

Central post-stroke pain due to injury of the spinothalamic tract in patients with cerebral infarction: a diffusion tensor tractography imaging study

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How to cite this article: Jang SH, Lee J, Yeo SS (2017) Central post-stroke pain due to injury of the spinothalamic tract in patients with cerebral infarction: a diffusion tensor tractography imaging study. *Neural Regen Res* 12(12):2021-2024.

Funding: This work was supported by the National Research Foundation (NRF) of Korea Grant funded by the Korean Government (MSIP), No. NRF-2015R1D1A1A01060314.

Abstract

Many studies using diffusion tensor tractography (DTT) have demonstrated that injury of the spinothalamic tract (STT) is the pathogenetic mechanism of central post-stroke pain (CPSP) in intracerebral hemorrhage; however, there is no DTT study reporting the pathogenetic mechanism of CPSP in cerebral infarction. In this study, we investigated injury of the STT in patients with CPSP following cerebral infarction, using DTT. Five patients with CPSP following cerebral infarction and eight age- and sex-matched healthy control subjects were recruited for this study. STT was examined using DTT. Among DTT parameters of the affected STT, fractional anisotropy and tract volume were decreased by more than two standard deviations in two patients (patients 1 and 2) and three patients (patients 3, 4, and 5), respectively, compared with those of the control subjects, while mean diffusivity value was increased by more than two standard deviations in one patient (patient 2). Regarding DTT configuration, all affected STTs passed through adjacent part of the infarct and three STTs showed narrowing. These findings suggest that injury of the STT might be a pathogenetic etiology of CPSP in patients with cerebral infarction.

Key Words: nerve regeneration; central post-stroke pain; cerebral infarction; spinothalamic tract; diffusion tensor imaging; neural regeneration

Introduction

Central post-stroke pain (CPSP) is a neuropathic pain syndrome occurring after stroke, characterized by stimulation-independent pain; shooting, lancinating, burning and electric shock-like sensation; and paresthesia (Devulder et al., 2002; Ofek and Defrin, 2007; Klit et al., 2009). Approximately, 8–14% of stroke patients have symptoms of CPSP (Kumar et al., 2009). There have been several theories for the pathogenesis of CPSP including central sensitization, neuronal excitability changes by disinhibition, alteration in spinothalamic tract function, thalamic changes, and inflammation of an involved neural tract (Cesaro et al., 1991; Wasner et al., 2008; Klit et al., 2009; Latremoliere and Woolf, 2009; Wang et al., 2017). In addition, many brain regions or structures including the cingulate gyrus, somatosensory cortex, inferior parietal lobe, lateral thalamus, spinothalamic tract (STT), and medial lemniscus have been suggested as being responsible for the pathogenesis of CPSP (Boivie et al., 1989; Vestergaard et al., 1995; Klit et al., 2009; Kumar et al., 2009; Hong et al., 2010b). However, it has not been fully elucidated so far.

Diffusion tensor tractography (DTT), derived from diffusion tensor imaging (DTI), provides three-dimensional visualization and estimation of the STT (Hong et al., 2010a; Jang

and Kwon, 2016a, b). Many studies using DTT have demonstrated that injury of the STT is the pathogenetic mechanism of CPSP in some brain pathologies including intracerebral hemorrhage and traumatic brain injury (Seghier et al., 2005; Goto et al., 2008; Hong et al., 2010b, 2012; Seo and Jang, 2013, 2014; Jang and Kwon, 2016a, b). However, no DTT study on patients with cerebral infarction has been reported so far.

In this study, we used DTT to investigate injury of the STT in patients with CPSP following cerebral infarction.

Subjects and Methods

Subjects

Five patients with cerebral infarct (two males, three females; mean age 61.6 years; range 59 to 65 years) and eight age- and sex-matched control subjects (four males; mean age 58 years; range 52 to 64 years) with no history of neurologic or psychiatric disease were randomly recruited for this study (**Table 1**). The inclusion criteria were as follows: (1) first-ever stroke, (2) central pain presenting the characteristics of neuropathic pain: stimulation-independent pain: shooting, lancinating, burning, electric shock-like sensation, and paresthesia (crawling, itching, tingling sensation); stimulus evoked pain: hyperalgesia or allodynia by environmental

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doi: 10.4103/1673-5374.221159

Accepted: 2017-04-10

Table 1 Demographic and clinical characteristics of the patients

Patient	Sex/age (year)	Duration to DTI (day)	Lesion site	Onset of CPSP (day)	Characteristics of CPSP	VAS score	CPSP site	DTT parameter
1	F/62	11	Corona radiata	0	Numbness	7	Leg	Decreased FA
2	M/59	11	Thalamus	0	Numbness	3	Arm	Decreased FA, increased MD
3	M/59	11	Pre- and post-central gyrus	0	Stiffness	3	Arm	Decreased TV
4	F/65	13	Corona radiata	0	Numbness	2	Finger and toe	Decreased TV
5	F/63	10	Thalamus	3	Numbness and allodynia	3	Arm and leg	Decreased TV

DTI: Diffusion tensor imaging; CPSP: central post stroke pain; VAS: visual analogue scale; DTT: diffusion tensor tractography; FA: fractional anisotropy; MD: mean diffusivity; TV: tract volume; F: female; M: male.

Table 2 Comparison of each parameter of diffusion tensor tractography in the spinothalamic tract between patients and control subjects

Patient	Affected hemisphere			Unaffected hemisphere		
	FA	MD	TV (number of voxels)	FA	MD	TV (number of voxels)
1	0.317*	0.946	2,068.000	0.433	0.884	1,544.000
2	0.307*	1.053**	2,834.000	0.345	0.994	2,904.000
3	0.417	0.794	58.000*	0.337	0.889	1,426.000
4	0.406	0.802	375.000*	0.409	0.889	3,954.000
5	0.372	0.813	428.000*	0.351	0.891	1,491.000

FA, MD, and TV in healthy controls are 0.402 ± 0.037 , 0.900 ± 0.060 , $2,994.125 \pm 1,228.035$, respectively and expressed as the mean \pm SD. FA: Fractional anisotropy; MD: mean diffusivity; TV: tract volume. *: When the diffusion tensor imaging parameters were decreased two standard deviations below those of controls. **:When the diffusion tensor imaging parameters were increased two standard deviations over those of controls.

stimuli (Woolf and Mannion, 1999; Dworkin et al., 2003; Klit et al., 2009), and (3) no radiculopathy or peripheral neuropathy as confirmed by electromyography and nerve conduction study. The study protocol was approved by the Institutional Review Board of Yeungnam University (YUH 14-01-425) and the study was conducted retrospectively.

Diffusion tensor image

Acquisition of DTI data was performed at 11 days on average (range: 10–13 days) after stroke onset using a 6-channel head coil on a 1.5 T Philips Gyro scan Intera (Philips, Best, The Netherlands) and single-shot echo-planar imaging. For each of the 32 non-collinear diffusion sensitizing gradients, 67 contiguous slices were acquired parallel to the anterior commissure–posterior commissure line. Imaging parameters were as follows: acquisition matrix = 96×96 ; reconstructed matrix = 192×192 ; field of view = $240 \times 240 \text{ mm}^2$; repetition time = 10,726 ms; echo time = 76 ms; parallel imaging reduction factor (SENSE factor) = 2; echo planar imaging (EPI) factor = 49; $b = 1,000 \text{ s/mm}^2$; number of excitations = 1; and a slice thickness of 2.5 mm with no gap (acquired voxel size $1.3 \times 1.3 \times 2.5 \text{ mm}^3$).

Probabilistic fiber tracking

The Oxford Centre for Functional Magnetic Resonance Im-

aging of the Brain (FMRIB) Software Library (FSL; www.fmrib.ox.ac.uk/fsl) was used for analysis of diffusion-weighted imaging data, and affine multi-scale 2-dimensional registration was used for correction of head motion effects and image distortions due to eddy currents. Fiber tracking was performed using a probabilistic tractography method based on a multi-fiber model, and applied using tractography routines implemented in FMRIB Diffusion (5,000 streamline samples, 0.5 mm step length, curvature threshold = 0.2).

The STTs were identified by selecting fibers passing through both regions of interest (ROIs). A seed ROI was placed in the posterolateral medulla on an axial slice and a target ROI was placed at the primary somatosensory cortex (S1) on an axial slice (Hong et al., 2010a). DTI parameters (fractional anisotropy (FA) and mean diffusivity (MD)) of the whole STT were measured. DTI parameters showing a deviation of more than 2 standard deviations (SD) of that of normal control values were defined as abnormal based on confidence interval. Out of 5,000 samples generated from each seed voxel, results for each contact were visualized threshold and weightings of tract probability at a minimum of one streamline through each voxel for analysis. Values of FA, MD, and tract volume of the STTs were measured.

Results

Patient 1

A 62-year-old female was diagnosed with an infarct in the right corona radiata (Table 1). The patient showed severe numbness sensation on the left leg immediately after onset. The characteristics and severity of pain were as follows: constant tingling and pricking sensation without allodynia or hyperalgesia (visual analogue scale [VAS] score: 7)(Flaherty, 1996). According to findings on 11-day DTT, FA value of the right STT was decreased by more than two standard deviations of those of control subjects. However, MD value and tract volume were within two standard deviations of those of control subjects (Table 2). The right STT ascended through the lateral portion of the infarct in the corona radiata (Figure 1).

Patient 2

A 59-year-old male underwent conservative management for an infarct in the right thalamus (Table 1). The patient complained of numbness sensation on the left arm immediately after onset. The characteristics and severity of

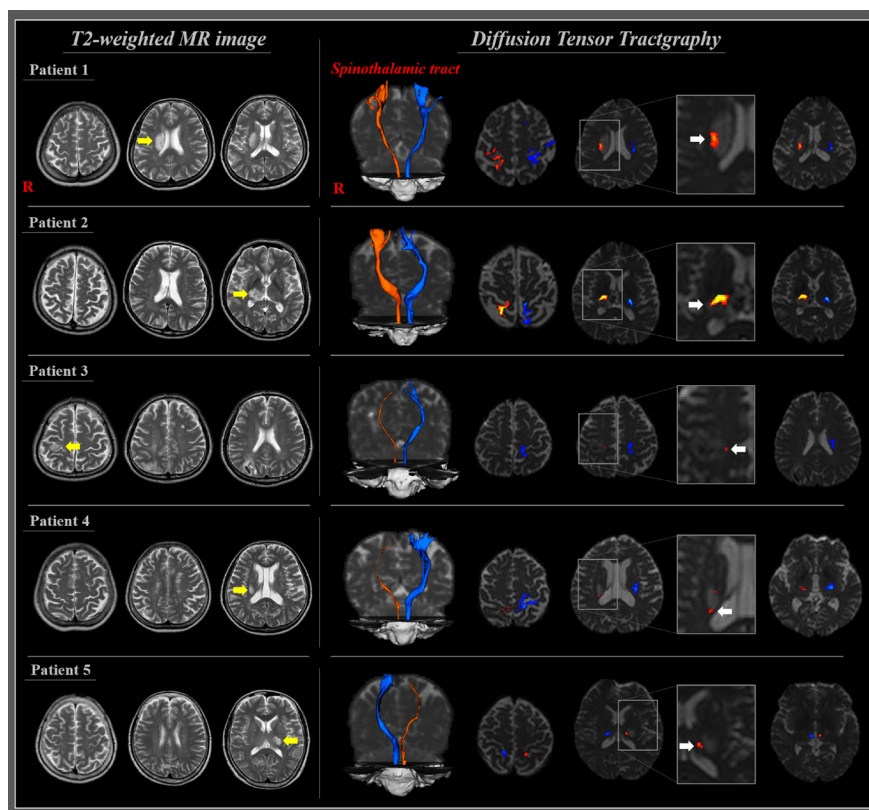


Figure 1 T2-weighted MRI and diffusion tensor tractography of patients with CPSP following cerebral infarction.

T2-weighted MR image of five patients with cerebral infarction (yellow arrows). Diffusion tensor tractography of five patients at 11 days on average after stroke onset; all the reconstructed spinothalamic tracts in the affected hemisphere originated from the posterolateral medulla and terminated at the primary somatosensory cortex through adjacent part of the infarct (white arrows) and narrowing in three patients (patients 3, 4, and 5).

pain were as follows: constant tingling sensation without allodynia or hyperalgesia (VAS score: 3). On 11-day DTT, FA and MD values of the right STT showed decrement and increment by more than two standard deviations of those of control subjects, respectively, while tract volume was within two standard deviations of that of control subjects (Table 2). The right STT passed through the anterior portion of the thalamic infarct (Figure 1)

Patient 3

A 59-year-old male was diagnosed as having an infarct in the right pre- and postcentral gyrus centered on the precentral knob and parieto-occipital lobe (Table 1). Since the day of the onset of infarct, the patient complained of stiffness sensation on the left arm. The characteristics and severity of pain were as follows: constant electric shock-like sensation without allodynia or hyperalgesia (VAS score: 3). On 11-day DTT, the right STT showed narrowing and decrement of tract volume by more than two standard deviations of those of control subjects. However, FA and MD value were within two standard deviations of those of control subjects (Table 2 and Figure 1).

Patient 4

A 65-year-old female underwent conservative management for an infarct in the right corona radiata (Table 1). The patient reported numbness sensation on the left finger and toe immediately after onset. The characteristics and severity of pain were as follows: constant tingling sensation without allodynia or hyperalgesia (VAS score: 2). On 13-day DTT, the right STT showed narrowing and tract volume was decreased by more than two standard deviations of that of control sub-

jects, while FA and MD values were within two standard deviations of those of control subjects (Table 2 and Figure 1).

Patient 5

A 63-year-old female was diagnosed as having an infarct in the left thalamus (Table 1). Three days after onset, the patient began to complain of numbness sensation on the right hand and foot. The characteristics and severity of pain were as follows: constant tingling sensation with allodynia (VAS score: 3). On 10-day DTT, the left STT showed narrowing and decrement of tract volume by more than two standard deviations of that of control subjects, while FA and MD values were within two standard deviations of those of control subjects (Table 2 and Figure 1).

Discussion

In this study, injury of the STT in terms of DTT configuration and parameters was investigated in patients who showed CPSP following cerebral infarction. Regarding DTT configuration, all affected STTs passed through the adjacent part of the infarct and three STTs showed narrowing, and significant differences in DTT parameters of the affected STT were observed in patients with CPSP compared to the normal controls. The FA value represents the white matter organization, while the MD value indicates the magnitude of water diffusion, which can increase in some pathological forms (Assaf and Pasternak, 2008). The tract volume is determined by counting the number of voxels contained within a neural tract (Jang et al., 2013). Therefore, these changes of DTT parameters of the affected STT appeared to indicate an injury of the STT. These findings on DTT parameters appeared to be

consistent with the finding of injury of affected STT on DTT configuration. As a result, the present data suggest that injury of the STT induces CPSP following cerebral infarction.

Since introduction of DTI, several previous studies have reported on pathogenesis of CPSP in patients with intracerebral hemorrhage (Seghier et al., 2005; Goto et al., 2008; Hong et al., 2010b, 2012). In 2005, using DTI, Seghier et al. reported CPSP in a patient with intracerebral hemorrhage; the patient showed selective loss of the lateral thalamo-parietal fibers without injury of medial reticulo-thalamo-cortical fibers and spinothalamic pathway below the thalamus. In 2008, Goto et al. reported that only 24% of patients with CPSP showed interruption of the pathway of the STT, while 76% of patients showed preservation of intact integrity of the STT even with symptoms of CPSP. In 2010, Hong et al. demonstrated close association of development of CPSP in patients with intracerebral hemorrhage with the decrement of tract volume of STT in the affected hemisphere (Hong et al., 2010b). Subsequently, Hong et al. (2012) reported that prevalence of CPSP in patients with intracerebral hemorrhage was more common in partial injury of the STT, compared with complete injury of the STT. Consequently, to the best of our knowledge, this is the first study to demonstrate injury of the STT in patients with CPSP following cerebral infarction. However, limitations of this study should be considered. First, DTT analysis is operator dependent and may underestimate the fiber tracts due to fiber complexity and crossing fiber effect (Yamada et al., 2009). Second, the study included a small number of patients. Conduct of further studies involving large numbers of patients should be encouraged, and further studies comparing other brain pathologies with central pain, especially intracerebral hemorrhage, would also be necessary.

In conclusion, we found injury of the STT in the affected hemisphere in five patients who showed CPSP following cerebral infarction. Injury of the STT might be a pathogenetic etiology of CPSP in patients with cerebral infarction. Our results help to diagnose CPSP in patients with cerebral infarction and investigate the related pathogenetic mechanism.

Author contributions: SHJ and SSY designed this study, collected and analyzed data, wrote and revised the paper. SHJ and JL participated in study design and data collection. All authors approved the final version of this paper.

Conflicts of interest: None declared.

Research ethics: The study was approved by the Institutional Review Board of Yeungnam University Hospital (YUH 14-01-425). This study followed the principles of the Declaration of Helsinki.

Declaration of participant consent: The authors certify that they have obtained all appropriate participant consent forms. In the form, the participants have given their consent for their images and other clinical information to be reported in the journal. The participants understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Data sharing statement: Datasets analyzed during the current study are available from the corresponding author on reasonable request.

Plagiarism check: Checked twice by iThenticate.

Peer review: Externally peer reviewed.

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Copyedited by Li CH, Song LP, Zhao M