● IMAGING IN NEURAL REGENERATION

Recovery of a degenerated corticospinal tract after injury in a patient with intracerebral hemorrhage: confirmed by diffusion tensor tractography imaging

The corticospinal tract (CST) is a major neuronal tract of motor function in the human brain (York, 1987; Davidoff, 1990; Jang, 2014). Recovery of an injured CST is one of the motor recovery mechanisms in stroke patients (Hendricks et al., 2003; Jang et al., 2006, 2007; Swayne et al., 2008; Kwon et al., 2011, 2013; Kwon and Jang, 2012; Yeo and Jang, 2013; Rong et al., 2014). Diffusion tensor tractography (DTT), derived from diffusion tensor imaging (DTI), and transcranial magnetic stimulation (TMS) have been widely used in demonstrating the recovery of an injured CST (Hendricks et al., 2003; Jang et al., 2006, 2007; Swayne et al., 2008; Pannek et al., 2009; Kwon et al., 2011, 2013; Kwon and Jang, 2012; Yeo and Jang, 2013; Rong et al., 2014). DTT has the advantage of enabling visualization of the architecture and integrity of the CST at the subcortical level in three dimensions (Mori et al., 1999; Kunimatsu et al., 2004). TMS has a unique advantage in that it can be used to evaluate change of the CST by analysis of the characteristics of the motor-evoked potential (MEP) (Rossini et al., 1994). The advantages of each method for evaluating the recovery of an injured CST allow more accurate estimation when they are employed concomitantly (Rossini et al., 1994; Kunimatsu et al., 2004; Jang, 2009). Many studies have demonstrated the recovery of an injured CST using DTT and TMS (Hendricks et al., 2003; Jang et al., 2006, 2007; Swayne et al., 2008; Pannek et al., 2009; Kwon et al., 2011; Kwon and Jang, 2012; Yang et al.,2008; Yeo and Jang, 2013; Rong et al., 2014). However, little is known about the recovery of a degenerated CST after injury in stroke patients (Jung, 2012).

In this study, we demonstrated the recovery of a degenerated CST after injury in a patient with intracerebral hemorrhage (ICH), using DTT and TMS.

A 51-year-old, right-handed asian male patient suffered spontaneous left side motor weakness. He underwent craniotomy and removal of hematoma, which resulted from the right putaminal hemorrhage, at the department of neurosurgery of a university hospital. At 6 weeks after onset of ICH, he was transferred to the rehabilitation department of another university hospital to undergo rehabilitation therapy in order to gain function regardless of their deficiencies. Brain CT, taken at onset, showed a hematoma in the right putamen, and brain MRI, scanned at 6 weeks after onset, showed a leukomalactic lesion at the left corona radiata and basal ganglia due to a previous putaminal ICH which had been neglected without exact diagnosis and was diagnosed as an old ICH by a neuroradiologist at this time (**Figure 1A**).

The standardized Motricity Index (MI) and Medical Research Council (MRC) were used for determination of motor function of the affected extremities (Gregson et al., 2000). The MI, with a maximum score of 100, is a measure of the integrity of the motor function of an extremity. The reliability and validity of the MI are well established (Demeurisse et al., 1980). MRC: 0, no contraction; 1, palpable contraction, but no visible movement; 2, movement without gravity, 3, movement against gravity; 4, movement against a resistance lower than the resistance overcome by the healthy side; 5, movement against a resistance equal to the maximum resistance overcome by the healthy side. He presented with complete weakness of the left upper and lower extremities at onset of ICH (MI: 0) (**Table 1**). For approximately 8.5 months, from 6 weeks to 10 months after onset, he received comprehensive rehabilitative management in the university hospital and a local rehabilitation hospital, including administration of neurotrophic drugs (methylphenidate 10 mg, pramipexole 1 mg, bromocriptine 10 mg, levodopa 750 mg, and amantadine 300 mg), movement therapy, procedures for spasticity control of the left finger flexors, and neuromuscular electrical stimulation of the left finger extensors and ankle dorsiflexors (Scheidtmann et al., 2001). Movement therapy focused on improvement of the motor function of the left upper and lower extremities and was performed five times per week. The patient recovered from severe weakness of the left upper and lower extremities: MI scores at the indicated times: stroke onset 0 points; 6 weeks: 31 points; 4 months, 51 points; 10 months, 64 points (**Table 1**). As a result, he regained the ability to perform grasp-release using the left hand and to walk independently. The patient provided signed, informed consent and our institutional review board approved the study protocol.

DTI data were acquired three times (6 weeks, 4 and 10 months after onset) using a 1.5 T Philips Gyroscan Intera system (Philips, Ltd, Best, the Netherlands) with single-shot echo-planar imaging. Seventy contiguous slices were acquired parallel to the anterior commissure-posterior commissure line for each of the 32 non-collinear diffusion sensitizing gradients. Imaging parameters were as follows: acquisition matrix = 96 × 96, repetition time = 10,398 ms, echo time = 72 ms, echo planar imaging factor = 59 and b = 1,000 s/mm^2, number of excitations = 1, and slice thickness = 2.5 mm.

The fiber assignment continuous tracking (FACT) algorithm implemented within the DTI task card software was used for fiber tracking (Mori et al., 1999). Fibers passing through two regions of interest (ROIs) at the upper and lower pons (portion of anterior blue color) were selected for CSTs (fractional anisotropy threshold: > 0.15, direction threshold: < 27° (Kunimatsu et al., 2004; Kwon and Jang, 2011).

Magstim Novametrix 200 magnetic stimulator with a 9-cm mean diameter circular coil was used for TMS study (Novametrix Inc. 45 WEST ST, suite 2, Attleboro, MA, USA). Counterclockwise current was employed for stimulation of the left hemisphere, and a clockwise current for stimulation of the right hemisphere. MEPs were obtained at both abductor pollicis brevis muscles in a relaxed state. The minimum stimulus required to elicit an MEP with a peak-to-peak amplitude of 50 μV or greater in two out of four attempts was

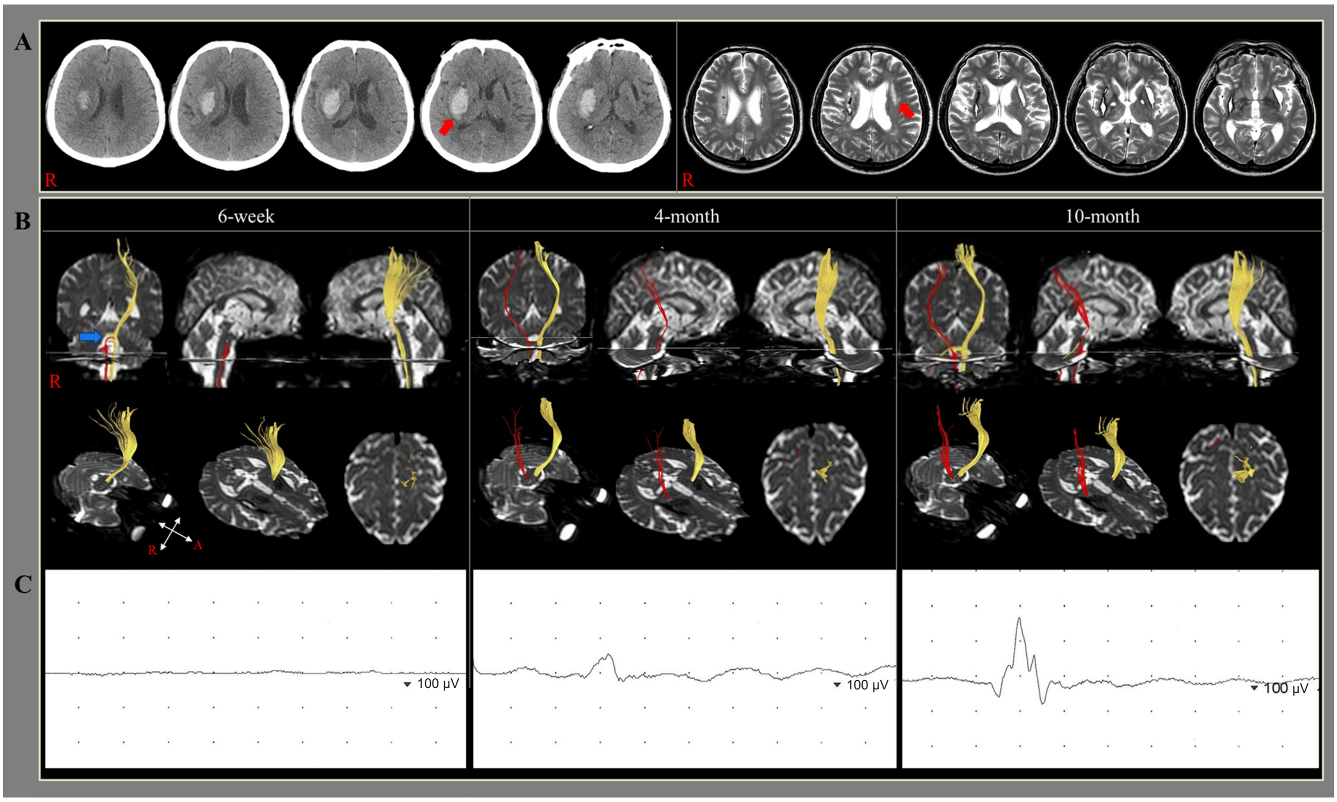

Figure 1 Brain CT, MRI, diffusion tensor tractography, and motor-evoked potential of a patient with intracerebral hemorrhage.
(A) Brain CT, taken at onset of intracerebral hemorrhage, shows a hematoma (arrow) in the right putamen and brain MRI at 6 weeks after onset shows a leukomalactic lesion (arrow) at the left corona radiata and basal ganglia due to a previous undiagnosed putaminal intracerebral hemorrhage. (B) Results of diffusion tensor tractography (DTT). The right corticospinal tract (CST) showed discontinuation (arrow) in the brainstem on 6-week DTT images. However, this discontinued right CST was elongated to the right primary motor cortex on 4-month DTT and had become thicker on 10-month DTT. (C) Motor-evoked potentials (MEPs) obtained from the left abductor pollicis brevis muscle. No MEP was evoked from the right hemisphere, even though stimulation intensity was increased to 100% of maximal output at 6 weeks. However, transcranial magnetic stimulation at 4 and 10 months showed that MEPs were evoked from the right hemisphere (4 months: latency 25.4 ms and amplitude 100 µV; 10 months: latency 22.9 ms and amplitude 270 µV).

Table 1 Changes of motor function in the patient with intracerebral hemorrhage

			After onset		
		Onset	6 weeks	4 months	10 months
MRC	Shoulder abductor	0	2	2	3
	Elbow flexor	0	2	3	3
	Finger flexor	0	0	2	3
	Finger extensor	0	0	2	2
	Hip flexor	0	2	3	4
	Knee extensor	0	3	3	4
	Ankle dorsiflexor	0	0	2	3
MI	Upper extremity	0	28	51	59
	Lower extremity	0	33	51	68
	Total	0	31	51	64

Data in the table are scores of MRC or MI. MRC: Medical Research Council. 0, No contraction; 1, palpable contraction, but no visible movement; 2, movement without gravity; 3, movement against gravity; 4, movement against a resistance lower than the resistance overcome by the healthy side; 5, movement against a resistance equal to the maximum resistance overcome by the healthy side. MI: Motricity Index. Higher MI indicates better motor function.

defined as the excitatory threshold. Stimulation intensity was fixed at the excitatory threshold + 20% of the maximum stimulator output.

Results of DTT of the unaffected hemisphere showed that the CST originated from the cerebral cortex, including the primary motor cortex, and descended along the known CST pathway (**Figure 1B**). By contrast, discontinuation of the right CST in the brainstem was observed on 6-week DTT images. However, this discontinued right CST was elongated to the right primary motor cortex on 4-month DTT images and had become thicker on 10-month DTT images.

We could not obtain any MEP from the right hemisphere stimulation at 6 weeks (**Figure 1C**). However, transcranial magnetic stimulation studies showed that at 4 and 10 months after injury, MEPs were evoked from the right hemisphere(4 months: latency 25.4 ms, amplitude 100 µV, excitatory threshold 100 %; 10 months: latency 22.9 ms, amplitude 270 µV, excitatory threshold 100 %).

In this patient, we followed up the changes of the CST along with the motor recovery until 10 months after onset, using DTT and TMS, in terms of clinical aspect of motor recovery, change of DTT for the injured CST, and change of

MEP on TMS study. Regarding the recovery of a degenerated CST after injury, in 2012, in 19 patients with ICH, Jung et al. reported that the discontinued CST which did not reach the hematoma at early stage (within 1 month after onset) showed recovery, like this patient, in three patients after 3 months from onset (Jung, 2012). Consequently, to the best of our knowledge, this is the first study to demonstrate the recovery of a degenerated CST after injury in a stroke patient, using DTT and TMS. However, limitations of DTI and TMS should be considered. Due to crossing fiber or partial volume effect, false positive or negative results can be obtained (Yamada, 2009). By contrast, TMS has the possibility of false negative results due to excessive high threshold at the early stage of stroke.

In conclusion, we report on a patient with ICH who showed recovery of a degenerated CST after injury, using DTT and TMS. These results provide evidence that recovery can occur even in case of severe injury of the CST; therefore, results of this study have important significance for rehabilitation for stroke patients.

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