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Diffusion tensor tract-specific analysis of the uncinate fasciculus in patients with amyotrophic lateral sclerosis

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Abstract
Introduction The uncinate fasciculus (UF) consists of core fibers connecting the frontal and temporal lobes and is considered to be related to cognitive/behavioral function. Using diffusion tensor tractography, we quantitatively evaluated changes in fractional anisotropy (FA) and the apparent diffusion coefficient (ADC) of the UF by tract-specific analysis to evaluate the damage of the UF in patients with amyotrophic lateral sclerosis (ALS).
Methods We obtained diffusion tensor images of 15 patients with ALS and 9 age-matched volunteers.
Results Patients with ALS showed significantly lower mean FA (P=0.029) compared with controls. No significant difference was seen in mean ADC.
Conclusion The results suggest that damage of the UF in patients with ALS can be quantitatively evaluated with FA.

Keywords Diffusion tensor imaging (DTI) · MRI · ALS · Uncinate fasciculus · Dementia

Introduction

Amyotrophic lateral sclerosis (ALS) is a degenerative motor neuron disease that was thought to spare cognitive function. However, ALS with cognitive/behavioral impairment has recently been described and has attracted attention among researchers [1–3].

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A large study revealed that 50% of sporadic ALS has some degree of cognitive impairment [2]. Another study reported that most patients with ALS have mild cognitive impairment, and 5% have a clinical subtype of frontotemporal lobar degeneration (FTLD) [3].

Changes in the frontal lobe, the temporal lobe, and the corticospinal tract (CST) have been described using various imaging techniques [4–6]. However, diffusion-tensor-derived parameters such as fractional anisotropy (FA) and apparent diffusion coefficient (ADC) are more useful for examining specific white matter changes. Several reports have shown lower FA values in the various neuron fiber tracts in patients with Alzheimer's disease and schizophrenia compared with controls [7–9]. In patients with ALS, many reports have shown lower FA and ADC in the pyramidal tract [10–13], but few studies [14, 15] have investigated FA and ADC in the fiber tracts related to cognitive/behavioral function.

The uncinate fasciculus (UF) is the fiber tract that connects the frontal and temporal lobes. Frontotemporal changes have been shown in both aspects of radiographic findings and pathological findings in past studies in patients with ALS with dementia [16, 17]. The UF is involved in the naming deficits and impairment in retrieval of memories [18, 19] that are often seen in patients with ALS [2, 3, 20], and lower FA of the UF in patients with FTLD has been reported [21]. Therefore, the UF is likely to be an important fiber tract that is related to the cognitive/behavioral impairment in patients with ALS. The aim of this study was to investigate FA and ADC changes in the UF in patients with ALS and compare them with healthy controls. To our knowledge, this is the first report investigating FA and ADC changes in the UF in patients with ALS.

Materials and methods

Subjects

We studied 15 patients with ALS and 9 age-matched volunteers. The mean age of the patients was 60.2± 9.9 years and that of the volunteers was 62.0±12.1 years. All patients met the revised EL Escorial criteria [22] as having definite, probable, or possible ALS. The study was approved by our institutional review board, and written informed consent was obtained from all patients and volunteers.

MRI acquisition

All scans were performed using a 1.5-T MRI unit (Signa Lx ver 9.0, General Electric) with a standard head coil. We obtained diffusion tensor images using echo planar imaging (TR/TE 6,000/78 ms, matrix size 128×128, slice thickness 5 mm, number of acquisitions 2, total acquisition time 5.5 min). Images were obtained with both 13-directional diffusion encoding (b=1,000 s/mm^2 for each direction) and no diffusion encoding (b=0 s/mm^2). We also acquired regular structural T1-weighted images and T2-weighted images.

DTI data postprocessing

Diffusion tensor data were transferred to an off-line workstation. Analysis was performed using dTV and VOLUME-ONE software (http://www.ut-radiology.umin.jp/people/masutani/dTV.htm) [23]. Interpolation along the Z-axis was performed to obtain isotropic data (voxel size 0.94×0.94×0.94 mm) [23] and to avoid voxel size-/shape-dependent change in FA values in regions with crossing fibers [24].

The seed regions of interest (ROI) were set in the frontal part of the UF in the coronal plane through the genu of the corpus callosum, just anterior to the anterior horn of the lateral ventricle. The target ROIs were manually set on the white matter in the coronal plane at the most anterior part of the temporal stem (Fig. 1). Color-coded FA maps were used to place these ROIs into the UF tracts precisely and objectively. A reconstructed sagittal section of the color-coded FA map was used to determine reconstructed coronal sections at the level of the genu of the corpus callosum. In the coronal slices of the color-coded maps, most of the UF tracts were displayed as green. The threshold of line tracking was set at FA=0.18.

The tracts of both sides of the UF of all patients and volunteers were then visualized, and voxelization was performed by the function of dTV. Next, we divided each of them into five sections with exactly the same distances between the plane of the seed and target ROIs. We limited the size of each ROI within 20–30 voxels to prevent variety of size. We calculated mean FA and ADC of tracts on both sides of the brain by tract-specific analysis and statistically analyzed them using the Student's t test.

Results

Tractographies of the UF were obtained as semicircular tracts in all patients with ALS and controls (Fig. 2). The UF coursed from the anterior part of the temporal lobe lateral to the amygdala to the lower region of the frontal lobe at the level of the anterior commissure. The mean FA was 0.410± 0.045 for patients with ALS and 0.459±0.056 for the controls (Fig. 3a), and the difference was statistically significant (P=0.029). The mean ADC were 0.820±

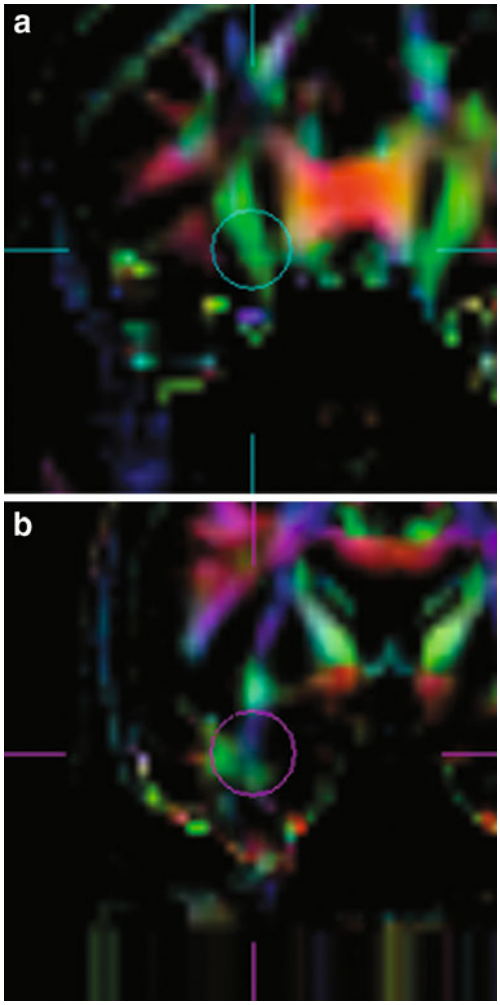

Fig. 1 Placement of the seed and target ROIs. **a** Coronal plane diffusion tensor image color-coded FA map through the genu of the corpus callosum. We set the seed ROI in the frontal part of the UF at this level. **b** Coronal plane diffusion tensor image color-coded FA map at the most anterior part of the temporal stem. We set the target ROI at this level

$0.039 \times 10^{-3}\,mm^2/s$ for patients with ALS and $0.801 \pm 0.033 \times 10^{-3}\,mm^2/s$ for the controls (Fig. 3b), which were not significantly different.

Discussion

The UF is one tract in the temporal stem. The UF makes up the core of the anterior temporal stem [25] and is critical for frontal–temporal interactions. When frontal–temporal interactions are disrupted, amnesia is more likely to occur than when only the frontal lobe or temporal lobe is involved [26]. In addition, lesions in the UF often result in the naming deficits and impairment in retrieval of memories [18, 19, 27] that are often seen in patients with ALS [2, 3, 20].

Fibers in the UF course from the temporal lobe laterally to the amygdala and hook around the sylvian fissure. The UF then curves upward through the anterior temporal stem, and the fibers fan out into the frontal lobe. The UF connects the anterior temporal lobe and the orbital and inferior frontal gyri of the frontal lobe. At its most superior level, it is below the level of the frontal horns of the lateral ventricles [25, 28]. The tracts we visualized in our study are consistent with this reported anatomy.

Characteristic changes seen in patients with ALS are behavioral variant frontotemporal dementia [2], the behavioral and personality changes [4, 29], impairments in executive functions, and impairments in verbal fluency [1–3, 20]. These impairments are difficult to detect, and patients with ALS with these changes have relatively normal scores on the Mini-Mental State Examination which is often used for evaluation of dementia [1, 30, 31]. Useful measures for assessment of cognitive or behavioral impair-

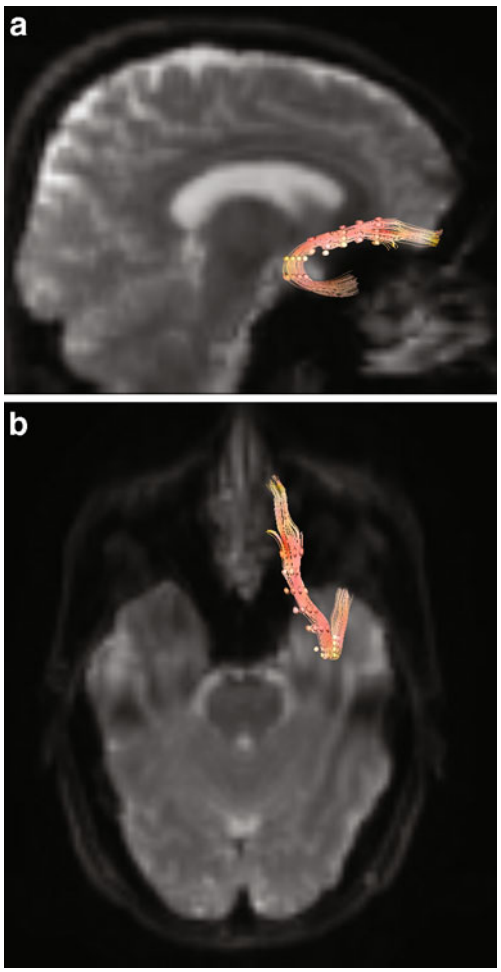

Fig. 2 Tractography of the UF. **a** Lateral view of the right UF superimposed on midsagittal reconstructed T2WI. **b** Horizontal view of the same patient, axial view superimposed on axial plane through the pons

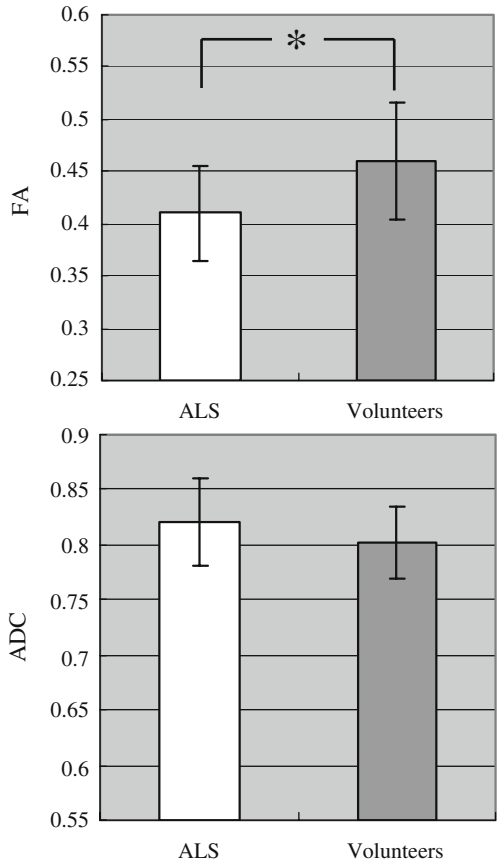

Fig. 3 Diffusion tensor parameters of the UF. **a** FA values of the UF. Patients with ALS demonstrated significantly lower FA values than healthy volunteers. (*P=0.029). **b** Apparent diffusion coefficient (*ADC*) values of the UF. There were no significant differences in ADC values ($\times 10^{-3}$ mm^2/s) between patients with ALS and healthy volunteers

ment in patients with ALS include executive measures, memory/learning measures, attention/concentration measures, language measures, and visual–spatial measures [1]. We think objective evaluation of neurodegeneration using imaging is very helpful to support these measures because carrying them out takes much time, and sometimes assessment can be misinterpreted under factors such as delirium.

One of the limitations of our study is that the FA was not compared with these measures. However, it can be said that most relevant reasons for lower FA of the UF in patients with ALS is their cognitive/behavioral impairment. Because other possible causes for lower FA such as motor neuron degeneration or aging are hard to think in this presented study. Motor neuron tracts do not run within the UF, and the control subjects were age-matched.

Second limitation is that education level of two groups were not matched, and the number of control subjects was small. We will recruit larger healthy controls and improve these in the future.

The exact pathological mechanism of changes of FA and ADC are not clear. Based on the perspective of diffusion tensor principles, FA represents the degree of diffusion anisotropy and decreases as irregularity in alignment of cellular structures. Thus, FA is somewhat linked to the quality and density of fibers. ADC represents the directionally averaged magnitude of diffusion. It may be related to the integrity of the local brain tissue [32–35]. We consider that FA reflects damages specific to the neuron fibers better than ADC based on these principles. A reduction in FA has been reported in some tracts in neuodegenerative diseases such as Alzheimer's disease and schizophrenia [7–9]. FA can be an objective parameter for measuring degenerative changes including changes related to cognitive/behavioral impairment.

Especially, the UF is considered to be deeply involved in cognitive/behavioral impairment and intelligence from several reports. One study reported a reduction in FA of the UF in asymptomatic progranulin gene mutation carriers which causes FTLD followed by aphasia onset [36]. The greatest decrease in mean FA of the UF was seen in advanced frontotemporal dementia among the corpus callosum (CC), bilateral arcuate fasciculi, inferior longitudinal fasciculi, and UF [21]. Another study reported the difference of FA between healthy adults with normal intelligence and high intelligence only in the UF among the CC, cingulum, UF, optic radiation, and CST. Thus, the UF is likely to be an important neural basis of human intelligence [37].

The FA of the UF may reflect higher cognitive function in humans, and it may be an objective and sensitive parameter for determining cognitive/behavioral impairment in patients with ALS. Our findings showed a decrease in FA of the UF in patients with ALS. These results suggest that the UF is damaged in patients with ALS, and FA can be used for objective evaluation of the damage of the UF which may be related to the cognitive/behavioral functional impairment.

Further studies, including those with a larger number subjects that have undergone clinical evaluation with consensus, are needed.

Conflict of interest statement We declare that we have no conflict of interest.

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