CASE REPORT

Diffusion Tensor Imaging in Familial Spastic Paraplegia with Mental Impairment and Thin Corpus Callosum

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We investigated 2 Japanese siblings with a complicated form of familial spastic paraplegia. Cranial magnetic resonance (MR) imaging revealed marked thinning of the corpus callosum. Diffusion tensor imaging (DTI) showed microstructural changes in the thalamus, basal ganglia, and cerebral white matter, and single photon emission computed tomography (SPECT) using ^{99m}Tc-ethylcysteinate dimer showed very similar findings. DTI and SPECT effectively revealed global changes not revealed by conventional MR imaging.

Keywords: *diffusion tensor imaging, familial spastic paraplegia, fractional anisotropy, mean diffusivity*

Introduction

Familial spastic paraplegia (FSP) is clinically and genetically heterogenous. It has been clinically classified into 2 categories, pure spastic paraplegia (pure FSP) and a “complicated” form.¹ In addition to spastic paraplegia, complicated FSP is associated with various somatic abnormalities and neurological deficits, including optic neuropathy, retinopathy, pyramidal symptom, neural amyotrophy, mental impairment, and cerebellar deficit.^{1,2}

We report 2 patients with complicated FSP whose unique complications include mental deterioration and thin corpus callosum (CC) on magnetic resonance (MR) imaging. We examined diffusion tensor imaging (DTI) studies of the 2 patients with FSP and normal controls. We also performed single photon emission computed tomography (SPECT) using ^{99m}Tc-ethylcysteinate dimer (^{99m}Tc-ECD) on the patients.

Case Report

We examined 2 brothers (Patient 1, aged 27 years; Patient 2, 17 years) in a Japanese nuclear family, both of whom were clearly affected by famil-

ial spastic paraplegia (FSP) and were admitted to our hospital with progressive gait disturbance that began in their teens and became spastic. Psychomotor development was almost normal. Neurological examination revealed pyramidal signs in the upper and lower limbs in Patient 1 and limited to the lower limbs in Patient 2. No cataracts, retinal degeneration, or cerebellar dysfunction were evident. Patient 1 showed amyotrophy of the upper and lower limbs and trunk, loss of vibratory sensation in the lower limbs, and bladder dysfunction. Patient 2 only exhibited weakness in his lower legs. Evaluation using the Wechsler Adult Intelligence Scale-Revised demonstrated intellectual decline (intelligence quotient [IQ]: Patient 1, 41; Patient 2, 64). Serum vitamin B₁₂, thyroid function, and plasma very-long-chain fatty acid levels were normal. Serum was negative for antihuman T-cell lymphotropic virus type-1 antibody.

Their father exhibited gait disturbance during his teens but showed no other neurological disturbance or mental deterioration. Their mother was free from degenerative neurological disorders. No other family member of the patients' or their parents' generation appeared to be affected by FSP.

The 2 siblings and 8 normal male controls (mean age = 27.8 ± 1.0 year) underwent magnetic resonance (MR) imaging; only the 2 siblings underwent single photon emission computed tomography

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(SPECT). We explained the nature and purpose of the diffusion tensor imaging (DTI), MR imaging, and SPECT examinations and received the patients' informed consent. The protocol was approved by the local ethics committee. A complete description of our method was reported previously.^{3,4} We performed MR imaging using a 1.0T unit (Magnetom Harmony; Siemens, Erlangen, Germany) with a head coil. Three-dimensional (3D) T₁-weighted images were scanned in the sagittal plane (repetition time/echo time [TR/TE], 2080/3.93 ms; flip angle, 15°; effective section thickness, 1.23 mm; slab thickness, 177 mm; matrix, 208 × 256; field of view [FOV], 256 × 315 mm; number of signals acquired, 1), yielding 144 contiguous slices through the head. In addition to 3D T₁-weighted images, we acquired conventional axial T₂-weighted turbo spin echo images (6580/89; slice thickness, 5 mm; intersection gap, 0.4 mm; matrix, 512 × 532; field of view, 230 × 230 mm; number of signals acquired, 1). DTI was performed in the axial plane (TE, 113 ms; TR, 10,100 ms; FOV, 230 × 230 mm²; matrix, 128 × 128; 40 continuous transverse slices; slice thickness 3 mm with no intersection gap). To enhance signal-to-noise ratio, we repeated acquisition 5 times. We measured diffusion along 12 non-collinear directions using a diffusion-weighted b factor in each direction of 700 s/mm², and we acquired one image without using a diffusion gradient. We performed SPECT of the brain using 3-head rotation gamma cameras (MultiSPECT3; Siemens Medical System, Inc., Hoffman Estate, IL) equipped with high-resolution fan-beam collimators with 600 MBq of 99mTc-ECD. For each camera, projection data were obtained in a 128 × 128 format for 24 angles at 50 s per angle. A Shepp and Logan Hanning filter was used for SPECT image reconstruction at 0.7 cycle/cm. Attenuation correction was performed using Chang's method.

In Patient 1, T₁- and T₂-weighted cranial MR imaging showed extreme thinning of the CC and atrophy of the frontal, temporal, and parietal cortices (Fig. 1A, B, C). T₂-weighted images showed subtle high intensity in the frontal and parietal white matter (Fig. 1C). In Patient 2, images showed only severe thinning of the CC (Fig. 2A), particularly in the anterior half. No atrophy or abnormal signals were indicated in the cerebral hemispheres, cerebellum, or brainstem, with the exception of mild enlargement of the left trigone of the lateral ventricle (Fig. 2A, B, C). We investigated the regional callosal size, genu, splenium, and body. The corpus callosum was manually traced on the midsagittal slice of the T₁-weighted MR image. In Patient 1, the size of the genu was 28.7 mm²;

body, 86.2 mm²; and splenium, 43.9 mm². In Patient 2, the size of the genu was 16.6 mm²; body, 99.9 mm²; and splenium, 96.8 mm². In controls, the mean sizes were: genu, 153.9 ± 19.0 mm²; body, 318.8 ± 39.5 mm²; and splenium, 83.1 ± 30.3 mm².

In Patient 1, 99mTc-ECD SPECT images showed diffuse decrease of blood flow in the cerebral cortex as well as both thalami and the left putamen (Fig. 1D). In Patient 2, SPECT images showed hypoperfusion in the left occipital cortex, both frontal cortices and thalami, and the left striatum (Fig. 2D).

We used the normalization method to investigate the differences of DTI metrics between the patients with FSP and healthy subjects. At normalization, the individual 3D T₁ image was first aligned to its b = 0 image using statistical parametric mapping (SPM2) (Wellcome Department of Imaging Neuroscience, London, UK), and the aligned T₁ image was normalized to the standard Montreal Neurological Institute space, then the transformation matrix was applied to the fractional anisotropy (FA) and mean diffusivity (MD). Further, to avoid the effect of cerebrospinal fluid (CSF) diffusivity, FA and MD map images were masked with the CSF image derived from the segmented 3D T₁ image using SPM2. Then, each map was spatially smoothed by 5-mm full-width at half the maximum Gaussian. Statistical analyses were performed using SPM2 software. Decrease of FA and increase of MD in the cerebrums of patients with FSP compared to controls were evaluated using 2-sample T-test. Only differences meeting these criteria were deemed statistically significant. In this case, a seed level of $P < 0.001$ (uncorrected) and a cluster level of $P < 0.05$ (uncorrected) were selected.

The FA and MD values showed significant differences between patients and controls (FA; Figs. 1 E-H and 2 E-H; MD: Figs. 1 I-L and 2 I-L). The DTI metrics, especially the MD values of patients were significantly changed in the thalamus, basal nuclei except for the caudate, and almost entire cerebral white matter in Patient 1. In Patient 2, the decrease of FA value was not obviously detected in thalami and basal nuclei, but MD values were clearly increased as in Patient 1.

Discussion

Complicated FSP is associated with slowly progressive spastic paraplegia of juvenile onset, probably autosomal recessive type inheritance, moderate-to-severe mental impairment, and often, markedly thin corpus callosum. Our patients had quite analogous manifestations and presented similar

Fig. 1. Patient 1, a 27-year-old man with familial spastic paraplegia. **A:** Sagittal T_1 -weighted image shows extremely thin corpus callosum (CC). **B:** Axial T_1 -weighted magnetic resonance (MR) image shows frontal, temporal cortical atrophy. The trigones of the lateral ventricle are dilated. **C:** Axial T_2 -weighted MR image shows subtle high intensity in the atrophic frontal and parietal white matter. **D:** Single photon emission computed tomography (SPECT) image shows diffuse decrease in blood flow in the cerebral cortex as well as both thalami and the left putamen. **E-H:** The decreased region of fractional anisotropy (FA) value depicted on the standard normalized space (2-sample t-test, statistical parametric mapping [SPM] 2). Significantly low FA values were detected in the thalamus and almost the entire cerebral white matter. **I-L:** The increased region of mean diffusivity (MD) value is shown. Similar to FA study, significantly high MD is revealed.

imaging findings to those of previously reported patients with FSP.⁵⁻⁷ CC thinning, a characteristic finding, could have resulted from atrophy or hypoplasia.⁵⁻⁹ However, Nakamura showed that CC thickness did not correlate with duration from onset, and they showed no change on MR imaging in a 5-year follow-up study.⁶ Hence, hypoplasia appears the most likely mechanism of CC thinning. Although previous studies discussed causality of hypoplasia, little is known about its origin.^{6,7}

Both patients showed global degeneration of white matter. In particular, degeneration of the thalami has been thought to contribute to intellectual decline in patients with FSP,⁷ and our results showed high MD in the thalami in both patients, findings consistent with previous postmortem and neuroimaging study.^{5,7,9,10} There are thalamic regions with only weak or diffuse cortical connections. Some connections obscured the directionality of diffusion, and the FA map detected no thalamic

changes. Additionally, the statistical power of FA was relatively low. Because spatial normalization of subcortical white matter is less effective,¹¹ the more heterogeneous FA map rather than the relatively uniform MD map cannot be normalized well.¹² So, we could not reveal global white matter change so clearly from statistics using FA than using MD in this study. We could not detect the changes in the CC by DTI analysis but obtained other parts of cerebral FA and MD maps in patients with FSP. Because the abnormal thin structural change of CC and widened lateral cerebral ventricles in patients with FSP influenced the SPM segmentation of 3D- T_1 images, the masking process of the DTI map was ineffective.

DTI revealed diffuse microstructural changes of the white matter not detected by conventional MR imaging. In Patient 2, these changes preceded cortical change. The changes in regional cerebral blood flow revealed by ^{99m}Tc -ECD SPECT also preceded-

Fig. 2. Patient 2, 17-year-old younger brother with familial spastic paraplegia. **A:** Sagittal T₁-weighted image showing thin corpus callosum (CC), particularly in the anterior half. **B:** Axial T₁-weighted MR image shows relatively preserved cortex. The trigone of the left lateral ventricle is slightly dilated. **C:** Axial T₂-weighted magnetic resonance (MR) image shows no abnormal signals. **D:** Single photon emission computed tomography (SPECT) image shows hypoperfusion in the left occipital cortex, both frontal cortices and thalami, and the left striatum. **E-H:** The decreased region of fractional anisotropy (FA) value depicted on the standard normalized space (2-sample t-test, statistical parametric mapping [SPM] 2). Significantly low FA value was detected in the entire cerebral white matter, especially the optic radiations. **I-L:** The increased region of MD value is shown. Significantly high MD was revealed, similar to the findings in Patient 1.

ed structural changes measured by conventional MR imaging. The present SPECT findings showed relative preservation of the caudate blood flow, which was consistent with DTI findings. Previous study investigating FSP using MR spectroscopy and DTI indicated that the primary pathophysiological process in FSP affects the axon, possibly as a result of impaired axonal trafficking.¹⁰ The same pattern of DTI metrics and cerebral blood flow changes reported here may be attributed to this pathophysiological process.

Conclusion

DTI revealed microstructural global changes of the white matter well, and such changes predate cortical deterioration. Changes in regional cerebral blood flow also preceded changes measured by conventional MR imaging, and DTI by MR and SPECT equally showed early pathophysiological

process in FSP. Furthermore, DTI does not expose patients to radiation and is cost effective. We therefore recommend noninvasive DTI as equivalent to SPECT for evaluating intracranial morphometric changes in patients affected by FSP.

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