

Characterization of Early White Matter Damages in Multiple Sclerosis patients with a Clinically Isolated Syndrome: a Tract Based Spatial Statistics Study

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Introduction

Diffusion tensor imaging (DTI) has been recognized as a sensitive technique for detecting and quantifying pathological changes in lesions and normal appearing white matter (NAWM) [1]. However, it is usually constrained by an operator-dependant selection of brain regions of interest (ROI). With the emergence of the “tract-based spatial statistics (TBSS)” method [2], whole brain statistical analysis can be performed on DTI data. By creating a mean skeleton of white matter from any diffusivity scalars such as fraction of anisotropy (FA), axial (λ_a) or radial (λ_r) diffusivities, TBSS provides voxel-wise statistics across groups of subjects. Therefore, the goal of this study was to characterize the early pathological processes occurring in WM of Multiple Sclerosis (MS) patients with a clinically isolated syndrome (CIS) [3].

Methods

This study included 12 CIS (33.0±6.7y) and 12 RR (30.5±6.4y) patients along with 12 control subjects (32.2±7.4y) matched for age and sex. All patients were diagnosed with definite MS according to McDonald’s criteria and their expanded disability status scale ratings (EDSS) measured. MR exams were performed on a 1.5 T Siemens Sonata system. DTI protocol included a spin-echo EPI sequence (TR=3800 ms, TE=96 ms) with 96x96 phases-encoding over a FOV of 240x240 mm and 51 axial slices of 2.5 mm thickness. Processing of DTI data was performed using FSL software [4]. Eddy current correction and brain extraction (factor of 0.35) were applied before generating diffusivity scalar maps (FA, λ_a , λ_r) using the FDT module. TBSS registration and tract skeletonisation were then processed. First, statistics based on voxel-wise cross-subject analysis were performed in between groups of patients and controls to produce maps of altered diffusivity scalars (Fig. 1). Second, the altered FA map was extracted as a ROI and applied on each subject to individually quantify changes of FA, λ_a and λ_r . One-Way ANOVA test was applied for group comparisons. Non-parametric Spearman’s test was used for analysing correlations between diffusivity scalars, disease duration (DD) and EDSS.

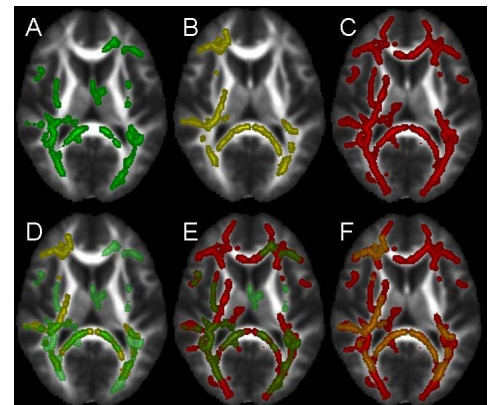


Fig 1: Significant FA decrease in green (A) and axial (λ_a) and radial diffusivities increases in red (C) in CIS patients. Maps of altered diffusivity scalars are overlapped FA+ λ_a (D), FA+ λ_r (E) and λ_a + λ_r (F).

Results

TBSS results showed significant FA decreases ($p < 0.01$) in several WM regions of CIS patients compared to controls including the corticospinal tract, inferior longitudinal, inferior fronto-occipital and superior longitudinal fasciculus, anterior thalamic radiation, WM optic radiation, superior corona radiata, external capsule, genu, splenium, body of the *Corpus Callosum*, forceps minor and forceps major. These regions were also found to be significantly altered when analysing λ_a and λ_r but to a different regional extent (Fig. 1). No significant FA and λ_r changes were observed when comparing CIS to RR patients while changes in λ_a were detected in few regions including the corticospinal tract, superior longitudinal fasciculus, internal capsule, anterior thalamic radiation and genu of the *Corpus Callosum* (Fig.2). The results of individual ROI analysis (Table 1) showed significant decreases of FA values and increases of λ_a and λ_r values in CIS and RR patients when compared to controls. A significant increase of λ_a values was also observed in RR compared to CIS patients. Significant correlations were found between λ_a and DD ($r=0.43$; $p < 0.05$), and between λ_a and EDSS ($r=0.42$; $p < 0.05$).

Subjects	FA	$\lambda_a \times 10^{-3}$	$\lambda_r \times 10^{-3}$
Control	0.431±0.015	1.142±0.025	0.569±0.021
CIS	0.392±0.020#	1.170±0.030	0.628±0.028#
RR	0.392±0.020#	1.203±0.031#*	0.645±0.040#

Table 1: Mean ± SD values of FA, λ_a and λ_r measured from FA ROI of CIS patients applied to each subject in different groups: # $p < 0.001$ patients vs. controls; * $p < 0.01$ CIS vs. RR.

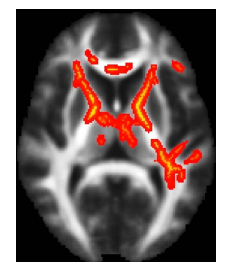


Fig 2: Regions of λ_a increases in RR vs. CIS

Discussion

These findings demonstrated significant alterations of diffusivity including FA decrease and axial and radial diffusivities increases in extensive white matter regions of CIS patients, with λ_r being the most affected. Moreover, changes in λ_a were greater in RR compared to CIS patients (Fig. 2). These results suggest that on one hand, λ_r alterations may reflect the demyelinating processes occurring in the early phases of MS, and on the other hand, λ_a can be more evocative of late appearing axonal damage [5] as confirmed by the increase of λ_a in RR compared to CIS patients. Further, the significant correlation observed between first λ_a and DD and second between λ_a and EDSS, suggest that λ_a constitutes a potential marker of axonal integrity, and moreover of neurodegenerative processes.

In conclusion, TBSS is an important tool for the characterization of early WM pathological processes occurring in MS and the follow-up of their regional and severity progression along with the disease evolution.

References

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