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Motor function reorganization in a patient with a brainstem lesion: DTT, fMRI and TMS study

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Abstract. *Objective:* We report on a hemiparetic patient who showed a new motor pathway posterior to the lesion in the midbrain and upper pons, demonstrated by three combined method of diffusion tensor tractography(DTT)/functional MRI(fMRI)/transcranial magnetic stimulation(TMS).
Methods: A 21-year-old left hemiparetic male who suffered from tuberous meningitis at the age of 12 months after birth. The evaluations were performed at 20 years after onset. Brain MRI showed focal encephalomalatic lesions due to infarcts in right anterior thalamus, midbrain and upper pons. DTT, fMRI and TMS were performed simultaneously.
Results: The contralateral primary sensori-motor cortex was activated during either affected or unaffected hand movements. DTT showed that the motor tracts descended along the known pathway of the CST, with the exception of the motor tract of the affected hemisphere, which descended along the posterior portion to the lesion in the right midbrain and the pons, and then rejoined the CST in the mid-pons. The TMS results suggested that the motor tract of the affected hemisphere had the characteristics of a CST.
Conclusion: We believe that the motor function of the affected hand in this patient had been recovered through the pathway posterior to the lesion in the midbrain and upper pons.

Keywords: Corticospinal tract, functional MRI, diffusion tensor MRI, transcranial magnetic stimulation, motor recovery

1. Introduction

Because fMRI is capable of precisely identifying cortical activation sites due to its excellent spatial resolution at the cortex, while TMS has a unique advantage in that it can distinguish between the corticospinal tract (CST) and the non-CST by analyzing the characteristics of the motor-evoked potential (MEP), combined approaches based on functional MRI (fMRI) and transcranial magnetic stimulation (TMS) have provided an ideal noninvasive research method for the motor recovery mechanism in patients with brain injury [8,9,11,12, 14,16]. However, the majority of these studies have focused on the cortex level [3,7]. Recent advances in diffusion tensor tractography (DTT), which is derived from diffusion tensor imaging (DTI), allow us to visualize and localize the CST at the subcortical level, and the recovery mechanism has begun to be elucidated at the subcortical level [1,6,8,10,14,17]. Moreover, it appears that the combined use of these three modalities (DTT/fMRI/TMS) will allow more accurate investigations of the CST status in patients with subcortical lesions [9,11].

In this study, we describe a hemiparetic patient who showed a new motor pathway to a lesion in the midbrain and upper pons, demonstrated by the combined method of DTT, fMRI, and TMS.

2. Patient and methods

A 21-year-old right-handed man was referred to our hospital for motor function evaluation and rehabili-

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tation. T2-weighted MR images showed focal encephalomalatic lesions due to infarcts in the right anterior thalamus, midbrain, and upper pons caused by tuberculous meningitis (Fig. 1-A). The patient signed an informed consent statement, and the study protocol was approved by our institutional review board prior to commencement of the study.

The patient suffered from tuberous meningitis at the age of 12 months after birth. He presented with severe weakness of the left upper and lower extremities at that time, but slowly recovered some function to the point of being able to move the affected upper extremity against gravity, and to walk independently at about 1 year after onset. At the time of the brain MRI scanning (20 years after onset), he was able to walk independently, but with a mild spastic gait pattern, and was able to move the affected upper extremity against some resistance.

2.1. Functional MRI

The blood oxygenation level-dependent (BOLD) fMRI measurement, which employs the Echo Planar Imaging (EPI) technique, was performed using a 1.5-T Philips Gyroscan Intera with a standard head coil. The EPI BOLD images were acquired over the same 20 axial sections, producing a total of 1200 images for the patient. Imaging parameters consisted of TR/TE $=$ 2 sec/60 msec, FOV $=$ 210 mm, matrix size $= 64 \times 64$, and slice thickness $=$ 5 mm. The patient was examined in a supine position with his eyes closed, and was firmly secured with the forearm pronated. For the motor task, the patient performed a repetitive alternating cycle of control (rest for 21 seconds) and stimulation (activity for 21 seconds) with grasp-release hand movements at a metronome-guided frequency of 1 Hz. Each of the "control and stimulation" (42 seconds) tasks was repeated three times.

Functional MRI data were analyzed using SPM2 software (Wellcome Department of Cognitive Neurology, UK) running under the MATLAB environment. All images were preprocessed with a slice timing correction and motion realignment. These data were then coregistered and resliced using the diffusion weighted-echo planar imaging volume with the highest signal-to-noise ratio (no diffusion weighting, $b = 0$) as a template for each subject [4]. The final processing was smoothed with an 8 mm isotropic Gaussian kernel. Statistical parametric maps were obtained, and voxels were considered significant at a $p-$value of 0.05, corrected for Familywise Error (FWE).

2.2. Diffusion tensor tractography

The DTIs were acquired using a sensitivity-encoding head coil on a 1.5-T Philips Gyroscan Intera using single-shot echo-planar imaging with a navigator echo. Sixty contiguous slices (matrix $= 128 \times 128$, field of view $=$ 221 mm, repetition time/echo time $=$ 10726/76 ms, b $=$ 600 $\mathrm{mm}^2\mathrm{s}^{-1}$, NEX $=$ 1, thickness $=$ 2.3 mm) were acquired for each of the 32 non-collinear diffusion-sensitizing gradients. The global magnet shim and the parallel imaging technique were employed to correct for possible image distortion. Parallel imaging allows the image to be reconstructed in half as many encoding steps as other methods and, thus, reduces the unique geometric image distortion of echo-planar imaging.

Diffusion weighted imaging data were analyzed using BEAR [18], an in-house MATLAB-based software package. EPI-based statistical maps were created in the SPM2 environment. The CST related to hand motor function was determined by choosing the fibers passing through both of the regions of interest (ROIs) (ROI 1: the activation area of the primary sensorimotor cortex including the precentral knob, ROI 2: known anatomical CST area-blue portion of the anterior pontomedullary junction on the color map) (Fig. 1-B).

The Probabilistic Index of Connectivity (PICo) probabilistic-fiber-tracking framework was applied to track the connection probability of the CST [15]. This approach produces a probability density function. The probability density function was defined at each voxel within the brain in order to provide an estimate of confidence in the orientation of the fiber tract. Probabilistic fiber tracking and mapping were performed by introducing uncertainty into the local fiber orientation at all points along its propagation using the standard Monte Carlo approach.

2.3. Transcranial magnetic stimulation

TMS was performed using a Magstim 200 magnetic stimulator with a 70 mm (mean diameter) butterfly coil (Novametrix Inc.). A cloth marked with spacings 1 cm apart and Cz referenced to the intersection of midsagittal and interaural lines was placed on the scalp. The intersection of the wings (center of the coil) was applied tangentially to the scalp, while the handgrips were placed so that they were parallel to the midsagittal line and faced the back. Magnetic stimulation was performed with the excitatory threshold (ET) plus 20% output. The MEPs were obtained from both abductor

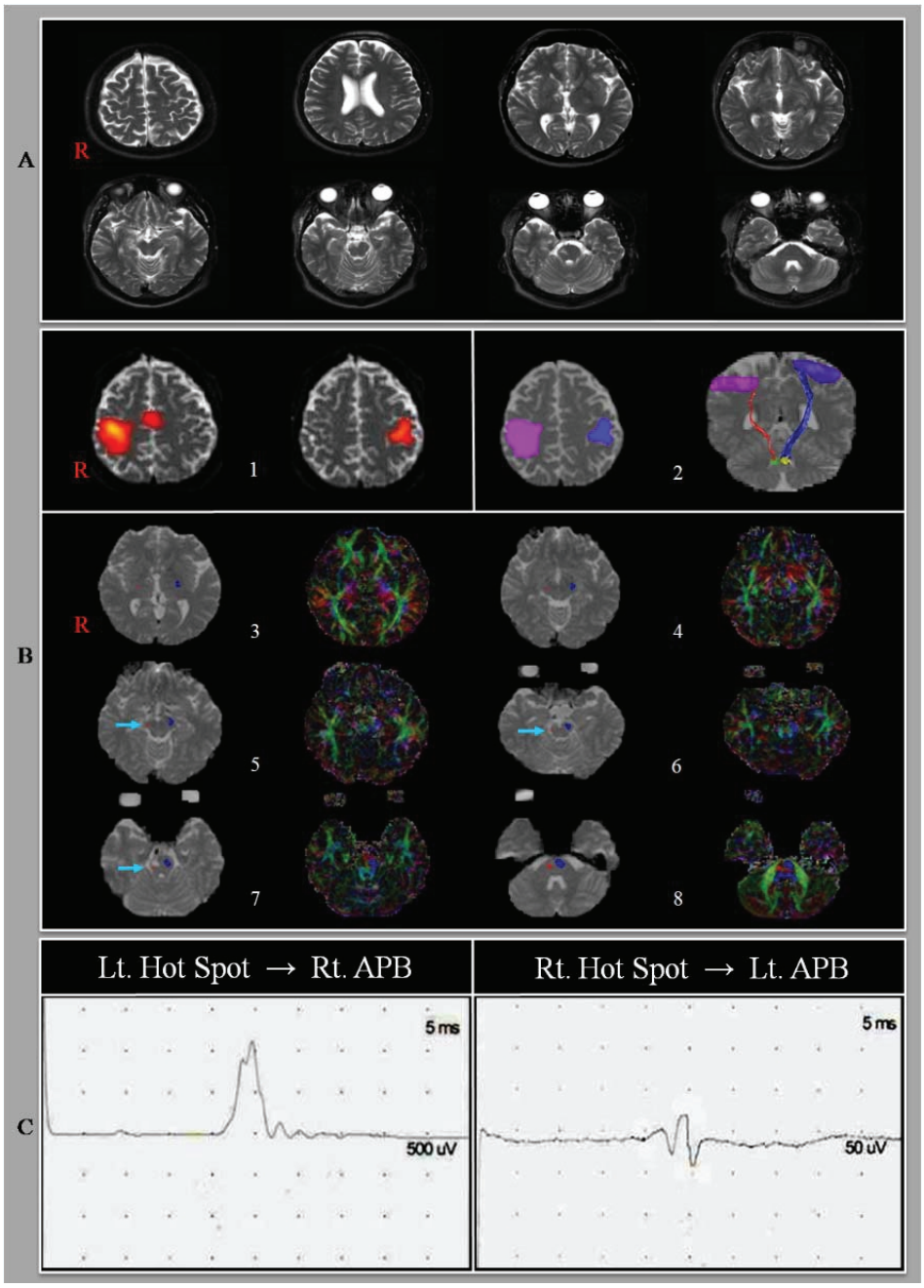

Fig. 1. **A.** T2-weighted MR images show focal encephalomalatic lesions due to an infarct from tuberculous meningitis in the right anterior thalamus, midbrain, and upper pons. **B.** Diffusion tensor tractography analyzed from functional MRI results. The contralateral primary sensorimotor cortex was activated by the movements of either hand (1). The fiber tract connecting region of interest 1 (the activated area on the primary sensorimotor cortex) and region of interest 2 (the known corticospinal tract area of the pontomedullary junction) (blue color – the motor tract of the affected hemisphere, red color – the motor tract of the unaffected hemisphere) (2–10). The probabilistic maps show the corticospinal tract pathway. The axial T2-weighted images (left) and color maps (right) at the posterior limb (3), midbrain (5,6), upper pons (7), and mid-pons (8) illustrate that the motor tracts descend along the known corticospinal tract in both hemispheres, except the motor tract of the right hemisphere descended through the posterior portion to the lesion in the midbrain and the upper pons (arrows), and then entered into the corticospinal tract in the mid-pons. **C.** Motor-evoked potentials obtained from the abductor pollicis brevis muscles (APBs) when stimulating the optimal scalp site of the contralateral motor cortex. The characteristics of motor-evoked potential from the right APB were latency, 20.1 msec, and amplitude, 1100 uV, and those from the left APB were latency, 19.8 msec, and amplitude, 80 uV.

pollicis brevis muscles (APB) in a relaxed state. Each site was stimulated three times at 1cm intervals, from which the shortest latency and the average of the peak-to-peak amplitudes were adopted. The site where the ET was lowest, latency was shortest, and average amplitude was largest was determined as the optimal scalp site.

3. Results

Only the contralateral primary sensorimotor cortex (SM1) was activated during movement of either hand (Fig. 1-B-1). Additional activation of both supplementary motor areas were observed in response to the affected (left) hand movements (Fig. 1-B-1-left).

The motor tract of the unaffected (left) hemisphere originated from the right SM1 and descended through the known pathway of the CST (Fig. 1-B) [5,19]. The motor tract of the left hemisphere originated from the SM1, and descended along a pathway similar to that of the right hemisphere. However, it descended through the posterior portion of the lesion in the midbrain and upper pons, and then entered the right CST at the mid-pons, where it rejoined the known pathway of the CST.

Four MEPs of the affected (left) APB were evoked by stimulation of the right hemisphere. The optimal scalp site was located at (6,0), and the characteristics of MEP from this site were latency, 19.8 msec; amplitude, 80 uV; and ET, 100% (Fig. 1-C). By contrast, the contralateral MEPs to the unaffected right APB from the unaffected left hemisphere were evoked from five sites around the optimal scalp site (-6, 0). The characteristics of the MEP from the optimal scalp site were latency, 20.1 msec; amplitude, 1100 uV; and ET, 80%.

4. Discussion

The results of this study indicate that the main motor functions of the affected hand seemed to have reorganized through a new pathway posterior to the lesion in the brainstem for the following reasons. First, only the contralateral SM1 was activated during affected hand movements, and it appeared that the affected (right) SM1, which is the known center of the CST, was responsible for the motor function of the affected (left) hand. Second, the tracts of both hemispheres originated from the motor cortex and descended along the known CST pathway, except the pathway posterior to the lesion in the right midbrain to the upper pons. However, with the exception of the posterior pathway of the lesion, other tracts were not observed in the affected brainstem [5,19]. Additional evidence of recovery was obtained by the TMS study. An MEP with a level of latency compatible with the CST was evoked from the affected hand when stimulating the optimal scalp site of the affected hemisphere [2,13,20]. In the current patient, the above evidence suggests that some portion of the infarcted brainstem other than the CST was responsible for the recovery of motor function, and the main motor function of the affected hand seemed to be controlled by this posterior pathway, which had characteristics similar to those of the CST.

Since the development of DTI technology, studies have actively attempted to elucidate the motor recovery mechanisms of patients with subcortical lesions [1, 6–8,10,17]. Most of these studies were performed to investigate the recovery of a damaged CST at the subcortical level [1,6,7,10,17]. Recently, one patient with a pontine infarct was found to have recovered through an apparent pyramidal tract in the brainstem [8]. In the current patient, we discovered a new motor pathway posterior to a lesion in the midbrain and upper pons. We think that the location of this pathway corresponds to the medial lemniscus in the midbrain, and transverse pontine fiber or CST in the upper pons. However, we cannot be sure of these locations, as this patient suffered from the injury approximately 20 years ago, when his brain had not yet matured [5,19]. However, we think that the alternative motor pathway at the subcortical level could be one of the mechanisms of motor recovery in patients with brain injury. Therefore, we think that further studies on this topic are needed.

5. Conclusion

In conclusion, we demonstrated that the motor function of the affected hand of this patient seemed to have reorganized through a new pathway posterior to the lesion in the midbrain and upper pons. It seems that the combined method of DTT, fMRI, and TMS would be helpful for the investigation of motor recovery mechanisms in patients with brain injury. This result has important implications in terms of the motor recovery and rehabilitation of patients with brain injury because it suggests the high possibility of motor recovery and motor recovery mechanism even though extensive pontine lesion in immature brain. This study is limited because it is a case report. Further complementary studies involving larger patients with immature brain injury who have various pontine lesions should be performed in the future.

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