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Tract based spatial statistics in multiple system atrophy: A comparison between clinical subtypes

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ABSTRACT

Objective: Using a novel method of tract-based spatial statistics (TBSS), this study aimed to investigate micro-structural white matter similarities and differences between the two MSA variants.
Methods: Diffusion tensor image data were acquired from 10 MSA-P, 15 MSA-C patients and 15 controls. Using TBSS, we performed pairwise comparison by examining the fractional anisotropy (FA), mean diffusivity, axial diffusivity (AD) and radial diffusivity (RD) maps of the white matter tract. Clusters showing diffusivity abnormalities were used as region of interests for correlation analysis.
Results: Both in MSA-C and MSA-P, we detected significantly decreased FA values in bilateral corticospinal tract (CST) and right anterior thalamic radiation (ATR), increased RD values in bilateral CST, which correlated significantly with clinical severity. Direct comparison of two variants showed higher AD values of superior longitudinal fasciculus (SLF) in MSA-P than in MSA-C.
Conclusions: These findings indicate that patients with MSA-C and MSA-P share similar diffusivity abnormalities in the bilateral CST and right ATR. Higher AD values of SLF in MSA-P than in MSA-C might be a reason for faster functional deterioration in MSA-P than in MSA-C.

1. Introduction

Multiple system atrophy (MSA) is a sporadic neurodegenerative disorder. It can be classified into two main types: a cerebellar (MSA-C) and a parkinsonian (MSA-P) variant [1]. Different phenotypes in MSA have a common pathological feature — oligodendrocyte cytoplasmic inclusions (GCIs) which prompt that the initial damage may in white matter. However, the emergence of noncerebellar symptoms, such as autonomic dysfunction and Parkinsonism, is often associated with a faster clinical course, shorter lifespan and poorer prognosis [2,3]. Thus, a precise characterization and quantification of subtle microstructural changes associated with different clinical MSA phenotypes may improve our understanding of the pathophysiology of this disorder, and provide an objective tool for the evaluation of disease progression. The faster functional deterioration in MSA-P than in MSA-C patients [4] has been investigated through technologies such as diffusion tensor image (DTI).

DTI non-invasively measures water diffusion within brain tissue, and reflects the integrity of white matter architecture and characteristics of fiber bundles by analyzing fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD). FA quantifies the preferential direction of water diffusion along white matter tracts [5], MD represents the magnitude of diffusion [6]. AD measures diffusion parallel to the white matter tracts [7]. RD appears to reflect diffusion perpendicular to white matter tracts. It is recommended to use multiple diffusion tensor measures to better characterize the tissue microstructure [8].

Methods including region of interest (ROI) and voxel-based morphometry (VBM) have been applied. ROI analyses demonstrated significantly increased trace of diffusion tensor (Trace (D)) values in putamen in MSA-P than in MSA-C and controls [9]. By VBM analysis, Po-Shan Wang et al. reported decreased FA values in the pyramidal tract, MCP and cerebellum in MSA-C and MSA-P compared to the controls [10,11].

To our knowledge, there are no reports of white matter differences between MSA clinical subtypes by using hypothesis-free group analyses. Tract based spatial statistics (TBSS) retains the

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strengths of voxel-based analysis while addressing some of its drawbacks, such as aligning images from multiple subjects [12]. It performs automated analysis of white matter integrity using the nonlinear registration method and projecting individual DTI data onto a common skeleton depicting the estimated bisecting surfaces of the major white matter tracts [12–14].

In this study, we performed pairwise comparisons by examining the FA, MD, RD and AD maps, and then detected correlations between DTI changes and clinical data in MSA-C or MSA-P groups, respectively. The aim of this investigation was to detect the similarities and differences between the two variants, and to investigate the clinical correlates of cerebral regional DTI changes.

2. Materials and methods

2.1. Subjects

Fifteen MSA-C patients (12 out of 15 patients fulfilled the criteria for 'probable MSA'; 3 were classified as 'possible MSA'), ten MSA-P patients (8 out of 10 patients fulfilled the criteria for 'probable MSA' and two were classified as 'possible MSA') [1] were recruited from Nanjing Brain Hospital, from January 2011 to August 2013. Fifteen age- and sex- matched healthy volunteers were included in the final analyses. This study was approved by the Institutional Review Board of Nanjing Brain Hospital, affiliated to Nanjing Medical University. Written informed consent was obtained from all subjects. A detailed medical history and clinical examinations were conducted for all subjects to exclude other neurological diseases. Furthermore, patients were evaluated using the complete Unified Multiple System Atrophy Rating Scale (UMSARS) including global disability scale, UMSARS part I (history review) and UMSARS part II (motor score).

2.2. MRI protocol

DTI was performed on a 3-T Siemens Verio scanner with an 8-channel radio frequency coil, using a single-shot spin-echo diffusion-weighted echo-planar pulse sequence. The parameters used for DTI were as follows: TR/TE 8800/88 ms, flip angle 90°, section thickness 3 mm without gap, 30 sections, NEX 5, FOV 23 × 23 cm, matrix 128 × 128, and in-plane spatial resolution 1.8 × 1.8 mm. The sensitizing diffusion gradients were applied on six axes with b values of 1000 s/mm^2 per axis. T1 and T2 weighted images were obtained with no diffusion gradient ($b = 0$ s/mm^2), as the latter is conducive to further exclusion of other diseases.

2.3. Image analyses

Our DTI images were processed and analyzed using the FSL (FMRIB Software Library, FMRIB, Oxford, UK) software package [15]. First, the data were corrected for eddy current induced distortion and head movement effect using the FDT (FMRIB's Diffusion Toolbox) "eddy_correct" function. A brain mask was then created from the b0 image using the brain extraction tool (the fractional intensity threshold is 0.2). Finally, the FA, MD, RD and AD maps were computed using the FDT tool "dtifit" to fit the tensor model at each voxel.

Using the FSL tool "TBSS", voxelwise analysis was conducted in which data were projected on a common pseudoanatomical skeleton (avoids smoothing). All subjects' FA data were first aligned to FMRIB58_FA standard-space image using the nonlinear registration tool. Next, the TBSS script created the mean FA image, and then skeletonized it using a protocol that searches and labels the skeleton voxels with maximum FA intensity along the perpendicular direction (breadth) of a white matter tract. To exclude grey matter, ventricle and cerebral spinal fluid, a FA threshold of 0.2 was set. Finally, the registered FA images were projected onto the skeleton before running the voxelwise cross-subject stats. The MD, RD and AD images were performed as described above, without the initial registrations.

2.4. Statistical analyses

Statistical analyses were performed with SPSS for Windows, 13.0 (SPSS Inc., Chicago, IL, USA). The significance level was set at $P < 0.05$. We first demonstrated the normality distribution of the clinical parameters by the Kolmogorov–Smirnov test. Only the sex and age were normally distributed. Differences in sex distribution among groups were then evaluated with the chi-square test. One-way analysis of variance (ANOVA) followed by *post hoc* Bonferroni correction was performed for comparison of age at examination. To assess the differences in disease duration, global disability scale, UMSARS part II score and UMSARS part I score between patient groups, the Mann–Whitney *U*-test was employed. By means of Fisher's test, group difference in autonomic dysfunction was tested.

To determine the diffusion indices skeleton voxels that were significantly different between the MSA-C and control groups, between the MSA-P and control groups, between the MSA-P and MSA-C groups, we estimated two contrasts. The age was entered into the analysis as a covariate to ensure that any observed difference of diffusion indices was independent of age. Next, a non-parametric group model using "randomize" in FSL was performed with 5000 permutations. The option threshold-free cluster enhancement (TFCE)—not having to define a cluster-forming threshold or perform smoothing—was applied for multiple comparisons correction. The results were viewed and overlaid onto the standard brain using Fslview at a family wise error (FWE) corrected threshold $P < 0.05$. The voxels in the significant clusters were localized by the "JHU ICBM-DTI-81 White Matter Labels Atlas" and "JHU White-Matter Tractography Atlas".

Correlation between diffusion indices and clinical variables was performed using ROI analysis. Circular regions of interest, each measuring 4 mm in diameter, were selected at clusters showing significant diffusion indices abnormality in MSA-C or MSA-P groups. In the MSA-P and MSA-C patient groups separately and combined, Spearman's rank-order correlation analyses were employed. The significance level was set at $P < 0.01$.

3. Results

3.1. Group characteristics

Demographic and clinical data of MSA-C, MSA-P patients and controls are listed in Table 1. There were no significant differences in age and sex among groups. Disease duration, global disability scale, UMSARS part II, UMSARS part I and autonomic dysfunction did not showed any differences between patient groups. A further five patients had pyramidal signs, and eight patients had autonomic dysfunction in MSA-P. Ten patients had pyramidal signs, and thirteen patients had autonomic dysfunction in MSA-C.

3.2. MSA-C

In MSA-C patients compared with controls, significantly decreased FA values were observed in the bilateral corticospinal tract (CST) and right anterior thalamic radiation (ATR). Significantly increased RD values were identified in the bilateral CST and right ATR. There was no region with significant differences in MD or AD values between controls and MSA-C (see Fig. 1 and Table 2).

3.3. MSA-P

In MSA-P patients compared with controls, FA values were significantly lower in the bilateral CST, right ATR and left superior longitudinal fasciculus (SLF). For MD, the values were increased in the left CST and ATR, right SLF and inferior fronto-occipital fasciculus (IFOF). For RD, higher values were noted in the bilateral CST and right SLF. For AD, the values were increased in the bilateral CST, left SLF and right IFOF (see Fig. 2 and Table 2).

3.4. Correlations with clinical data by ROI

Based on the TBSS results, ROI analyses were conducted in the MSA-P and MSA-C patient groups separately and combined. In the separate MSA-C group, negative correlations were observed in FA

Table 1
Demographic and clinical data of subjects.

Characteristics	MSA-P ($n = 10$)	MSA-C ($n = 15$)	control ($n = 15$)	*P*
Age at DTI, mean (SD)	59.90 (7.64)	60.67 (5.58)	59.40 (5.77)	0.86
Gender (male: female)	7:3	6:9	7:8	0.32
Disease duration at DTI, median (range)	2 (1–6)	2 (1–6)	NA	0.24
Global disability scale, median (range)	3.50 (2–4)	2 (1–4)	NA	0.27
UMSARS part II, median (range)	31.50 (10–40)	21 (10–35)	NA	0.65
UMSARS part I, median (range)	13.5 (9–25)	20 (10–29)	NA	0.42
Autonomic dysfunction, *n*	8	13	NA	0.53

SD = standard deviation; UMSARS = Unified Multiple System Atrophy Rating Scale; NA = not applicable.