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White matter diffusion abnormalities in migraine and medication overuse headache: A 1.5-T tract-based spatial statistics study

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ABSTRACT

Objectives: Migraine and medication overuse headache are common, but its pathophysiology remains unclear. Differential diagnosis of chronic headache is still challenging. Conventional brain imaging techniques exclude secondary causes of headache but cannot produce a proper diagnosis. Accordingly, more sensitive diagnostic methods are needed for certain diagnosis. In the present study, we performed voxel-wise tract-based spatial statistics of 1.5-T diffusion tensor imaging in migraine patients and healthy volunteers.

Patients and methods: One hundred and three migraine patents and 46 healthy volunteers were registered. The fractional anisotropy values in the white matter of each group compared to age-matched healthy volunteers.

Results: Compared to the controls, the migraine without aura with medication overuse headache had remarkable fractional anisotropy decrease in the white matter in several regions. The migraine with aura without medication overuse headache also had significant fractional anisotropy decrease compared to the controls. The disease duration and frequency of migraine attack were not correlated with fractional anisotropy values of the corpus callosum.

Conclusion: Our 1.5-T DTI study demonstrated significantly lower fractional anisotropy in the white matter in the MoA with medication overuse headache and MwA without medication overuse headache groups, suggesting that fractional anisotropy abnormalities may be useful biomarkers in headache patients.

1. Introduction

Migraine is a disorder of typically unilateral pulsatile headache, frequently associated with photophobia, nausea, and vomiting. Although 10%–20% of the population suffers from migraines [1–3], the pathophysiology remains unclear. The diagnostic criteria are defined in the International Classification of Headache Disorders (ICHD) [4,5]. However, because diagnostic criteria include only clinical symptoms, when the clinical features of a patient are not clear a correct diagnosis of migraine might be challenging. There is no reliable diagnostic test or imaging modality available for migraines. Conventional brain imaging techniques may exclude secondary causes but do not aid in the diagnosis. Clinically, migraines are divided into those without aura (MoA) and those with aura (MwA) [4,5]. The pathophysiological differences between these subtypes are not fully understood. Only minor imaging differences between MoA and MwA have been reported [6].

Medication overuse headache (MOH) is headache induced by analgesia overuse, as defined in the ICHD [4,5]. MOH introduces clinically challenging problems, and the pathophysiology of MOH is not fully understood. Objective tests are needed to facilitate MOH diagnosis in complex clinical cases.

In migraineurs, imaging often reveals clinically silent brain lesions, including white matter abnormalities and infarct-like lesions [7,8]. T2-weighted magnetic resonance imaging (MRI) shows high intensity in such lesions, and diffusion tensor imaging (DTI) shows white matter abnormalities [6,9,10]. DTI is an MRI technique visualizing microstructural features in the central nervous system [11,12]. Fractional anisotropy (FA), axonal diffusivity (AD), radial diffusivity (RD), and mean diffusivity (MD), the parameters analyzed on DTI, reflect the preferential directionality and amount of water diffusion. Some studies have reported that a decreased FA is correlated with attack frequency [9], suggesting that DTI may be used to diagnose migraine; however, the FA values are sensitive to region specificity [13]. Registration and standardization are also critical. Tract-based spatial statistics (TBSS)

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improve the quality through carefully tuned automated nonlinear registration followed by projection onto an alignment-invariant tract representation [14,15]. Recently, TBSS has been applied to the diagnosis of migraine [9,16,17]. Of note, all of these MRI studies have been conducted using 3-T MR machines [9,16,17]. The 1.5-T MR scanners are more widely available than the 3-T machines. A DTI study of migraine using 1.5-T MR scanners has not yet been reported.

In the present study, we performed 1.5-T DTI with TBSS in migraine patients and healthy volunteers. Our hypothesis is that 1.5-T DTI can reveal pathological and diagnostic findings unique to patients with MoA, MwA, and MOH.

2. Materials and methods

2.1. Study population

In this study 103 migraine patients (12 males, 91 females) were treated at a single institute (Mito Medical Center, Mito Kyodo General Hospital, University of Tsukuba) between September 2010 and September 2013. All patients met the criteria of the ICHD 2nd edition (ICHD-2) for the diagnosis of migraine [4]. The diagnoses of MoA, MwA, and MOH were also made according to the ICHD-2. The diagnosis of MOH was made for the migraine patients who had been taking triptan for more than 10 days or analgesia for more than 15 days per month for more than 3 months, according to the definition of MOH in ICHD [4,5]. Ultimately, 103 migraine patients were divided into 4 groups: 1) MoA with MOH, 2) MoA without MOH, 3) MwA with MOH, and 4) MwA without MOH (Table 1). All patients were examined with T2/fluid attenuated inversion recovery (FLAIR) MRI, and those with T2/FLAIR hyperintensities more than 5 mm of diameter were excluded from the study. The inclusion criteria for this study are 1) a diagnosis of migraine; 2) fully examined with MRI and DTI without significant artifacts; 3) no pathological lesions on MRI, including hyperintensity on T2/FLAIR; and 4) written informed consent provided for this study. The ICHD 3rd edition beta version (ICHD-3β) [5] was published at the end of this study period. The diagnostic criteria of MwA and MOH are identical between ICHD-2 and ICHD-3β, but there are some minor differences in the diagnostic criteria of MwA. To ensure a homogenous patient population, we used only the ICHD-2 for the diagnosis.

The data of 46 age-matched healthy controls (9 males, 37 females) were examined for comparison with the 103 patients with migraine (Table 1). None of the healthy volunteers had a history of neurological disease, severe headache, head trauma, psychiatric disorder, or any intracranial morphological abnormalities on MRI.

2.2. Image acquisition

All MR images of the patients were acquired on a 1.5 T MR unit (Siemens Symphony; Siemens, Erlangen, Germany) with a maximum gradient strength of 30 m T/m and a maximum slew rate of 125 m T/m/s. DTI was performed using a multi-section single-shot spin-echo echo-planar imaging sequence (TR/TE: 11000/97 ms; field of view: 260 × 260 mm; matrix: 128 × 128; slice thickness: 3 mm without a gap; number of slices: 50; number of acquisitions: 4; b values: 0 and 1000s/mm^2 in 6 different directions; total scan time 5 min 21 s) with an 8 channel head coil. DTI was acquired once at migraine attack interval period before the initial period of medical treatment. In the healthy volunteer group, DTI imaging was also performed once.

2.3. DTI analysis

DTI data were processed using FMRIB Software Library 5.0.8 (Oxford University Centre for Functional MRI of the Brain, UK; fsl.fmrib.or.ac.uk) on Linux-based system. The eddy current distortion and head motion were corrected with the eddy correct tool. The brain mask was prepared from the brain-extracted b0 image using the bet tool [18]. FA maps were then obtained using the dtifit program [12]. Voxel-wise statistical analysis of the FA data including age and sex as covariates was carried out using TBSS [14], part of FMRIB Software Library [19]. First, the FA images were eroded slightly and the end slices were zeroed to remove likely outliers from the diffusion tensor fitting using the tbss_1_preproc script in FMRIB Software Library. The FA maps were nonlinearly registered to 1 × 1 × 1 mm FMRIB58-FA standard-space images by the tbss_2_reg script in FMRIB Software Library. The registered FA images were aligned to the MNI152 space and averaged, and then the mean FA image was skeletonized using the tbss_3_postreg script in FMRIB Software Library. The skeletonized FA image was thresholded at an FA value of 0.2 by the tbss_4_prestats script in FMRIB Software Library. The aligned FA data of each subject was projected onto the skeleton map. The same analyses of MD, AD and RD were repeated for each subgroup.

The ROI method was used to detect fine quantitative changes in the FA value. Because the ROI method may be arbitrary, ROIs were automatically located at the body of the corpus callosum based on Johns Hopkins University DTI-based white matter atlases (http://neuro.debian.net/pkgs/fsl-jhu-dti-whitematter-atlas.html). We selected the body of corpus callosum because this is one of the largest structure of homogenously high FA.

2.4. Clinical information

We also analyzed clinical information, such as duration and

Table 1
Clinical information.

	Migraine				Control	
	MoA		MwA			
	MOH(+)	MOH(-)	MOH(+)	MOH(-)		p
n	13	68	5	17	46	
age	43.4 ± 15.7	40.8 ± 16.5	38.0 ± 4.5	40.1 ± 17.8	38.4 ± 12.7	0.844
sex(M:F)	00:13	09:59	0:5	03:14	09:37	0.366
duration (Years)	21.6 ± 5.0	18.1 ± 1.8	20.4 ± 4.3	13.9 ± 2.6		0.51
frequency (/months)	8.6 ± 1.8	5.0 ± 0.6	8.0 ± 2.1	3.3 ± 0.6		0.016
Triptan	5	28	1	8		
lomerizine + Triptan	5	29	4	6		
valproic acid + Triptan	3	6	0	1		
no medication	0	5	0	2		

age, duration, frequency: one-way ANOVA.
sex: chi-square test.