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Clinical commentary

White matter microstructural alterations in clinically isolated syndrome and multiple sclerosis

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ABSTRACT

This study aims to determine whether and how diffusion alteration occurs in the earliest stage of multiple sclerosis (MS) and the differences in diffusion metrics between CIS and MS by using the tract-based spatial statistics (TBSS) method based on diffusion tensor imaging (DTI). Thirty-six CIS patients (mean age ± SD: 34.0 years ± 12.6), 36 relapsing-remitting multiple sclerosis (RRMS) patients (mean age ± SD: 35.0 years ± 9.4) and 36 age- and gender-matched normal controls (NCs) were included in this study. Voxel-wise analyses were performed with TBSS using multiple diffusion metrics, including fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (λ_1) and radial diffusivity (λ_{23}). In the CIS patients, TBSS analyses revealed diffusion alterations in a few white matter (WM) regions including the anterior thalamic radiation, corticospinal tract, inferior fronto-occipital fasciculus, superior longitudinal fasciculus, body and splenium of the corpus callosum, internal capsule, external capsule, and cerebral peduncle. MS patients showed more widespread diffusion changes (decreased FA, increased λ_1, λ_{23} and MD) than CIS. Exploratory analyses also revealed the possible associations between WM diffusion metrics and clinical variables (Expanded Disability Status Scale and disease duration) in the patients. This study provided imaging evidence for DTI abnormalities in CIS and MS and suggested that DTI can improve our knowledge of the path physiology of CIS and MS and clinical progression.

1. Introduction

Diffusion tensor imaging (DTI) can provide microstructure information in the brain by the measurement of water diffusion, and it is a valuable tool for detecting subtle damage that appears normal on T2-weighted MRI in clinically isolated syndrome (CIS) and multiple sclerosis (MS) patients [1,2]. The most widely used DTI metrics for evaluation of brain microstructure white matter changes are fractional anisotropy (FA) and mean diffusivity (MD) [3,4]. Additionally, two other DTI metrics, axial diffusivity (AD, λ_1) and radial diffusivity (RD, λ_{23}) can offer more dedicated information such as axonal damage and demyelination [5,6].

Previous DTI studies detected widespread DTI abnormalities with decreased FA and increased MD in both the WM lesions and normal appearing white matter (NAWM) [7–9] in patients with MS. By using various analysis methods, increased RD (implying demyelination) in several WM tracts, such as the corpus callosum, corticospinal tracts and external capsule, was reported in MS by previous studies, while controversial findings were observed in AD alterations, which has been reported to be decreased, increased, or unchanged [10–12]. CIS is known as the first attack of MS, presenting as an acute or sub-acute episode of neurological disturbance of the optic nerves, brainstem, or spinal cord [13,14]. Few study has investigated diffusion changes in CIS [15,16] and the differences in diffusion measures between CIS and MS remain largely unclear.

To explore WM diffusion changes across the whole brain in patients with CIS and MS, this study utilized the tract-based spatial statistics (TBSS) method based on DTI to assess (i) whether and how diffusion alteration occurs in the earliest stage of MS (CIS), (ii) the differences of diffusion metrics between CIS and MS, and (iii) the relationship between diffusion alteration and clinical scores.

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2. Methods

2.1. Subjects

Thirty-six CIS patients (mean age ± SD: 34.0 years ± 12.6), 36 relapsing-remitting multiple sclerosis (RRMS) patients (mean age ± SD: 35.0 years ± 9.4) and 36 age- and gender-matched normal controls (NC, mean age ± SD: 33.7 years ± 10.1) participated in this study. We recruited all patients and normal controls with right-handed to exclude the potential influence of the handedness on diffusion measures[17]. All CIS patients were prospectively examined within 6 months from onset according to the following criteria: 1) a single clinical episode suggestive of MS; 2) exclusion of other possible diagnoses (e.g., neuromyelitis optical spectrum diseases (NMOSD), certain inflammatory or infectious disorders); and 3) sufficient image quality. All MS patients fulfilled the McDonald's criteria for MS [18]. All subjects were assessed clinically by an experienced neurologist (J.Y), who was unaware of the MRI results. None of the CIS and MS patients had been treated with medications (e.g., corticosteroids and immune-suppressants) within 4 weeks before MRI scanning. Our study is approved by the institutional review board of Xuanwu Hospital. Written informed consent was obtained from each participant.

2.2. Data acquisition

Imaging was performed on a 1.5 T MR unit (Sonata; Siemens Medical Systems, Erlangen, Germany) with an 8-channel head coil. The brain was imaged by using the following sequences with an identical field of view (240 mm × 210 mm), number of axial slices (30), slice thickness (4 mm), and inter-slice gap (0.4 mm): (a) T1-weighted spin echo (TR/TE = 650/6 ms; NEX = 3; matrix = 256 × 224), (b) T2-weighted turbo spin echo (repetition time (TR)/echo time (TE) = 5500/94 ms; number of excitation (NEX) = 3; echo train length = 11; matrix = 256 × 224), and (c).

DTI data were acquired using spin-echo single-shot echo planar (EPI) pulse sequences with the following imaging parameters: TR/TE = 5000/100 ms; NEX = 10; matrix = 128 × 128. A total of seven image sets were acquired: six with non-collinear diffusion-weighting gradients and a b value of 1000 s/mm^2 and one without diffusion weighting. Post-contrast (gadolinium) T1WI was also acquired to exclude active lesions in CIS and MS patients.

2.3. Image analysis and post-processing

2.3.1. Tract-based spatial statistics (TBSS) analysis

All DTI images were processed following the TBSS analysis in the FMRIB software library (FSL, http://www.fmrib.ox.ac.uk/fsl), and then FA, MD, λ_1 and λ_{23} were carried out. Briefly, the steps of TBSS analysis in our study were the following: 1) FA images from all subjects were nonlinearly aligned to a pre-defined target FA image (FMRIB58 FA); 2) The nonlinear transformation was used to align all subjects' FA images into MNI152 space (1 mm × 1 mm × 1 mm) and then averaged to create a study-specific FA atlas; 3) The mean FA image and its skeleton (mean FA skeleton) from all subjects was created; 4) Each subjects' FA images were projected onto the skeleton; 5) Voxel-wise statistics were performed over the common skeleton; 6) The same projections used for FA values were applied to the MD, λ_1 and λ_{23} images to create aligned skeletons for these metrics.

2.3.2. Atlas-based tract analysis

To validate the TBSS findings, we performed atlas-based tract analysis. We identified 13 main fiber tracts based on the JHU ICBM-DTI-81 (http://cmrm.med.jhmi.edu/) digital WM atlas [19]. The JHU-WM atlas was overlaid on the WM skeleton of each patient and normal control in the ICBM-DTI-81 space. Then, we calculated FA, MD, λ_1 and λ_{23} at the skeleton voxels within each tract. The following tracts were examined: the genu, body and splenium of the corpus callosum (CC), bilateral corticospinal tract (CST), cerebral peduncle (CP), cingulated gyrus (CG), hippocampus (HIP), anterior (ICA) and posterior (ICP) internal capsules, external capsule (EC), superior longitudinal fascicule (SLF), superior fronto-occipital fasciculus (SFO), superior and inferior cerebellar peduncle and uncinate fasciculus (UNC).

2.4. Statistical analyses

Voxel-wise group comparisons were performed using non-parametric, two-sample *t*-tests between the following groups: CIS versus NC, MS versus NC, and CIS versus MS. Voxel-wise analysis in TBSS was performed by the randomized permutation algorithm from the FSL library with 5000 permutations. The significance level for between-group differences was set at $p < .05$ using threshold-free cluster enhancement (TFCE)[20] [family-wise error (FWE) correction for multiple comparisons].

The mean FA skeleton was used as a mask (thresholded at 0.2 to include only voxels indicative of WM). Similarly, group comparisons of MD, λ_1, and λ_{23} images were performed. We performed one-way ANOVA to compare FA, MD, λ_1 and λ_{23} among three groups for the diffusion changes in the atlas-based tract analysis.

The correlations between diffusion measures (FA, λ_1, λ_{23}, and MD) and clinical variables including EDSS scores and disease durations of the MS patients were assessed by the Pearson's correlation analysis, taking age as a covariance. A p-value of less than .01 was considered to be significant.

3. Results

3.1. Demographic and clinical characteristics

Clinical (age, disease duration, and EDSS) and MRI characteristics of all patients and matched normal controls are provided in Table 1. No significant differences in sex and age were observed

Table 1
Demographics and clinical characteristics of all participants.

Characteristics	CIS (*n* = 36)	MS (*n* = 36)	NC (*n* = 36)	*p*-values
Mean age (range) [years]	34.0 (15–60)	35.0 (18–55)	33.7 (18–58)	p = 0.86[a]
Gender (M/F)	13/26	13/26	13/26	>0.99[b]
Median EDSS (range)	2.7 (1–6)	3.2 (1–8.5)	–	0.21[c]
Median disease duration (range) [months]	1.23 (0.2–3)	46.39 (3–204)	–	0.32[c]
Median TWMLL (range) [mm^3]	1996.1 (1528.4–2782.6)	7326.2 (78.1–25481.5)	–	–

Abbreviations: CIS = clinically isolated syndrome; MS = multiple sclerosis; NC = normal control; EDSS = expanded disability status scale; TWMLL = total white matter lesion loads. All subjects (NC, CIS, MS) were matched for age and gender.
[a] Main effect of group in ANOVA.
[b] Chi-squared test.
[c] Two-sample *t*-test.

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