

REGIONAL ASSESSMENT OF WM AND GM DAMAGE IN PATIENTS WITH EARLY MS: A VBM AND TBSS INVESTIGATION

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INTRODUCTION

Diffuse MRI abnormalities have been largely described in patients with multiple sclerosis (MS), involving both white (WM) and grey matter (GM) tissues, even at the earliest stages of the disease [1-3]. However, the relationship between WM and GM damage evolution is not fully understood. Patients with early MS represent an interesting model to improve the comprehension of the pathophysiological mechanisms underlying WM and GM changes in MS, without the confounding effect of long term treatments. The aim of this study was to quantify, from a group of patients with early MS, the extension and localization of WM and GM damage with an unbiased voxel-wise approach including the whole brain. To this purpose, voxel-based morphometry (VBM) and tract-based spatial statistics (TBSS) have been used in combination.

METHODS

We recruited for this study 34 consecutive patients (F/M=21/13; mean [SD] age=31.7 [7.7] years) presenting with symptoms suggestive of a first episode of MS. All patients underwent a neurological examination [median EDSS score=1.5 (range 0-3)], and a first MRI scan at 1.5 T, including the following acquisitions: 1) Axial dual-echo turbo spin echo (TSE) (TR=2000 ms, TE=30/120); Axial T1-weighted SE (TR=550 ms, TE=12 ms) before and after i.v. gadolinium administration; 3) Axial 3D T1-MPRAGE (150 slices, TR=30, TE=4, FA=30) Axial single-shot diffusion tensor imaging (DTI) (TR=3694 ms, TE=124 ms, number of means=10) with gradients applied along 6 noncollinear directions. The same MRI acquisition protocol was repeated on all patients 3 months later. Sixteen age- and sex-matched healthy volunteers were also enrolled in the study and served as controls. They underwent the same MRI protocol of patients with the exception of post-gadolinium acquisition. Conventional MRI scans were reviewed by an expert neuroradiologist to classify the patients according to the revised McDonald criteria [4] and to exclude any macroscopic abnormalities in controls. T2-lesion volumes (LV) were assessed in each patient using a semi-automatic technique (Jim 4.0 software; Xinapse System, Leicester). Statistical Parametric Mapping 5 (SPM5) (Wellcome Department of Cognitive Neurology, London, UK) and FMRIB Software Library (FSL) 4.0 package (FMRIB Image Analysis Group, Oxford, UK) [5] were respectively used for VBM GM and WM analyses. Regional volumetric GM evaluation was carried out according to the optimized VBM protocol [6], modified to account for the presence of white matter lesions. Maps of fractional anisotropy (FA) were computed for all subjects from the DTI, after eddy currents correction using FDT (FMRIB's Diffusion Toolbox), part of FSL. FA maps were fed into TBSS, also part of FSL, in order to create a "skeletonised" FA image for each subject and to compare FA values across groups.

RESULTS

Following the revised McDonald criteria, patients were divided in two subgroups, 24 with early MS and 10 with clinically isolated syndrome (CIS). The two subgroups did not show any significant difference in demographic characteristics (gender, age, sex), mean EDSS score, and LV. All MS patients compared to controls did not reveal significant differences in global GM, WM, and CSF volume. VBM analysis did not show any regional difference in GM volumes between MS patients and controls. Conversely, TBSS analysis revealed a diffuse decrease in regional FA in MS patients at voxel level ($p < 0.05$, corrected for multiple comparisons). As shown in Fig.1, these regions were widespread along WM fiber tracts, with a prominent involvement of the corticospinal tracts, the corpus callosum, and the superior and inferior longitudinal fasciculi. Moreover, visual inspection of these results together with the average lesion mask from all patients showed that most of the abnormalities highlighted by TBSS were localized in the normal appearing WM. When the patients were divided in 2 subgroups (CIS and early MS) no significant differences in regional FA could be found between them.

DISCUSSION

This study demonstrates that diffuse WM damage is detectable in MS since the earliest stages of the disease. This damage involves most of the WM tracts, which are relevant for both motor and higher level functions. Conversely, no significant changes were observable when considering regional GM volumes. These findings suggest that WM damage (both at a macro- and micro-scopic level) plays the most relevant role in determining the early steps of brain tissue damage in relapsing-remitting MS. This study contributes in addressing a long-term controversy, concerning the interpretation of the evolution of WM and GM damage in MS course [7]. According to our results, the accumulation of GM damage is more likely to be secondary to Wallerian degeneration mechanisms rather than being related to a direct implication of GM. Further studies on larger populations of patients are needed to confirm and extend our findings.

REFERENCES

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Fig. 1. Maps of the average FA skeleton (light blue), regions of reduced FA in MS patients (red-yellow) and average lesion mask (dark blue). Images are overlaid onto a T1-weighted template in standard space.