Fornix Injury in a Patient with Rotavirus Encephalopathy: Diffusion Tensor Tractography Study

Su Min Son, M.D., Sung Ho Jang, M.D., Eun Sil Lee, M.D., Sang Ho Ahn, M.D., Dong Gyu Lee, M.D., Hee Kyung Cho, M.D.

Departments of Physical Medicine and Rehabilitation, Pediatrics, College of Medicine, Yeungnam University, Daegu 705-717, Korea

Rotavirus encephalopathy (RE) is a benign afebrile seizure associated with acute gastroenteritis caused by rotavirus infection. We investigated the diffusion tensor tractography (DTT) findings of a patient with RE. The patient was a 30-month-old female that had experienced a brief, generalized convulsive seizure. On the day of admission, the patient had vomiting and experienced watery diarrhea. Her stool was positive for rotavirus antigen. At onset, the patient displayed a drowsy and delirious mental status; later, a splenial lesion of the corpus callosum was found on MRI. One week later, the patient’s condition improved and the splenial lesion had disappeared by conventional MRI. Initial DTI showed decreased fractional anisotropy (FA) values of fornix, as well as of the corpus callosum. A follow-up DTT showed a restored interrupted right fonical crus and increased FA values of corpus callosum and fornix. These results highlight the implications of the probability of not only a corpus callosum injury, but a fornix injury as well, in this patient with RE.

Key Words Diffusion tensor tractography, Rotavirus encephalopathy, Fornix
splenial lesion (MERS). Drowsy or delirious behavior seems to be one of the main clinical features in patients with MERS. However, these studies were mainly conducted using conventional brain MRI, and did not reveal the microstructural status of white matter pathology. The recent development of diffusion tensor imaging (DTI) allows the evaluation of the integrity and orientation of neural tracts at the subcortical level. Diffusion tensor tractography (DTT), a 3-dimensional visualized version of DTI, is useful for the concrete description of the architecture and integrity of the neural tracts.

In the current study, we used DTT to investigate a patient with RE and to examine the detailed characteristics of a splenial lesion of the corpus callosum.

**CASE REPORT**

A 30-month-old female was brought to the emergency department after a brief (<5 minutes) generalized convulsive seizure. The patient had displayed a fever for the 3 days before admission, had vomited approximately 15 times, and had experienced 2 or 3 episodes of watery diarrhea on the day of admission. Before arrival at the emergency department, the patient experienced an episode of shaking of the arms and legs, with the eyes rolling upward. The witnesses’ descriptions were consistent with a generalized tonic-clonic seizure. The patient’s past medical history, family history, growth history, and developmental history were otherwise unremarkable. The patient’s temperature was 37.5°C, heart rate 110, respiratory rate 28, weight 13.1 kg (50-75th percentile) and length 96.7 cm (95-97th percentile). The patient exhibited a drowsy mental status, but other neurological examinations did not reveal other defined abnormal findings. The patient underwent extensive diagnostic evaluations. The results of lab tests performed on admission were positive for rotavirus antigen in stool. Laboratory findings included a WBC count of 12,600/μl and platelet count of 905,000/μl; both were mildly elevated from normal. There were non-specific findings on all other laboratory tests, including a comprehensive metabolic panel, spinal fluid, blood culture, and urine culture. The patient was diagnosed with RE by a pediatric neurologist. The patient received effective replacement of fluids and electrolytes. Anticonvulsant medication was used.

![Fig. 1. Results of conventional T2-weighted MRI and DTT. (A) T2-weighted images showed an encephalomalatic lesion (arrow) in the splenial lesion of the corpus callosum that disappeared in one week later follow-up MRI. (B) DTT at onset for the corpus callosum and cingulum showed no definite abnormal finding, although a splenial lesion was apparent on conventional MRI. However, the integrity of right fornical crus (arrow) was interrupted. A second DTT taken 1 week later from onset, integrity of the fornix was restored and well preserved. DTT of corpus callosum and cingulum findings were normal at follow up DTT. DTT: Diffusion tensor tractography.]
not taken without recurrent seizures. After one week, the
patient displayed a much improved condition and was
discharged 2 weeks after onset. Brain MRI, including
DTI, was performed at onset and one week after onset.
Lesions were well defined and ovoid in the SCC. The
SCC lesion was homogeneously hyperintense on T2-
weighted images and isointense or slightly hypointense
on T1-weighted images; the lesion was not detected in
MRI conducted one week later (Fig. 1). DTI data were
acquired twice simultaneously with a conventional MRI
(onset and one week after onset) using a 1.5-T Philips
Gyrosan Intera system equipped with a multi-channel
head coil with a single-shot spin echo-planar imaging
sequence. For each of the 32 non-collinear and non-
coplanar diffusion-sensitizing gradients, 60 contiguous
slices were acquired parallel to the anterior commissure-
posterior commissure line. Imaging parameters were as
follows: matrix=128x128 matrix; field of view=221x221
mm$^2$; TE=76 ms; TR=10,726 ms; SENSE factor=2;
EPI factor=49; b=1,000 mm$^2$s$^{-1}$; NEX=1; and a slice
thickness of 2.3 mm. Eddy current image distortions
and motion artifacts were removed using affine multi-
scale 2-dimensional registration, which was performed
using the Oxford Centre for Functional Magnetic
Resonance Imaging of Brain (FMRIB) Software Library
(FSL, http://www.fmrib.ox.ac.uk/fsl). The analysis for
callosal projections was conducted using a single region
of interest (ROI) approach using DTI-studio software
CMRM (Johns Hopkins Medical Institute, Baltimore,
USA). A callosal ROI was defined manually at the red
portion of the midsagittal plane on the color map.
Additional fiber tracking for the fornix and the cingulum
were identified using fibers passing through two ROIs
on the color map. The seed ROI of the fornix was placed
on the junction between the column and body, and the
target ROI was the junction between the body and crus.
For the cingulum, the seed ROI was located in the green
portion of the anterior cingulum areas and the target
ROI was in the green portion of the posterior cingulum
areas on the coronal slice.\(^6\) Fiber tracking was initiated
at the center of a seed voxel with a fractional anisotropy
(FA) >0.2 and ended at a voxel with a fiber assignment
of FA <0.2 and a tract turning-angle of <60 degrees. Also,
the FA values of cingulum, corpus callosum and fornix
were measured. The whole corpus callosum was divided
into 5 regions (genu, rostral body, body, isthmus and
splenium) according to a well-established protocol,
with 7 subdivisions of the corpus callosum,\(^7\) and FA and
apparent diffusion coefficient (ADC) values of each of
the 5 regions of the corpus callosum were measured. We
evaluated the FA and ADC values of 3 divided regions of
the fornix (column, body and crus) (Table 1).

The initial FA value of SCC at onset (0.66) was noticeably
lower than that of follow-up FA value at one week after
onset (0.77). However, the other regions of the corpus
callosum showed no definite differences in FA values
between the initial and follow-up data. For the fornix,
only the region of the right crus had prominent interval
changes between initial (0.33) and follow-up value (0.40).

The cingulum showed no definite differences between
initial and follow-up data. The initial ADC value was
decreased and the follow-up value was increased, in
the SCC and right fornical crus regions. For the other
regions, there were no definite differences between initial
and follow-up ADC values. The results of initial DTT
demonstrated spared integrity of the corpus callosum,
although a spared lesion was apparent on conventional

| Region          | FA At onset | FA One week after onset | ADC (mm$^2$/s) At onset | ADC (mm$^2$/s) One week after onset |
|-----------------|-------------|-------------------------|-------------------------|-----------------------------------|
| Corpus callosum |             |                         |                         |                                   |
| Genu            | 0.69        | 0.69                    | 0.88                    | 0.87                              |
| Rostral body    | 0.67        | 0.65                    | 0.85                    | 0.89                              |
| Body            | 0.55        | 0.55                    | 0.93                    | 0.96                              |
| Isthmus         | 0.71        | 0.73                    | 0.85                    | 0.87                              |
| Splenium        | 0.66        | 0.77                    | 0.78                    | 0.94                              |
| Fornix          |             |                         |                         |                                   |
| Right column    | 0.36        | 0.37                    | 1.00                    | 0.97                              |
| Left column     | 0.36        | 0.34                    | 1.17                    | 1.17                              |
| Body            | 0.50        | 0.52                    | 1.30                    | 1.23                              |
| Right crus      | 0.33        | 0.40                    | 0.75                    | 1.48                              |
| Left crus       | 0.43        | 0.43                    | 1.48                    | 1.44                              |
| Cingulum        |             |                         |                         |                                   |
| Right           | 0.38        | 0.38                    | 0.90                    | 0.91                              |
| Left            | 0.41        | 0.39                    | 0.93                    | 0.90                              |

FA: Fractional anisotropy values, ADC: Apparent diffusion coefficient values
MRI. However, fornix revealed discontinuity of the right fornical crus. On the follow-up DTT at one week after onset, the interrupted right fornical crus was restored. In the cingulum, there were no definite abnormal findings at onset or at follow-up DTT (Table 1, Fig. 1).

**DISCUSSION**

In the current case study, we observed changes in DTT along with clinical changes in a patient with RE. At the time of the first DTI scan, this patient had a generalized convulsive seizure and appeared drowsy. On DTT, it revealed a decreased FA value, with spared integrity of the SCC, although a definite encephalomalatic lesion in the SCC was visible on conventional MRI. Additionally, he showed cognitive impairment on the day of admission. On DTT, the fornix showed not only disrupted integrity, but decreased FA value of the right crus. After treatment, the patient recovered to normal alertness and awareness, and theses clinical changes area well correlate with DTT changes. At the time of follow-up conventional MRI, DTI and DTT revealed normal findings of the fornix and corpus callosum.

Salmi et al. was the first to describe central nervous system involvement with a rotavirus. The 1978 study reported on 2 children with RE. The first case developed a fatal Reye’s syndrome and the other patient showed symptoms of encephalitis with slow recovery. In 2009, a neuroimaging study about RE described a 2-year-old boy who experienced persistent diarrhea, vomiting, and a sudden disturbance of consciousness. Initial brain diffusion-weighted MRI demonstrated high signal intensity on the SCC, but the splenial signal returned to normal within 6 days as the disturbed consciousness improved. The clinical features and neuroimaging findings of the current study are very similar to those of these previous studies. The most likely mechanisms for the reversible SCC lesion in RE was proposed by Tada et al. They posited that the reversible SCC lesions may be related to the transiently decreased ADC values of the lesions: intramyelinic edema from separation of myelin layers, or an influx of inflammatory cells and macromolecules. Furthermore, they postulated that the isolated involvement of SCC is from a different arterial supply from the vertebrobasilar system, contrary to other parts of the corpus callosum supplied by the carotid system, which has special affinity for the receptors on splenial axons or surrounding myelin sheaths to viral antigens or receptors on the antibodies induced by the antigen, resulting in increased vulnerability of the SCC.

Although the pathophysiology of delirium is not well established, delirium in RE is related to both cerebral hemispheres and connections of both hemispheres, rather than one hemisphere. The causes of delirium are intoxication, fever or encephalitis and generalized disruption of higher cognitive function may develop in delirium. The SCC connects the bilateral occipital and temporal lobes and is closely related to the limbic system. Therefore, encephalomalatic lesion in the SCC revealed by decreased FA value on DTI may lead to the disconnection of both temporal and occipital lobes and development of higher cognitive dysfunction, thus resulting in the altered behavior. Moreover, the authors presumed that not only splenial lesion of the corpus callosum, but also other microstructural pathophysiological mechanisms around corpus callosum may result in abnormal neurologic symptoms.

The fornix is an important component of the Papez circuit and limbic system. It connects the hippocampus and prefrontal cortex and plays an important role in cognitive function, such as intelligence, visuospatial memory, overall episodic memory, and affect. Consequently, fornical injury may lead to significant impairment of cognitive function in various diseases. In 2010, Zhuang et al. investigated the correlation between fornix and cognitive function using DTI in 165 mild cognitive impairment patients; the best discrimination between mild cognitive impairment patients and normal controls was achieved by combining FA measures for the SCC and those of the fornical crus. Another study examined a patient with diffuse axonal injury using DTT. Their results revealed that both cingulum and fornix showed severe degeneration as his memory impairment had been aggravated. As the fornix was disrupted on right crus on the first DTT in our study, the authors proposed that patients who demonstrated severe cognitive impairment and delirious behavior as sequelae of RE might to the result of both a splenial lesion and a fornix injury.

In addition, we used the diffusion parameter and DTT for the detailed microstructural evaluation of white matter lesion. The FA value is the most widely used DTI
Fornix Injury in Rotavirus Encephalopathy

parameter and represents the degree of directionality of microstructures (e.g., axons, myelin and microtubules). Reduced FA values of the SCC and fornical crus appear to be related to disintegration of neuronal fibers. However, the corpus callosum is the largest and main fiber tract for cerebral hemispheric transfer with at least 200 million nerve fibers. On the contrary, the fornix is a long and thin structure and the crus is located close to the posterior portion of the corpus callosum, and probably appears to be more vulnerable to rota virus infection than the corpus callosum; however, it is very difficult to assess this by conventional MRI due to the deep location within the brain. The authors suggest that this may be the reason for different results for integrity of corpus callosum and fornix in DTT.

In conclusion, we demonstrate that DTT can be a useful modality to assess microstructural lesions in a patient with RE that is related not only to SCC injury, but also to fornical injury. To the best of our knowledge, there has been no study about microstructural pathology using DTT in patients with RE. However, it is unclear whether this observation is an epiphenomenon or plays a more definite role in diagnosing RE as it is only a single case. Moreover, clinical functional evaluation, such as memory function, could not be obtained due to the patient’s young age. Further complementary studies involving larger case numbers and detailed functional evaluation are warranted to corroborate these findings.

ACKNOWLEDGEMENTS

This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (2010-0015251).

REFERENCES

1. Salmi TT, Arstila P, Koivikko A. Central nervous system involvement in patients with rotavirus gastroenteritis. Scand J Infect Dis 1978; 10: 29-31
2. Fukuda S, Kishi K, Yasuda K, Sejima H, Yamaguchi S. Rotavirus-associated encephalopathy with a reversible splenial lesion. Pediatr Neurol 2009; 40: 131-133
3. Tada H, Takanashi J, Barkovich AJ, Oba H, Maeda M, Tsukahara H, Suzuki M, Yamamoto T, Shimono T, Ichiyama T, et al. Clinically mild encephalitis/encephalopathy with a reversible splenial lesion. Neurology 2004; 63: 1854-1858
4. Takanashi J, Tada H, Kuroki H, Barkovich AJ. Delirious behavior in influenza is associated with a reversible splenial lesion. Brain Dev 2009; 31: 423-426
5. Malykhin N, Concha L, Seres P, Beaulieu C, Coupland NJ. Diffusion tensor imaging tractography and reliability analysis for limbic and paralimbic white matter tracts. Psychiatry Res 2008; 164: 132-142
6. Hong JH, Jang SH. Degeneration of cingulum and fornix in a patient with traumatic brain injury: diffuse tensor tractography study. J Rehabil Med 2010; 42: 979-981
7. Witelson SF. Hand and sex differences in the isthmus and genu of the human corpus callosum. A postmortem morphological study. Brain 1989; 112: 799-835
8. Bulakbasi N, Kocaoglu M, Tayfun C, Ucoz T. Tansient splenial lesion of the corpus callosum in clinically mild influenza-associated encephalitis/encephalopathy. Am J Neuroradiol 2006; 27: 1983-1086
9. Vachha B, Adams RC, Rollins NK. Limbic tract anomalies in pediatric myelomeningocele and Chiari II malformation: anatomic correlations with memory and learning--initial investigation. Radiology 2006; 240: 194-202
10. Zhuang L, Wen W, Zhu W, Trollor J, Kochan N, Crawford J, Reppermund S, Brodaty H, Sachdev P. White matter integrity in mild cognitive impairment: a tract-based spatial statistics study. Neuroimage 2010; 53: 16-25