IMAGING IN NEURAL REGENERATION

Unusual neural connection between injured cingulum and brainstem in a patient with subarachnoid hemorrhage

The human brain is known to have six cholinergic nuclei (Selden et al., 1998; Nieuwenhuys et al., 2008). The cerebral cortex obtains cholinergic innervation mainly from the basalis nucleus of Meynert (Ch 4) in the basal forebrain through the medial and lateral cholinergic pathways (Selden et al., 1998; Mesulam et al., 1983). The cingulum, the neural fiber bundle connecting the basal forebrain and the medial temporal lobe, contains the medial cholinergic pathway (Selden et al., 1998; Hong and Jang, 2010). In addition, the other cholinergic nuclei in the basal forebrain (Ch 1: medial septal nucleus, Ch 2: vertical nucleus of the diagonal band) are connected to the cingulum (Nieuwenhuys et al., 2008). Therefore, the cingulum is an important pathway for cholinergic innervation for the cerebral cortex. On the other hand, two cholinergic nuclei are located in the brainstem (Ch 5: pedunculopontine nucleus and Ch 6: laterodorsal tegmental nucleus), and are connected to the thalamus (Nieuwenhuys et al., 2008; Mesulam, 1990; Wainer et al., 1993; Lucas-Meunier et al., 2003). Many studies have reported connections between the cholinergic nuclei, especially between the cholinergic nuclei in the basal forebrain and those in the brainstem via the fornix and thalamus (Mesulam, 1990; Wainer et al., 1993; Woolf and Butcher, 1986; Marina et al., 2002; Paxinos, 2004). However, little is known about the connection between cholinergic nuclei in the basal forebrain and cholinergic nuclei in the brainstem *via* the cingulum (Yeo et al., 2012).

Diffusion tensor tractography (DTT), derived from diffusion tensor imaging (DTI), has the unique advantage of allowing for three-dimensional visualization and estimation of neural tracts in the live human brain (Concha et al., 2005; Malykhin et al., 2008; Yeo et al., 2013). A recent DTT study reported an unusual neural connection between an injured cingulum and a cholinergic nucleus in the brainstem in a patient with traumatic brain injury, suggesting a recovery mechanism following cingulum injury (Yeo et al., 2012). However, no study on this phenomenon in other brain pathology has been reported.

In this study, we report on a patient who showed unusual neural connections between injured cingulums and brainstem cholinergic nuclei following aneurysmal subarachnoid hemorrhage, using DTT. Ten age- and sex-matched normal control subjects (seven males; mean age: 27.57 years) were recruited for control.

A 50-year-old male patient underwent craniotomy and clipping for a ruptured aneurysm of the anterior communicating artery after subarachnoid hemorrhage at the neurosurgery department of a university hospital (Figure 1A). At 4 weeks after onset, he was transferred to the rehabilitation department of the same hospital. Brain MRI taken at 4 weeks after onset showed leukomalactic lesions in the left frontal lobe (Figure 1A). The patient showed memory impairment at 5 weeks after onset: Wechsler Adult Intelligence Scale: 104, and the Memory Assessment Scale (global memory: 79 (8%ile), short term memory: 111 (77%ile), verbal memory: 94 (35%ile), and visual memory: 71 (3%ile) (Wechsler, 1981; Williams, 1991). His memory function showed improvement, within normal range, at 7 months after onset: Wechsler Adult Intelligence Scale: 125, and the Memory Assessment Scale (global memory: 104 (61%ile), short term memory: 114 (83%ile), verbal memory: 111 (77%ile), and visual memory: 97 (42%ile) (Mesulam, 1990; Williams, 1991).

A 6-channel head coil on a 1.5-T Philips Gyroscan Intera scanner (Hoffman-LaRoche, Ltd., Best, the Netherlands) was used for acquisition of DTI data two times at 1 and 7 months after onset. For each of the 32 non-collinear diffusion sensitizing gradients, we acquired 67 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; b = 1,000 s/mm^2; number of excitations = 1; and slice thickness = 2.5 mm. The fiber assignment continuous tracking (FACT) algorithm was used in performance of fiber tracking (Stieltjes et al., 2001). The cingulum areas were reconstructed using fibers passing through two regions of interest (middle and posterior portion of the cingulum). Termination criteria were fractional anisotropy < 0.15 and an angle change > 27° (Yeo et al., 2012; Malykhin et al., 2008).

On both 1- and 7-month DTTs of the patient, we observed discontinuations of both cingulums above the genu of the corpus callosum. On 1-month DTT, both cingulums were connected to each Ch 5 bilaterally via the neural tracts that passed through the thalamus; in contrast, the left neural tract had disappeared on 7-month DTT and the right neural tract was connected to the right Ch 6 (Figure 1B).

In this study, we found unusual neural connections between the injured cingulums and the brainstem cholinergic nuclei in a patient with aneurysmal subarachnoid hemorrhage. The patient showed severe injury of both anterior cingulums on 1- and 7-month DTT. On 1-month DTT, the neural connections between the anterior portion of injured cingulums and Ch 5 were observed in both hemispheres. By contrast, on 7-month DTT, the left neural connection had disappeared and the right neural connection was connected to Ch 6 instead of Ch 5. These neural connections between the cingulum and the cholinergic nuclei were not observed in any of the control subjects. We assume that these neural connections resulted from an attempt for neural reorganization by the injured cingulum in order to obtain cholinergic innervation from the brainstem cholinergic nuclei after losing cholinergic innervation from cholinergic nuclei in the basal forebrain. The fact that the patient showed good cognition, including memory function, appears to be additional evidence for this assumption.

The brain has the characteristics of plasticity for reorganization following an injury. The basic mechanisms of brain plasticity are as follows: collateral sprouting from intact cells to a denervated region after normal input has been destroyed and unmasking of reserve axons and synapses for particular functions after failure of the normally dominant system (Bach-y-Rita, 1981; Bach y Rita, 1981). The fact that the unusual neural connections between the injured cingulum and brainstem were observed during early stage after onset on 1-month DTT might indicate that these connections were attributed to the unmasking of an already existing latent neural pathway rather than collateral sprouting. Further follow up studies from the acute stage to chronic stage after the onset of subarachnoid hemorrhage will be necessary in order to clarify this topic.

In conclusion, we report on a patient who showed unusual neural connections between the anterior portion of injured cingulums and the brainstem cholinergic nuclei. We believe that our findings may suggest one of the recovery mechanisms for cholinergic innervations of injured cingulums in patients with subarachnoid hemorrhage. A similar phenomenon was reported in a patient with traumatic brain injury, who showed a neural connection between the injured cingulum and Ch 5 (Yeo et al., 2012). Therefore, this is the first study to report on unusual neural connection in stroke patients. Further studies on the clinical significance of this unusual neural connection should be encouraged.

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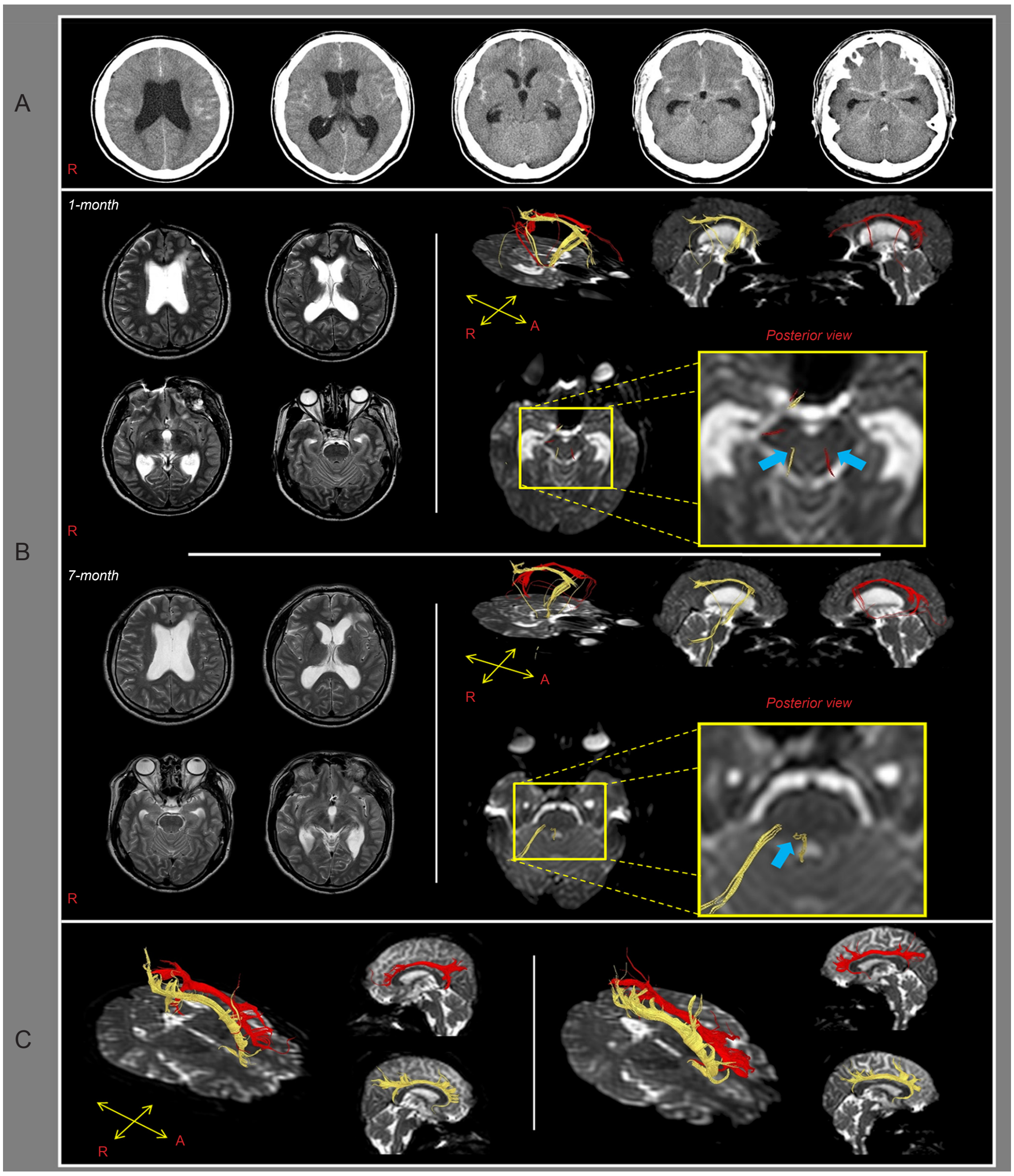

(A) Brain CT images at onset show a subarachnoid hemorrhage by ruptured aneurysm of the anterior communicating artery; (B) 1-month diffusion tensor tractographies (DTTs) revealed discontinuations of both cingulums above the genu of the corpus callosum, and both cingulums were connected to the pedunculopontine nuclei bilaterally (arrows). However, the left neural connection had disappeared on 7-month DTT and the right neural tract was connected to the right laterodorsal tegmental nucleus (arrow) instead of the right pedunculopontine nucleus; (C) DTT images of the cingulum in two control subjects. SAH: Subarachnoid hemorrhage; R: right; A: anterior.

Figure 1 DTT and CT images in a 50-year-old male patient ongoing craniotomy and clipping for a ruptured aneurysm of the anterior communicating artery after SAH.

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