Wallerian Degeneration of Insufficiently Affected White Matters in Old Infarction: Tract of Interest Analysis of Diffusion Tensor Imaging

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Abstract

The application of diffusion tensor imaging (DTI) and fiber tractography to Wallerian degeneration (WD) is important because this technique is a very potent tools for quantitatively evaluating fiber tracts in vivo brain. We analyzed a case and control using tracts of interest (TOI) analysis to quantify WD. We scanned a case of old infarction and an age-matched healthy volunteer. T1 magnetization prepared rapid acquisition gradient echo (MPRAGE), fluid attenuated inversion recovery (FLAIR) and 12-direction diffusion tensor imaging (DTI) were obtained and analyzed using TOI analysis. The value of mean diffusity (D_{av}) and fracional anisotrophy (FA) were analyzed statistically by MWU test. A p-value of less than 0.05 was considered to indicate statistical significance. A comparison of the global fiber diffusion characteristics shows WD of both the corpus callosum and the ipsilateral superior longitudinal fasciculus. The corpus callosum in particular showed trans-hemispherical degeneration. Local fiber characteristics along the geodesic paths show WD in the corpus callosum, ipsilateral superior longitudinal fasciculus, ipsilateral corticospinal tract, and ipsilateral corticothalamic tract. We have demonstrated changes in D_{av} and FA values and a clear correspondence with the WD in various tracts. TOI analysis successfully revealed radial WD in white matter tracts from a region of encephalomalacia and primary gliosis, although they were only slightly affected.

Key words : diffusion tensor imaging, white matter disease, imaging processing

I. INTRODUCTION

Wallerian degeneration (WD) after ischemic stroke is a well-known phenomenon that involves the degeneration of distal parts of nerves after injury to the proximal axon or cell body. It was first reported by Waller[1].WD involves the breakdown of the myelin sheath and the disintegration of axonal microfilaments[2], and develops through four different stages[3]. The most commonly recognizable cause of WD is cerebral infarction, although it can also result from a variety of conditions including hemorrhage, trauma, necrosis, and focal demyelination[3,4]. Some studies have reported WD of the fibers of the corpus callosum, the optic radiations, fornices and cerebellar peduncles[5-7].

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Because the diagnosis of WD with computed tomography (CT) depends on the detection of the atrophy of the pyramidal tracts, CT is not a sensitive test for WD in the acute to subacute periods. Magnetic resonance imaging (MRI) is superior to CT in the diagnosis of WD[8,9]. However, conventional MRI shows changes in the white matter only after 20 days (stage 2). Yamada et al. showed WD of various tracts, such as the corpus callosum, corticospinal tract, and limbic system and Simone et al. also described WD of the pontocerebellar fibers[7,10]. However, these studies were limited to tracts considerably affected with WD. Diffusion-weighted imaging is useful in the identification of acute white-matter injury corresponding to stage 1 of WD, which is not detectable with conventional MRI[11]. Diffusion tenor imaging (DTI) and fiber tractography have been used to detect and quantify WD in adult patients with stroke[13-16]. This modality provides information on microstructural properties[16] and can visualize and quantify changes in the integrity and orientation of white-matter tracts transected by a focal ischemic lesion. The loss of integrity of these directional structures is consistent

with reduced anisotropy in the corticospinal tract, ipsilateral to the cerebral infarction. DTI has shown that, in the chronic stage of stroke, fractional anisotropy(FA) is reduced along the pyramidal tract on the affected side below the primary lesion months to years after a stroke[12,13]. Moreover, DTI has detected WD changes in the pyramidal tract months to years after a stroke[12,13] and the characteristic changes reflecting early WD[15].

However, most DTI studies have been limited in that they have only focused on the corticospinal tract. Various insufficiently affected tracts have never been evaluated, because only regions of interest (ROIs) specified by the user have been compared or a voxel-based analysis performed, both of which cause problems in the reliable specification of small ROIs or the ambiguous definition of tracts[17]. Therefore, various tracts in the hemisphere, such as the callosal fibers, association fibers, and projection fibers, have not been investigated, despite the ability of DTI to detect the early changes of WD.

DTI tractography-based metrics used to assess abnormalities in cerebral white matter have recently been reported[18,19]. In this method, quantitative tractography evaluating specific fiber bundles (track of interests, TOI[20]) with their diffusion properties provides relevant white-matter ROIs, so that disease-related injuries to specific white-matter pathways can be clearly assessed. Therefore, we used TOI analysis of DTI to analyze a patient with an old infarction and to demonstrate radial WD from encephalomalatic cavities.

II. MATERIALS AND METHODS

A. Subjects and Scanning Methods

We selected a 70-year-old man with an old unilateral infarction who has no evidence of WD on previous Routine MRI scan (Fig.1) as our case study and an age-matched volunteer as the control. An MRI scan was performed after written informed consent was obtained. This study was approved by the Institutional Review Board of the National Medical Center, Korea. The control subject had no history of disease and no abnormal signal in the brain parenchyma on routine MRI. Scanning was performed on a 1.5T MR system (Siemens AVANTO, Erlangen, Germany), equipped with hardware for echo-planar imaging (EPI), shielded gradients, and a standard quadrature headcoil. T1-weighted high- resolution (1 x 1 x 1 mm) structural images were obtained using a magnetization-prepared rapid acquisition gradient echo (MPRA GE) sequence. The echo time and repetition time (TE/TR) were 4.7/1140 ms. A field of view (FOV) of 223 x 256 mm^2 and matrix of 256 x 240 were used. Scanning was performed in the sagittal plane, with alignment parallel to the plane through the falx. The average number of scans was one. Fluid-attenuated inversion recovery (FLAIR) imaging sequences, with parameters of 9000/119/1 (repetition time/echo time/excitations), an inversion

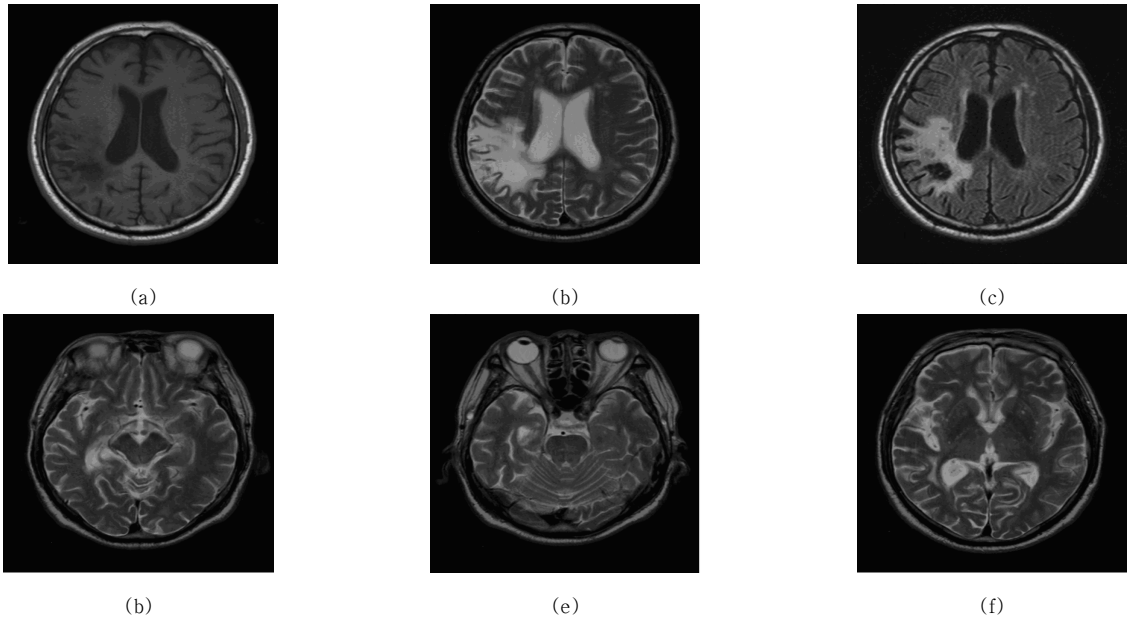
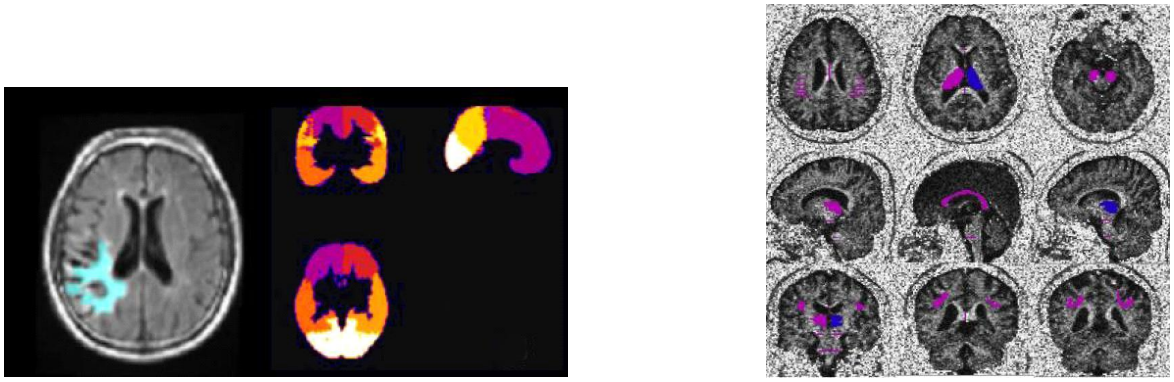


Fig. 1. The patient, a 70-year-old man with old infarction. AC, Abnormal signal intensities related to an infarction in the right parietal lobe. Hypointensities on a T1-weighted image (a), hyperintensities on a T2-weighted image (b), and encephalomalacia with gliosis on FLAIR (c) are noted on axial scans of a routine MRI. DF, No evidence of abnormal signal intensity or asymmetric atrophy at the level of the basal ganglia (d), midbrain (e), or pons (f) on a T2-weighted image.



(a) (b)

Fig. 2. The starting ROIs and the second ROIs for defining four tracts. The segemted infracted area in patient and parietal lobe template in control (a). The second ROIs for four white matter tracts on FA map in control case (b)

time of 2500 ms, FOV of 159 x 210 mm^2, matrix of 256 x 179, and section thickness of 5.1 mm were used, and scanning was performed in the axial plane with alignment parallel to the plane through the orbitmeatal line. In DTI, multisection, single-shot diffusion-weighted EPI of the whole brain was performed in 12 orthogonal directions, with a b value of 1000 s/mm^2. For each diffusion direction, a combination of x, y and z gradients was used to apply a strength of 30 mT/m and a slew rate of 150 mT/m/s. A TE/TR of 83/9200 ms, FOV of 194 x 256 mm^2, matrix of 128 x 112, 100% acquisition, EPI factor of 112, and a scan time of 65 s were used for 2 mm sections with no section gaps.

B. Description of Technique : TOI Analysis

All data sets were transferred to digital imaging and communication (DICOM) format from the MR scanner to a Xeon (TM) 2.8 GHz PC workstation and converted to ANALYZE format using the free software MRIcro for Windows (www.sph.sc.edu/co-md/rorden/mricro.html).

In this study, we focused on four TOIs in each hemisphere: the corpus callosum, corticothalamic tract, corticospinal tract, and superior longitudinal fasciculus were selected. Each tract was guided by two ROIs methods which were defined by one of the authors (CCH) using the ROI toolbox included in MRIcro. The starting ROI was infarction area in case which was semiautomatically segmented based on b0 and FLAIR images as the first ROI. In control, right parietal lobe was used (Fig. 2A). The second ROIs were defined three-dimensional ROIs that were believed to contain a section of the desired seed structures on an image showing FA by cross-referencing neuroanatomical works (Fig. 2B). The postprocessings applied are summarized in Figure 3. Both parietal lobes as an starting ROIs were defined in control using templete (Fig. 3B). The infarction area in the parietal lobe of the patient was semiautomatically segmented based on b0 and FLAIR images (Fig. 3C). T1-weighted high-resolution structural imaging and DTI of the subjects were normalized to the template of the Montreal Neurological Institute[21] (MNI) (Fig. 3D). After normalization, diffusion parameters such as the mean diffusion (D_{av}), FA, and the major eigenvectors and eigenvalues were calculated (Fig. 3E). Tractography was performed on each subject using in-house software implemented on MATLAB (Mathworks, Natick, MA, USA) and fiber tracking was performed using the fiber assignments with continuous tracking (FACT) algorithm[22] (Fig. 3F). The corpus callosum, superior longitudinal fasciculus, corticothalamic tract, and corticospinal tract are classified in Figure 4. We estimated the principal orientation of the diffusion tensor at a point within the ROI, moved a distance of 0.5 mm in that direction, and determined the diffusion tensor at this new location using a B-spline-interpolated continuous tensor field. We then moved a further 0.5 mm in this new principal direction until the FA fell below the threshold of 0.1. The procedure was repeated in both directions for each seed point within the initial ROI. After fiber reconstruction, fibers represented as polylines were reparameterized by equivalent-arc-length distance curves (Fig. 3G). This ensured equidistant sampling along each fiber. D_{av} and FA were then extracted at each point using a linear interpolation scheme (Fig. 3H). These points allowed us to evaluate both the global and local fiber properties. The mean D_{av} and FA over each TOI were calculated for each subject, and these were compared between subjects. The local fiber diffusion properties were compared using reliably identified points with the same arc-length along the fiber. The values of D_{av} and FA were analyzed statistically to compare those of the patient with those of the control using the MannWhitney U test

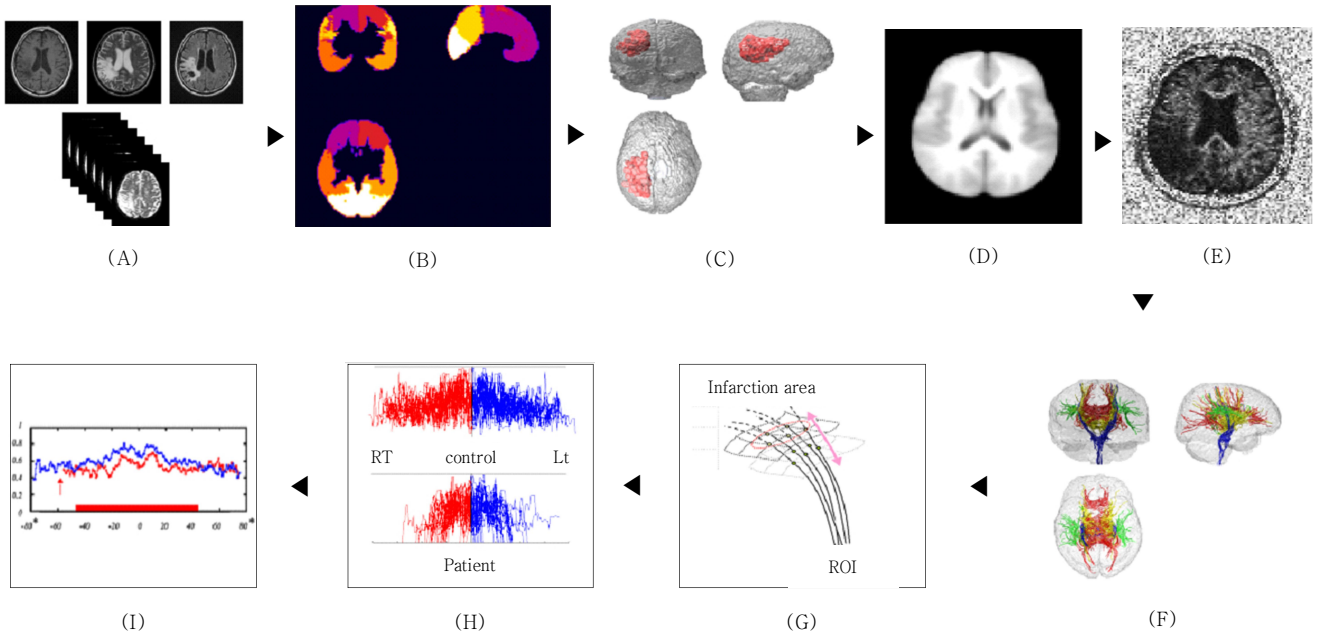


Fig. 3. Imaging data processing and TOI analysis consisted of the following steps: imaging data (A); defining seed regions in control using the ROI tool box in MRIcro (B); segmentation of the infarction area based on b0 and FLAIR in case (C); normalization of T1-weighted high-resolution images and DTI to the MNI template (D); computation of DTI parameters (D_{av}, FA, major eigenvectors and eigenvalues) (E); tractography by FACT guided by ROI method (FA > 0.1, angle < 30°) (F); parameterization of fibers by arc-length distances (G); extraction of DTI parameters at each point using a linear interpolation scheme (H); statistical analysis with the MannWhitney U test ($P < 0.05$) (I).

(Fig. 3I). A P value of less than 0.05 was considered to indicate statistical significance.

III. RESULT

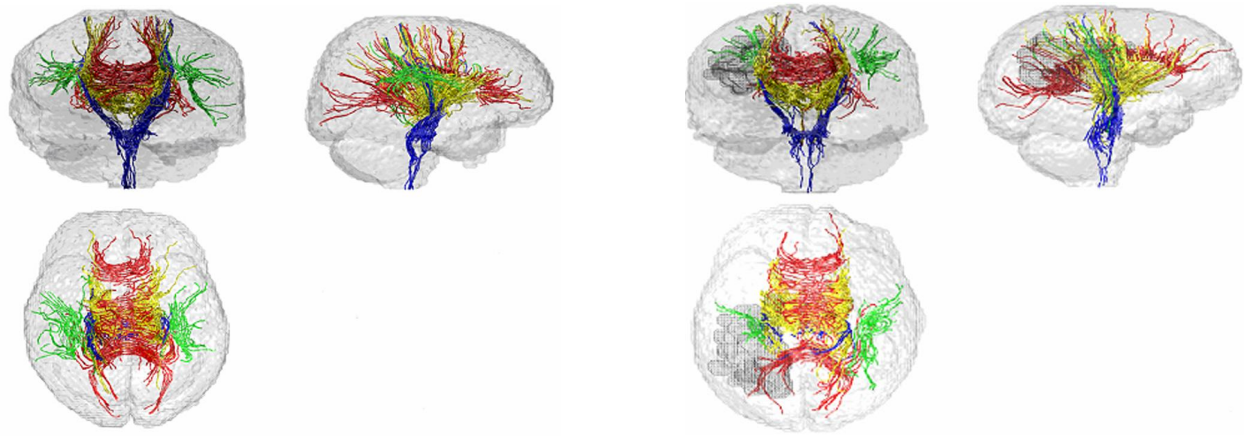
On gross tractography, the corpus callosum and superior longitudinal fasciculus on the infarction side were directly affected up to the infarction area and the fibers were reduced, cut, or bent (Fig. 4B).

A comparison of the global fiber diffusion characteristics is plotted in Figure 5. In brief, this result shows WD of both the corpus callosum and the ipsilateral superior longitudinal fasciculus, which is consistent with the results of previous studies that focused on the corticospinal tract[12-15]. The corpus callosum in particular showed trans-hemispherical degeneration, consistent with previous reports[23,24]. Local fiber characteristics along the geodesic paths in Figure 6 ($P< 0.05$) show WD in the corpus callosum, ipsilateral superior longitudinal fasciculus, ipsilateral corticospinal tract, and ipsilateral corticothalamic tract. Note that WD in the ipsilateral corticospinal tract and corticothalamic tract were not defined in the global assessments (Fig. 5A,C). Significant differences between subjects in the mean D_{av} and FA values for the corticothalamic tract near both thalami and in the FA values for the contralateral corticospinal tracts were noted (Fig. 6C,D). Corpus callosum, superior longitudinal fasciculus, and corticospinal tracts showed no statistically significant differences at the subcortical areas (Fig. 6A,B,C). The corpus callosum and superior longitudinal fasciculus tracts werecut at the point of necrosis in the right parietal lobe because most of the tracts were directly affected (Fig. 6A,B). We have demonstrated changes in $D_{av}$and FA values and a clear correspondence with the WD in various tracts.

IV. DISCUSSION

In this case, a neurological examination showed only left lower facial weakness, with no general motor or sensory weakness. This unilateral central facial weakness (lower face muscles) is known to be due to a lesion on the contralateral cortex, subcortical white matter, or internal capsule. In addition to facial weakness, symptoms may include hemiparesis, hemisensory loss, or hemineglect[25].

TOI analysis was successful in WD, even in the presence of an infarct involving parts of various tracts, which causes the clinical findings to be subtle. This tool is intuitive and has the advantage of excluding the incoherent portions of each tract. Pierpaoli et al[12] have reported that the corpus callosum,



(A) (B)

Fig. 4. Glass brain with white-matter tracts in the control (A) and patient (B). Tractography was performed using MATLAB and the FACT algorithm. White-matter tracts were classified in different colors. Red fibers are corpus callosum (CC), green are superior longitudinal fasciculus (SLF), blue are corticospinal tracts (CST), and yellow are corticothalamic tracts (CT). The black meshed area in the right parietal lobe is the segmented infarction area (B). Note that the CC and SLF on the infarction side are directly affected, (B) showing fibers that are reduced, cut, or bent.

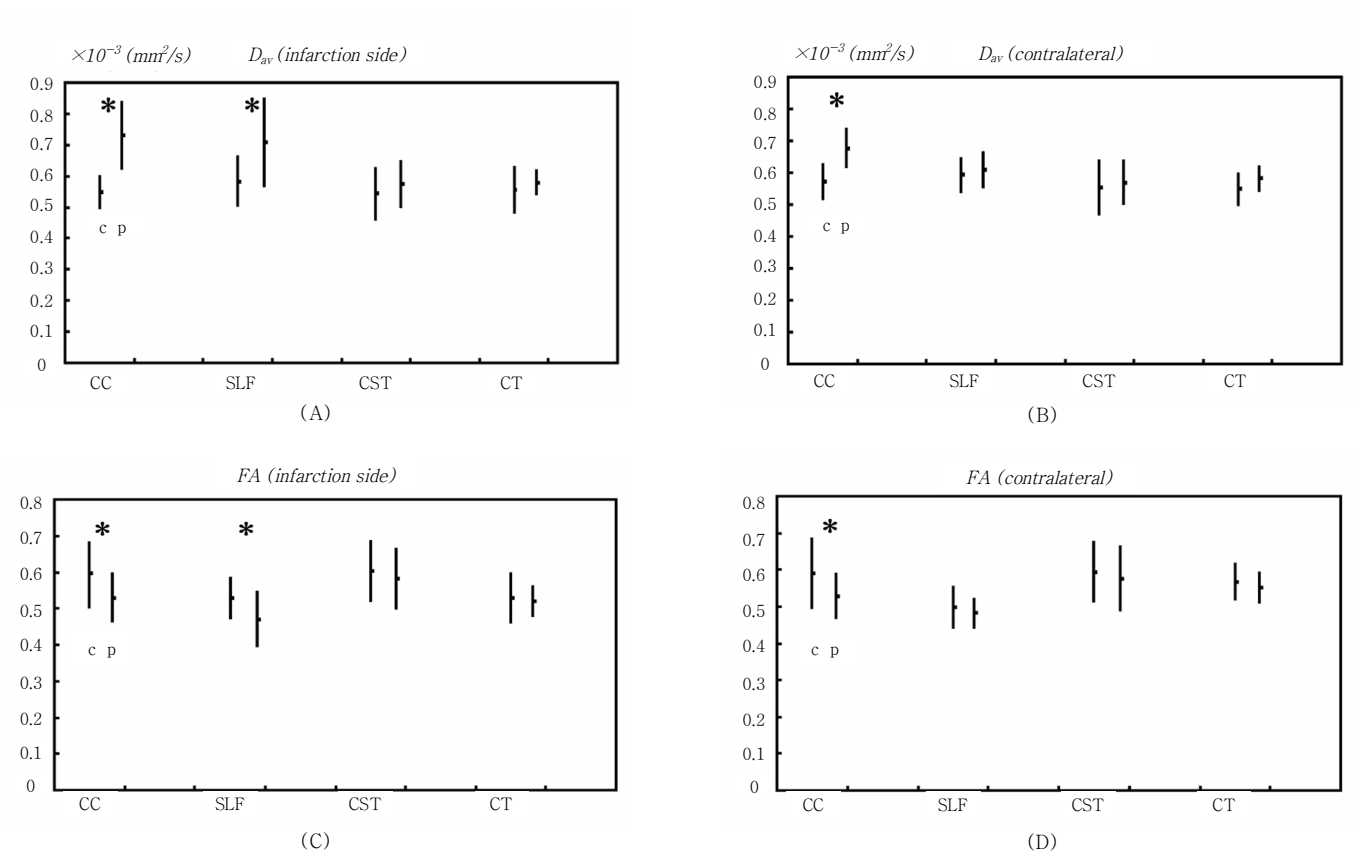


Fig. 5. Graphs of the means and SD for mean diffusion (D_{av}) and fractional anisotropy (FA) for each tract by TOI analysis, compared between the patient (P) and the control (C). The upper row is D_{av} (A, B), the lower is FA (C, D). The right column is the infarction side (A, C) and left is the contralateral side (B, D). A statistiacally significant signal (asterisk) in the corpus callosum (CC) on both sides, and the superior longitudinal fasciculus (SLF) on the infarction side. There was no significant signal in the corticospinal tract (CST) or the thalamic tract (CT) (* $P < 0.05$).

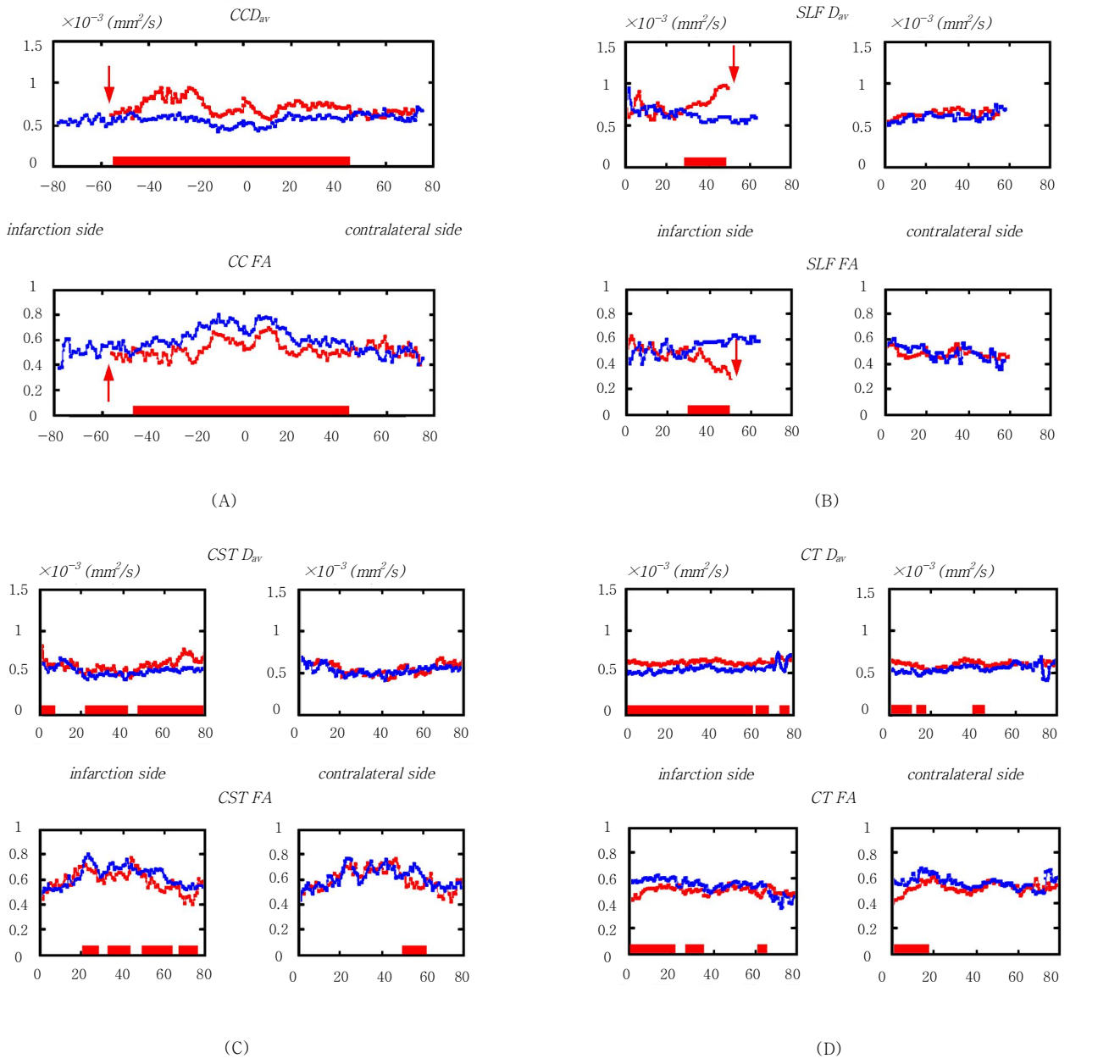


Fig. 6. Graphs of the statistical analysis of DTI parameters extracted at each point. The x axis represent the scale of the normalized length of each tract. The upper row shows mean diffusion (D_{av}); the lower shows fractional anisotrophy (FA); red curves represent the patient and blue curves are the control; and the red bars indicate the area of a statistically significant interval of tracts (AD).
A, corpus callosum (CC). B, superior longitudinal fasciculus (SLF). C, corticospinal tracts (CST). D, corticothalamic tracts (CT). CC, SLF and CT showed no statistically significant differences at both ends of tracts correspoding to the subcortical areas. CC and SLF are cut at the point of necrosis in the right parietal lobe (red arrow). Note the transcallosal degeneration of the CC (A). Positive findings noted in the SLF, CST, and CT on the infarction side (BD).

internal capsule, and cerebral peduncle, where fibers are coherently orientedwithin the voxel, have higher anisotropy than do the centrum semiovale and other subcortical areas, where there is less coherence in the intravoxel orientation of fibers because of their structural characteristics: subcortical U-fibers, more fiber crossing, and limitations on DTI resolution. In this patient, WD in the ipsilateral corticospinal tract and corticothalamic tract were defined only on their local diffusion properties, which means that TOI analysis made possible the exclusion of incoherent areas.

The significant signal in the corticothalamic tracts near both thalami and the contralateral corticospinal tract suggest chronic ischemic insult or pathological changes resulting from hypertension or diabetes mellitus, so further studies of groups of patients with these maladies are required.

This study showed the FA values of the superior longitudinal fasciculus, corticospinal tract, and corticothalamic tract were higher in control case than those reported elsewhere. In particular, Shimony et al. reported that the FA of the splenium of the corpus callosum was 0.50, that of the projection fibers was 0.3～0.45, and that of the association fibers was 0.19～0.26. They also reported that the anisotropy values for the association tracts were less than those for the projection tracts, which in turn were lower than those for the commissural tracts[26]. Differences between user-defined ROI and TOI are possible. We expect that TOI analysis will reduce the partial volume effect caused by ambiguous ROI, but more cases and further investigations are required.

V. CONCLUSIONS

In an old infarction, WD in various white-matter tracts developed radially from a region of encephalomalacia and primary gliosis. TOI analysis of DTI successfully revealed WD, although the area was only slightly affected. This method can analyze fiber tracts quantitatively that is not apparent on visual inspection, in a comparison of ROIs specified by users, or with a voxel-based analysis. Therefore, it may be a useful tool for identifying abnormalities of a disease of the white matter.

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