IMAGING IN NEURAL REGENERATION

Improvement of ataxia in a patient with cerebellar infarction by recovery of injured cortico-ponto-cerebellar tract and dentato-rubro-thalamic tract: a diffusion tensor tractography study

Coordinated movement is generated by communication between the cerebrum and cerebellum *via* the cerebellar peduncles (CPs). The CPs are classified into three types (superior, middle, and inferior), and each includes a variety of neural tracts. Among those tracts, the cortico-ponto-cerebellar tract (CPCT), a middle CP, is involved in motor planning and initiation of movement, while the dentato-rubro-thalamic tract (DRTT), a superior CP, is involved in motor coordination, movement timing, verbal fluency, and working memory (Kase et al., 1993; Middleton and Strick, 1998; Afifi and Bergman, 2005; Mendoza and Foundas, 2007; Datar and Rabinstein, 2014; Javalkar et al., 2014; Meola et al., 2016). Injuries of these two neural tracts in various brain pathologies are commonly accompanied by ataxia (Kitamura et al., 2008; Min et al., 2012; Akhlaghi et al., 2014; Jang and Kwon, 2015, 2017; Marek et al., 2015; Jang et al., 2016; Schulz et al., 2017). In particular, cerebellar infarction results in inevitable injuries of the CPCT and the DRTT, and over 50% of patients with cerebellar infarction experience ataxia (Kase et al., 1993; Afifi and Bergman, 2005; Mendoza and Foundas, 2007; Datar and Rabinstein, 2014; Javalkar et al., 2014).

CPCTs and DRTTs cannot be fully evaluated due to their anatomical features, including tract length, presence of multiple synapses, poor discrimination from adjacent neural tracts, and decussation to the opposite hemisphere (Middleton and Strick, 1998; Meola et al., 2016). Regardless, the recently developed diffusion tensor tractography (DTT) method, which is derived from diffusion tensor imaging (DTI), allows estimation and visualization of the microstructural integrity of various tracts, including the CPCT and the DRTT (Hong and Jang, 2011; Kwon et al., 2011). Since the introduction of DTI, several studies have used DTT to describe injury and recovery of the CPCT or the DRTT in patients with brain injuries, including those resulting from neurodegenerative disease, cerebellar infarction, pontine hemorrhage, and trauma (Kitamura et al., 2008; Min et al., 2012; Akhlaghi et al., 2014; Jang and Kwon, 2015, 2017; Marek et al., 2015; Jang et al., 2016; Schulz et al., 2017). However, no previous study has reported on the concurrent recovery of the CPCT and DRTT injuries and ataxia after a cerebellar infarct.

In this study, by applying serial DTT, we described the recovery of CPCT and DRTT injuries in a cerebellar infarct patient.

At the neurology department of a university hospital, a 52-year-old male patient underwent conservative management for an infarct in the right cerebellum (**Figure 1A**). At 1 month after onset, he was transferred to the rehabilitation department of the same university hospital. At that time, he presented mild motor weakness (Medical Research Council scale (1976): full score = 5 points; patient's score = 4 points on the upper and lower extremities), moderate resting and intentional tremor on both hands, and truncal ataxia. The patient's Scale for Assessment and Rating of Ataxia (SARA, range 0–40 points with a higher score indicating a poorer state) and Functional Ambulation Category (FAC, full score 5 points) scores were determined as previously described (Cunha et al., 2002; Weyer et al., 2007). At the beginning of rehabilitation (1 month after onset), the patient's SARA and FAC scores were 18 and 1.5 points, respectively, and he was unable to walk independently. However, with rehabilitation, his motor function improved. At 3 months after onset, his scores were 10 points for SARA and 3.5 points for FAC. Moreover, at 14 months after onset, his motor function was further improved (SARA = 7 points and FAC = 4.5 points), and he was able to walk independently on an even floor. The patient provided written informed consent for participation in this study, and the study protocol was approved by the Institutional Review Board of Yeungnam University Hospital (YUMC 2015-07-065-011) on August 28, 2015.

DTT data were acquired twice (at 1 and 14 months after onset) using a 1.5 T Philips Gyroscan Intera (Philips, Amsterdam, the Netherlands) with 32 gradients. Imaging parameters were as follows: acquisition matrix = 96 × 96; reconstructed to matrix = 192 × 192; field of view = 240 mm × 240 mm; echo time = 10,398 ms; repetition time = 72 ms; b = 1000 s/mm^2; and slice thickness = 2.5 mm. Prior to fiber tracking, to correct for head motion effects and image distortion, eddy current correction was performed using the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB) software library (FSL; www.fmrib.ox.ac.uk/fsl) as previously described (Smith et al., 2004; Behrens et al., 2007). For fiber tracking, we used FMRIB software with the results based on probability tracking with a threshold of two streamlines as previously described (Smith et al., 2004; Behrens et al., 2007). For CPCT and DRTT reconstruction, regions of interest (ROIs) were selected as previously described (Hong and Jang, 2011; Kwon et al., 2011). In each tract, there were three ROIs. For the CPCT: ROI1 was the primary sensorimotor cortex on the axial image; ROI2, the anterior pons on the axial image; and ROI3, the contralateral cerebellar hemisphere on the coronal image. For the DRTT, ROI1 was the dentate nucleus on the coronal image; ROI2, the junction of the superior cerebellar peduncle on the coronal image; and ROI3, the contralateral red nucleus of the upper midbrain on the axial image.

In the DTT results obtained at 1-month after onset, the CPCTs appeared thin in both hemispheres whereas the DRTTs were not reconstructed in either hemisphere compared to a normal subject (51-year-old male) recruited from the same University hospital. In contrast, the 14-month post-onset DTT results showed the CPCTs in both hemispheres had thickened and reconstruction of the right DRTT had occurred (**Figure 1B**).

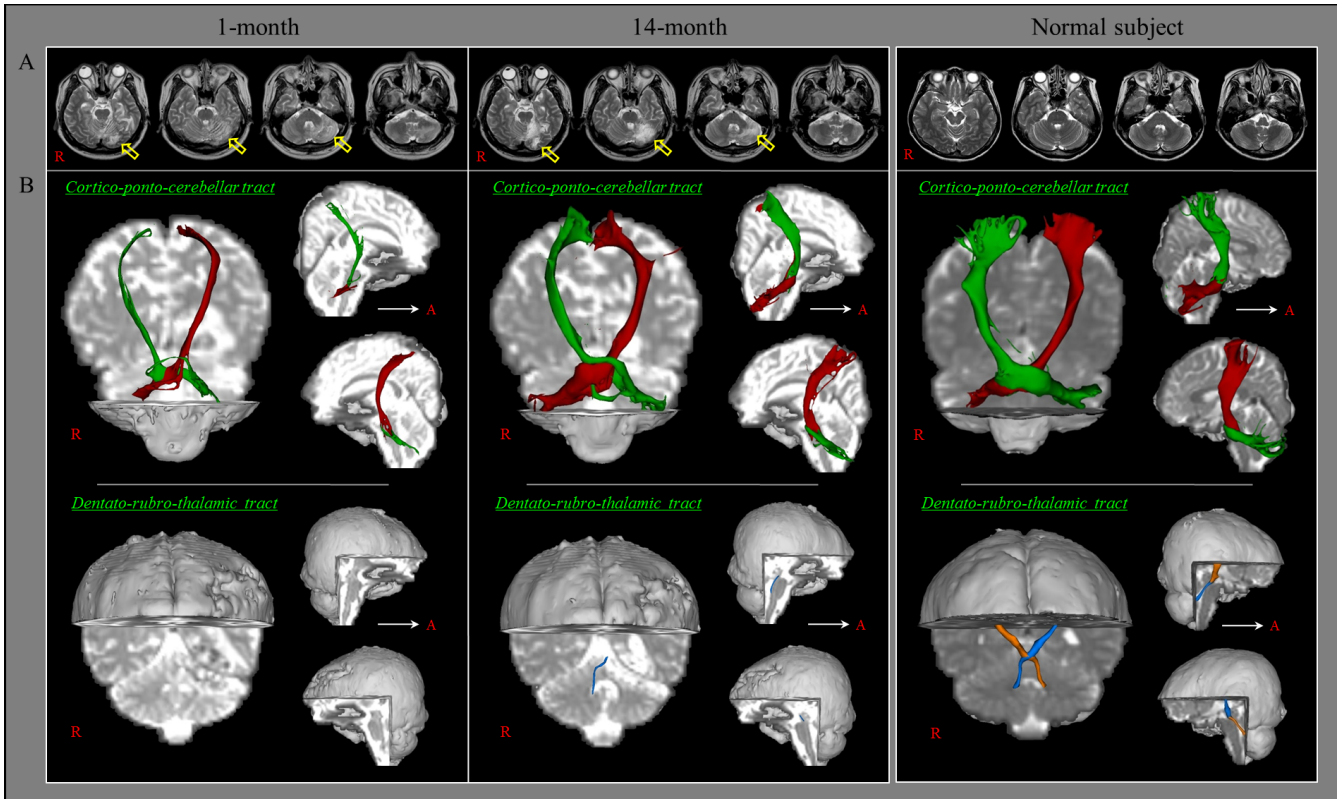

Figure 1 Results of diffusion tensor tractography for the cortico-ponto-cerebellar tract and dentato-rubro-thalamic tract of a patient at 1 and 14 months after onset.

(A) T2-weighted magnetic resonance images of the study patient at 1 and 14 months after onset showing evidence of an infarct in the right cerebellum (yellow arrows) and images of a normal subject (51-year-old male). (B) Results of diffusion tensor tractography for the cortico-ponto-cerebellar tract (CPCT) and dentato-rubro-thalamic tract (DRTT). Compared to the normal subject, on 1-month DTT, the CPCTs appeared thin in both hemispheres whereas the DRTTs in both hemispheres were not reconstructed. In contrast, on 14-month DTT, the CPCTs in both hemispheres were thicker and the right DRTT was reconstructed (blue). R: Right; A: anterior; red: right CPCT; green: left CPCT; blue: right DRTT; orange: left DRTT.

In the current study, we observed changes in injured CPCTs and DRTTs by performing serial DTT and monitored clinical improvement of ataxia in a patient with cerebellar infarction. On 1-month DTT, the CPCTs (thin) and DRTTs (not reconstructed) in hemispheres were injured; in contrast, on 14-month DTT, both CPCTs (thickened) and the right DRTT (partially reconstructed) exhibited injury recovery. During the same period, the patient's clinical scores for ataxia (SARA) and gait (FAC) were also increased. As a result, at 14 months post-onset, he was able to walk independently on an even floor.

It has been reported that substantial spontaneous recovery occurs in the weeks to months following brain injury, with the remaining amount of recovery usually occurring as a result of rehabilitation (Nudo, 2013). In this study, the patient underwent rehabilitation for 13 months, during which his motor functions gradually improved. During that same period, the status of the patient's CPCTs and the right DRTT improved. Therefore, we believe that improvement of the patient's clinical function can be ascribed, at least in part, to the observed CPCT and DRTT recoveries.

Several studies have used DTI to report on CPCT and DRTT injuries in patients following various brain injuries (Kitamura et al., 2008; Min et al., 2012; Akhlaghi et al., 2014; Jang and Kwon, 2015, 2017; Marek et al., 2015; Jang et al., 2016), and one study reported concurrent CPCT and DRTT injuries in patients with brain injury. In 2017, Schulz et al. reported that concurrent CPCT and DRTT injuries were associated with residual motor function in 26 patients with chronic ischemic stroke. To the best of our knowledge, the present case study is the first to demonstrate, by using serial DTT, concurrent recovery of motor function and injured CPCTs and DRTTs in a patient with cerebellar infarction. However, this study has limitations, mainly because it is a single case report. In addition, we were unable to investigate the relationships between the degree of ataxia and the status of the neural tract. The other limitation is that we could not obtain DTT data at onset. Compared to the features of DTI, DTT is unique as it provides three-dimensional visualization and quantification data, such as volume and thickness of neural tracts, which are useful in the analysis of specific neural tracts. Regardless, both DTI and DTT have limitations. First, both are operator-dependent. Second, neither method can reflect functional or synaptic connections. Third, DTT can produce false-positive and false-negative results due to the presence of multiple fiber directions within a voxel or a result of a partial volume effect present in the white matter of the brain (Yamada et al., 2009; Fillard et al., 2011). Therefore, we suggest that further studies that include large numbers of patients should be undertaken to overcome these limitations.

In conclusion, using DTT, we demonstrated recovery of injured CPCTs and DRTTs in a patient who concurrently showed clinical recovery of ataxia following a cerebellar infarct. Our results suggest that evaluation of the CPCTs and DRTTs would be helpful in the evaluation of patients who have movement disorders such as ataxia and tremor following cerebellar infarction.

Sung Ho Jang, Hyeok Gyu Kwon*
Department of Physical Medicine and Rehabilitation, College of Medicine, Yeungnam University, Daegu, Republic of Korea (Jang SH)
Department of Physical Therapy, College of Health Science, Eulji University, Gyeonggi, Republic of Korea (Kwon HG)
***Correspondence to:** *Hyeok Gyu Kwon, PhD, khg0715@hanmail.net.*
***orcid:** 0000-0002-6654-302X (Hyeok Gyu Kwon)*
***Received:** June 20, 2018*
***Accepted:** January 5, 2019*

***doi:** 10.4103/1673-5374.253533*
***Author contributions:** Conception and design of the study, data acquisition, manuscript development and writing: SHJ; data acquisition and analysis, fundraising, manuscript writing and technical support: HGK. Both authors approved the final version of this paper.*
***Conflicts of interest:** The authors declare that they have no conflicts of interest.*
***Financial support:** This study was supported by Bumsuk Academic Research Fund in 2017 (to HGK). The funding body played no role in the study conception design, in the collection, analysis and inter pretation of data, in the preparation and writing of the report, and in the decision to submit the article for publication.*
***Institutional review board statement:** Approval for the study was obtained from the Institutional Review Board of Yeungnam University Hospital (YUMC 2015-07-065-011) on August 28, 2015.*
***Declaration of participant consent:** The authors certify that they have obtained the appropriate participant consent forms. In the forms 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.*

***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.*

References

Afifi AK, Bergman RA (2005) Functional neuroanatomy: text and atlas, 2nd ed. New York: Lange Medical Books/McGraw-Hill.
Akhlaghi H, Yu J, Corben L, Georgiou-Karistianis N, Bradshaw JL, Storey E, Delatycki MB, Egan GF (2014) Cognitive deficits in Friedreich ataxia correlate with micro-structural changes in dentatorubral tract. Cerebellum 13:187-198.
Behrens TE, Berg HJ, Jbabdi S, Rushworth MF, Woolrich MW (2007) Probabilistic diffusion tractography with multiple fibre orientations: What can we gain? Neuroimage 34:144-155.
Cunha IT, Lim PA, Henson H, Monga T, Qureshy H, Protas EJ (2002) Performance-based gait tests for acute stroke patients. Am J Phys Med Rehabil 81:848-856.
Datar S, Rabinstein AA (2014) Cerebellar infarction. Neurol Clin 32:979-991.
Fillard P, Descoteaux M, Goh A, Gouttard S, Jeurissen B, Malcolm J, Ramirez-Manzanares A, Reisert M, Sakaie K, Tensaouti F, Yo T, Mangin JF, Poupon C (2011) Quantitative evaluation of 10 tractography algorithms on a realistic diffusion MR phantom. Neuroimage 56:220-234.
Hong JH, Jang SH (2011) Functional magnetic resonance imaging and diffusion tensor tractography of the corticopontocerebellar tract in the human brain. Neural Regen Res 6:76-80.
Jang SH, Kwon HG (2015) Injury of the dentato-rubro-thalamic tract in a patient with mild traumatic brain injury. Brain Inj 29:1725-1728.
Jang SH, Kwon HG (2017) Injury of the dentato-rubro-thalamic tract in patients with cerebellar infarct: Case report. Medicine (Baltimore) 96:e7220.
Jang SH, Chang CH, Jung YJ, Kwon HG (2016) Severe ataxia due to injuries of neural tract detected by diffusion tensor tractography in a patient with pontine hemorrhage: A case report. Medicine (Baltimore) 95:e5590.
Javalkar V, Khan M, Davis DE (2014) Clinical manifestations of cerebellar disease. Neurol Clin 32:871-879.
Kase CS, Norrving B, Levine SR, Babikian VL, Chodosh EH, Wolf PA, Welch KM (1993) Cerebellar infarction. Clinical and anatomic observations in 66 cases. Stroke 24:76-83.
Kitamura K, Nakayama K, Kosaka S, Yamada E, Shimada H, Miki T, Inoue Y (2008) Diffusion tensor imaging of the cortico-ponto-cerebellar pathway in patients with adult-onset ataxic neurodegenerative disease. Neuroradiology 50:285-292.
Kwon HG, Hong JH, Hong CP, Lee DH, Ahn SH, Jang SH (2011) Dentatorubrothalamic tract in human brain: diffusion tensor tractography study. Neuroradiology 53:787-791.
Marek M, Paus S, Allert N, Madler B, Klockgether T, Urbach H, Coenen VA (2015) Ataxia and tremor due to lesions involving cerebellar projection pathways: a DTI tractographic study in six patients. J Neurol 262:54-58.
Medical Research Council (1976) Aids to examination of the peripheral nervous system. Memorandum no. 45. London: Her Majesty's Stationary Office.
Mendoza JE, Foundas AL (2007) Clinical neuroanatomy: a neurobehavioral approach. New York: Springer.
Meola A, Comert A, Yeh FC, Sivakanthan S, Fernandez-Miranda JC (2016) The nondecussating pathway of the dentatorubrothalamic tract in humans: human connectome-based tractographic study and microdissection validation. J Neurosurg 124:1406-1412.
Middleton FA, Strick PL (1998) Cerebellar output: motor and cognitive channels. Trends Cogn Sci 2:348-354.
Min Y, Park SH, Hwang SB (2012) Corticospinal tract and ponto-cerebellar fiber of central pontine myelinolysis. Ann Rehabil Med 36:887-892.
Nudo RJ (2013) Recovery after brain injury: mechanisms and principles. Front Hum Neurosci 7:887.
Schulz R, Frey BM, Koch P, Zimerman M, Bonstrup M, Feldheim J, Timmermann JE, Schon G, Cheng B, Thomalla G, Gerloff C, Hummel FC (2017) Cortico-cerebellar structural connectivity is related to residual motor output in chronic stroke. Cereb Cortex 27:635-645.
Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, Bannister PR, De Luca M, Drobnjak I, Flitney DE, Niazy RK, Saunders J, Vickers J, Zhang Y, De Stefano N, Brady JM, Matthews PM (2004) Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage 23 Suppl 1:S208-219.
Weyer A, Abele M, Schmitz-Hubsch T, Schoch B, Frings M, Timmann D, Klockgether T (2007) Reliability and validity of the scale for the assessment and rating of ataxia: a study in 64 ataxia patients. Mov Disord 22:1633-1637.
Yamada K, Sakai K, Akazawa K, Yuen S, Nishimura T (2009) MR tractography: a review of its clinical applications. Magn Reson Med Sci 8:165-174.

C-Editor: Zhao M; S-Editor: Li CH; L-Editor: Song LP; T-Editor: Liu XL