



● IMAGING IN NEURAL REGENERATION

Delayed degeneration of an injured spinothalamic tract in a patient with diffuse axonal injury

Diffuse axonal injury (DAI) is one of the devastating mechanisms of traumatic brain injury (TBI) and shows extensive subcortical lesions due to shearing forces induced by rapid acceleration-deceleration and rotation of the brain (Adams et al., 1982; Meythaler et al., 2001). As a result, conventional brain imaging techniques including brain MRI have been limited in demonstrating neuronal degeneration in patients with DAI. However, diffusion tensor tractography (DTT), which is derived from diffusion tensor imaging (DTI) has enabled three-dimensional reconstruction of the neural tracts (Jang and Seo, 2014). Since the introduction of DTI, several studies have demonstrated neuronal degeneration after TBI (Tomaiuolo et al., 2005; Hong and Jang, 2010; Kwon and Jang, 2014). However, little is known about delayed neuronal degeneration in patients with TBI.

The spinothalamic tract (STT) is the somatosensory neural tract responsible for pain and touch from the contralateral extremities and body (Hong et al., 2011). Many studies have reported on injury of the STT in patients with brain injury (Goto et al., 2008; Hong et al., 2012; Seo and Jang, 2013, 2014; Kim et al., 2015). In addition, injury of the STT has been suggested as the most plausible pathogenetic mechanism of central pain. However, to the best of our knowledge, no DTT study on delayed degeneration of an injured STT following DAI has been reported.

In this study, we reported on a patient who showed delayed degeneration of an injured STT following DAI, which was demonstrated with DTI.

A 27-year-old male who had suffered from head trauma resulting from colliding with a truck while sitting in a passenger seat in a sedan experienced loss of consciousness for 3 months. He underwent a compressive operation for a depressed skull fracture in the left frontal lobe. Brain MRI at onset corresponded to DAI (Figure 1A): grade 3 (hemorrhagic DAI lesions in the corpus callosum and pons) (Adams et al., 1982; Parizel et al., 1998). He had begun to feel pain in both hands and legs, and trunk since approximately 5 years after onset of head trauma. The characteristics and severity of pain were as follows: constant tingling and pricking sensation without allodynia or hyperalgesia (Visual Analogue Scale score: 3). Somatosensory function was determined using the subscales for tactile sensation and kinesthetic sensation of the Nottingham Sensory Assessment was normal (Lincoln et al., 1998). The electromyography study showed no evidence of peripheral nerve injury or radiculopathy. The study protocol was approved by the institutional review board of Yeungnam University Hospital (YUMC 2015-07-064).

DTI data were acquired twice (1 and 7 years after onset) using a 6-channel head coil on a 1.5T Philips Gyroscan Intera (Philips, Ltd., Best, the Netherlands) with 32 gradients. Imaging parameters were as follows: acquisition matrix = 96×96 , reconstructed to matrix = 192×192 , field of view = $240 \times 240 \text{ mm}^2$, repetition time = 10,398 ms, echo time = 72 ms, $b = 1,000 \text{ s/mm}^2$, and a slice thickness of 2.5 mm. Analysis of DTI data was performed using the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain Software Library (FSL:www.fmrib.ox.ac.uk/fsl) based on the probabilistic tractography method (5,000 streamline samples, 0.5 mm step lengths, curvature thresholds = 0.2) (Smith et al., 2004). For fiber tracking of the STT, the seed region of interest was placed on the isolated STT area (posterolateral to the inferior olivary nucleus and anterior to the inferior cerebellar peduncle in

the medulla) (Jang and Kwon, 2013). Two target regions of interest were placed on the portion of the ventro-postero-lateral nucleus of the thalamus and primary somatosensory cortex on the axial images (Jang and Kwon, 2013). The threshold of 2 streamlines was applied for the results of fiber tracking.

Partial tearing at the subcortical white matter in both STTs observed on 1-year DTT and both partially torn STTs showed severe degeneration at the subcortical white matter on 7-year DTT (Figure 1B).

In this study, the STT was followed up on DTT in a patient who showed delayed onset of central pain which had started 5 years after head trauma. On this patient's 1-year DTT, both STTs had already sustained mild injury because partial tearing was observed at the subcortical white matter. Because the conventional brain MRI did not show abnormality in the subcortical white matter and was compatible with DAI, we believe that the injuries of both STTs were caused by traumatic axonal injury (Adams et al., 1982; Alexander, 1995; Parizel et al., 1998). Although both STTs were partially injured on 1-year DTT, he did not complain central pain. However, after approximately 5 years after onset, the patient suffered from central pain in both hands and legs, and trunk. Consequently, delayed degeneration and central pain occurred 5 years after onset in both mildly injured STTs, and might be associated with delayed degeneration of both mildly injured STTs.

A few studies have reported on injury of the STT in patients with central pain following TBI (Seo and Jang, 2013, 2014; Kim et al., 2015). In 2014, Seo and Jang reported on damage of both STTs in a patient with central pain after mild TBI. The next year, Kim et al. (2015) demonstrated that injury of the STT was associated with the occurrence of central pain in 32 patients with mild TBI. On the other hand, regarding the central pain, Ofek and Defrin (2007) reported that a large portion of central pain in TBI started late following TBI: central pain in TBI first appeared at a mean onset time of 6.6 months after TBI (range: 6–66 months) and in 10 % of patients, onset of pain occurred after 12 months. Therefore, we think a significant portion of central pain in TBI might be associated with delayed degeneration of the STT. In-depth studies on this topic should be encouraged.

Two kinds of neuronal degeneration after primary direct insult to neuronal cells in the central nervous system have been suggested: primary and secondary degeneration (Li et al., 2014). Primary degeneration means the death of neurons and glial cells

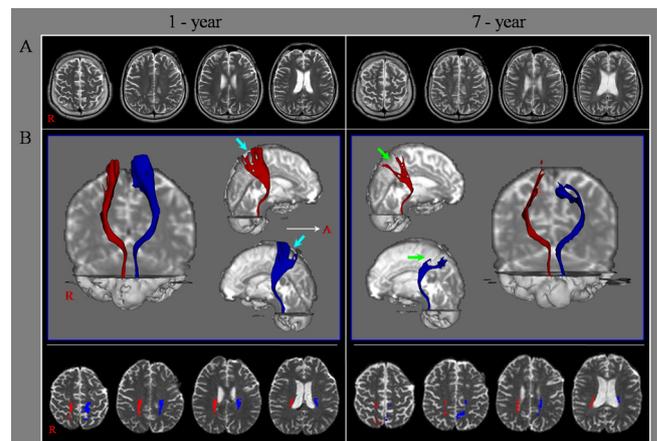


Figure 1 Brain MRI imaging and diffusion tensor tractography for a 27-year-old male patient with diffuse axonal injury. (A) Brain MR images at 1 and 7 years after onset show no abnormality. (B) Results of diffusion tensor tractography (DTT) for the spinothalamic tract (STT) in both hemispheres. Partial tearing at the subcortical white matter in both STTs is observed on 1-year DTT (sky-blue arrows) and both partially torn STTs show severe degeneration at the subcortical white matter on 7-year DTT (green arrows). A: Anterior; R: right.



as an early consequence of the primary pathological insult (Li et al., 2014). By contrast, secondary degeneration indicates the degeneration of neurons and glial cells caused by noxious factors released from neurons or glial cells damaged by the primary direct insult (Li et al., 2014). Secondary degeneration is initiated by pathological factors (calcium dysregulation, excessive free radicals, activation of proteases, overexpression of pro-apoptotic proteins, hydrolytic enzymes, and high-level glutamate) released by tissues damaged by the primary insult (Farkas and Povlishock, 2007; Li et al., 2014). Both apoptosis and necrosis are known to be involved in this degeneration (Farkas and Povlishock, 2007; Stoica and Faden, 2010; Li et al., 2014). Differentiation of secondary degeneration from primary degeneration based on the time-points after injury is difficult because there is no absolute time when primary damage evolves into delayed effects after TBI (LaPlaca et al., 2007; Li et al., 2014). On the other hand, Shiozaki et al. (2001) reported delayed neuronal loss which meant sudden appearance of a low-density area in the affected hemisphere at several months post-TBI in 8 out of 17 patients with severe head injury. Considering that the central pain started at 5 years after onset in this patient, we think that secondary or delayed degeneration was caused by the degeneration of the STT.

In conclusion, delayed degeneration of the STT was demonstrated in a patient who developed delayed-onset central pain following DAI. Our results suggest evaluation of the STT using DTT in patients with TBI complaining of delayed central pain having the characteristics of neuropathic pain. This study is limited because it was based on a single case; thus further complementary studies involving larger numbers of patients are required.

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