brainstem cholinergic nuclei concurrent with recovery of short-term memory at chronic stage of traumatic brain injury. We believe that this case may suggest one of the mechanisms for recovery of an injured cingulum following traumatic brain injury and it can provide a basis for development of a new therapeutic modality for treatment of an injured cingulum However, our results are limited to this case report. Further studies involving larger numbers of patients are required.

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