● IMAGING IN NEURAL REGENERATION

Recovery of an injured ascending reticular activating system with recovery from a minimally conscious state to normal consciousness in a stroke patient: a diffusion tensor tractography study

Consciousness is controlled by the ascending reticular activating system (ARAS) (Teasdale and Jennett, 1974; Jang and Lee, 2015; Jang et al., 2016a). Scientific medical strategies for recovery in patients with impaired consciousness are relatively few compared with other diseases. Therefore, research to clarify the neural structures in the ARAS involved in the recovery of impaired consciousness should be encouraged (Teasdale and Jennett, 1974; Schiff, 2010; Jang and Lee, 2015; Jang et al., 2016a). Several studies revealed that recovery of an injured ARAS contributed to recovery of impaired consciousness in several brain injuries (Teasdale and Jennett, 1974; Laureys et al., 2000; Giacino et al., 2004; Schiff, 2010; Jang et al., 2015, 2016a; Jang and Lee, 2015). However, there are no related diffusion tensor tractography (DTT) reports.

In our study, we report on DTT findings of an injured ARAS during recovery from a minimally conscious state (MCS) to normal consciousness in a stroke patient.

A 33-year-old male patient underwent extraventricular drainage and craniectomy for management of right putaminal intracerebral and intraventricular hemorrhage which occurred because of the rupture of the arteriovenous malformation in the right basal ganglia at 8 weeks after onset. The patient also underwent ventriculoperitoneal shunt operation for hydrocephalus (**Figure 1A**). He was transferred to the rehabilitation department from other university hospital at 5 months after onset. He had impaired consciousness, with a Glasgow Coma Scale score (GCS) of 9 (full GCS score 15: covering eye opening: 3, best verbal response: 2, and best motor response: 4; Teasdale and Jennett, 1974) and a Coma Recovery Scale-Revised (CRS-R) score of 8 (full CRS-R score 23: covering auditory: 1, visual: 2, motor: 3, verbal: 1, communication: 0, and arousal: 1; Giacino et al., 2004). He underwent rehabilitative therapy (physical therapy and occupational therapy). He took neurotropic drugs (methylphenidate, amantadine, levodopa, bromocriptine, venlafaxine, and baclofen) (Jang et al., 2014). After 3 months of rehabilitation at the university hospital, his consciousness was improved to full recovery (clearly distinct consciousness) on both GCS score 15 and CRS-R score 23 (Folstein et al., 1975; Yeo et al., 2013). The Mental State Exam (MMSE) score was 0 at 5 months after onset when he started rehabilitation and it increased to 18 after 3 months of rehabilitation (Jang and Kwon, 2015). He underwent rehabilitation at two other local rehabilitation hospitals and his consciousness level was maintained. The patient provided signed informed consent. This study was conducted retrospectively, and approval for the study was obtained from the Institutional Review Board of Yeungnam University Hospital (YUMC-2018-10-042) on October 22, 2018.

DTT data were acquired twice (5 and 22 months after onset) using a 6-channel head coil on a 1.5 T Philips Gyroscan Intera (Philips, Amsterdam, the Netherlands) with single-shot echo-planar imaging. Imaging scanning conditions 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 (SENSE factor) = 2, echo-planar imaging factor = 59, b = 1000 s/mm^2, slice gap = 0 mm, and slice thickness = 2.5 mm.

For the lower dorsal ARAS, the first region of interest (ROI) was placed at the reticular formation of the pons and the second ROI was placed at the thalamic intralaminar nucleus. For the lower ventral ARAS, the first ROI was placed at the reticular formation of the pons, and the second ROI was placed at the hypothalamus. For the connectivity of thalamic intralaminar nucleus, the first ROI was placed at the thalamic intralaminar nucleus (Motofei and Rowland, 2014; Jang et al., 2016b, c).

The right lower dorsal ARAS was not reconstructed on 5- and 22-month DTT images. The thin left lower dorsal ARAS observed on the 5-month DTT image had become thicker on 22-month DTT image. The lower ventral ARAS on both sides was not reconstructed on the 5-month DTT image; however, it was well-reconstructed on both sides on the 22-month DTT image. On the 5-month DTT image, the neural connectivity of the upper ARAS between the thalamic intralaminar nucleus and the cerebral cortex was decreased in bilateral prefrontal cortex, parietal cortex, bilateral basal forebrain, and the right thalamus. By contrast, on 22-month DTT image, the neural connectivity of the upper ARAS was increased in the left prefrontal cortex and parietal cortex (**Figure 1B**).

In this study, we evaluated the change of an injured ARAS in a stroke patient who showed good recovery of severely impaired

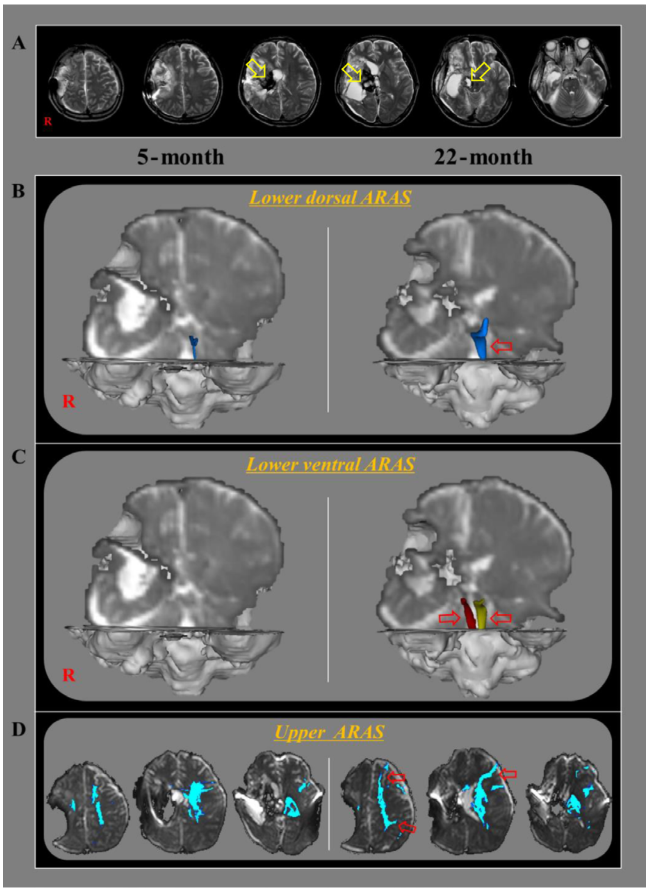

Figure 1 DTT for the ARAS of a 33-year-old male stroke patient.
(A) DTT images taken at 5 months after onset reveal leukomalactic lesions in the right basal ganglia and thalamus, and midbrain (yellow arrows). (B) On 5-month and 22-month DTT images, the right lower dorsal ARAS was not reconstructed on both hemispheres, while thin left lower dorsal ARAS observed on the 5-month DTT image had become thicker on the 22-month DTT image (red arrow). (C) On 5-month DTT image, the lower ventral ARAS was not reconstructed in the both hemispheres, however, it was well-reconstructed on both sides on 22-month DTT image (red arrows). (D) On 5-month DTT image, the neural connectivity of the upper ARAS between the ILN and cerebral cortex was decreased in bilateral prefrontal cortex, parietal cortex, bilateral basal forebrain, and the right thalamus. By contrast, the neural connectivity of the upper ARAS was increased in the left prefrontal cortex and parietal cortex on the 22-month DTT image (red arrows). ARAS: Ascending reticular activating system; DTT: diffusion tensor tractography; ILN: intralaminar nucleus; R: right.

consciousness after 3 months of comprehensive rehabilitation. The change of the injured ARAS on DTT images indicates recovery of the injured neural tracts as follows: 1) the left lower dorsal ARAS (**Figure 1B**), 2) both lower ventral ARAS (**Figure 1C**), and 3) the upper ARAS to left prefrontal cortex (especially), parietal cortex (**Figure 1D**). Consequently, in this patient, the recovery of the injured neural tracts in the prefrontal cortex, parietal cortex, lower dorsal ARAS, and lower ventral ARAS contributed to the recovery of impaired consciousness. Because the upper ARAS is responsible for conscious awareness and the lower dorsal and ventral ARAS are responsible for arousal and sleep, respectively, the recovery of the injured upper ARAS mainly contributes to the recovery of impaired consciousness in this patient (Paus, 2000; Parker and Alexander, 2005; Cavanna et al., 2011; Goldfine and Schiff, 2011; Jang, 2016).

Several studies have demonstrated the change of injured ARAS during recovery of impaired consciousness in patients with several brain injuries (Teasdale and Jennett, 1974; Laureys et al., 2000; Giacino et al., 2004; Schiff, 2010; Jang et al., 2015, 2016a). Laureys et al. (2000) reported resolution of the metabolic decrement in the posterior associative cortices during recovery from a vegetative state to a normal state of consciousness in a patient with CO intoxication. Jang et al. (2015) demonstrated that the recovery of an injured lower dorsal ARAS in a traumatic brain injury patient who showed recovery of the impaired consciousness from a minimally conscious state to a normal conscious state. Jang and Lee (2015) reported the recovery of the injured lower dorsal ARAS and the injured upper ARAS of the patient who recovered from a vegetative state to a minimally conscious state following hypoxic/ischemic brain injury. Jang et al. (2016d) reported recovery of an injured ARAS in a stroke patient who recovered from a minimally conscious state to a normal state over a period of 3 weeks in the early stage of hypoxic/ischemic brain injury. During the same year, Jang et al. (2016e) reported that in a stroke patient, the recovery of the injured upper ARAS was concurrent with the recovery from a vegetable state to a minimally conscious state. Also in 2016, Jang et al. demonstrated changes in the upper ARAS were concurrent with the recovery from a vegetable state to a minimally conscious state in a traumatic brain injury patient (Jang et al., 2016a). Recently, Jang and Lee (2017) reported that in a stroke patient, the recovery of consciousness from a vegetable state to a normal conscious state was concurrent with the recovery of the injured ARAS. Our results in this patient appear to support those in the aforementioned studies (Teasdale and Jennett, 1974; Laureys et al., 2000; Giacino et al., 2004; Schiff, 2010; Jang et al., 2015, 2016a).

In conclusion, changes of an injured ARAS were demonstrated in a stroke patient who showed good recovery of consciousness. The increased neural connectivity in the upper ARAS (prefrontal cortex and parietal cortex) mainly contributed to the recovery of impaired consciousness in this patient. Further studies regarding the contributions of other portions of the ARAS to the recovery of impaired consciousness should be warrented. The limitation of DTT studies should be considered. DTT may result in false negative results due to fiber complexity and crossing of the regions (Parker and Alexander, 2005).

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