Increased microstructural damage in the normal appearing white matter appears to distinguish SPMS from RRMS

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TARGET AUDIENCE: Neurologists, neuropsychologists, and imaging scientists interested in multiple sclerosis.

BACKGROUND/PURPOSE: To many patients, the eventual pathway of relapsing-remitting multiple sclerosis (RRMS) is secondary progressive (SP) MS, which marks a dramatic change in not only clinical presentation and management, but also subclinical pathology of the disease.[1] Compared to RRMS, there is reported scarcity in active inflammation[1], however, neurological disability continues to accumulate in SPMS patients. No consistent explanations. One of the diffusion tensor imaging (DTI) studies of SPMS shows increased loss of tissue anisotropy in the corpus callosum of patients with acute lesions[2], but both focal and diffuse white matter damage is also observed in RRMS, at diverse stages[3]. To understand the mechanisms associated with distinct disability, we examined patients with mild RRMS and advanced SPMS as compared to healthy controls using DTI and standard MRI, with a focus on the corpus callosum.
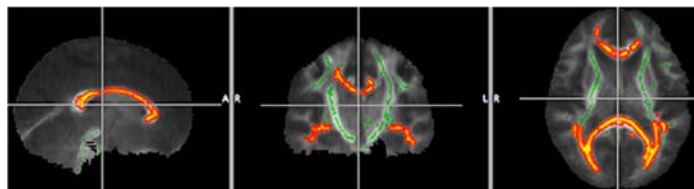

Fig.1: Threshold-free TBSS analysis. White matter tracts with greater damage in patients than in controls are highlighted in red, as seen the whole territory of corpus callosum is affected.

METHODS: We recruited 19 MS patients (all females; mean age=59 years) and 19 matched controls. Ten patients had mild RRMS within 5 years of diagnosis and 9 had advanced SPMS. Mean (range) disability score was 2.0 (0 to 3) in RRMS and 6.6 (6.0-7.0) in SPMS patients. All subjects were imaged at 3T that included T2 (TR/TE=3000/80ms, slice=3mm), T1 (TR/TE = 8/3 ms, slice =1mm), and DTI images (TR/TE=10000/78 ms; slice=3mm; b=1000; 23 directions; and 5 averages for b0), with the same FOV (24 cm^2) and matrix (256x256) in all images. We used a region-growing program to quantify T2 lesion load, intensity thresholding to generate the area, anteroposterior length, and mask of corpus callosum, and FSL (FMRIB Library, Oxford) to compute the volume of brain partitions (in T1 MRI) and DTI indices. After eddy correction, we calculated the fractional anisotropy (FA), and mean (MD), axial (AD), and radial (RD) diffusivity of each subject. We then performed Track Based Spatial Statistics (TBSS) to identify voxel-based deficit in tissue anisotropy in MS versus controls. Mixed-effects modeling was used for statistical analysis; $p \le 0.05$ set as significance.
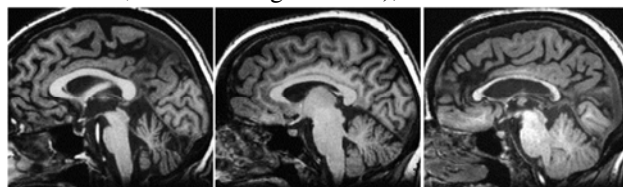

Fig. 2. T1 MRI of control, RRMS and SPMS subjects (left to right). The corpus callosum is more atrophic in SPMS than in the other subjects, so is whole brain white matter.
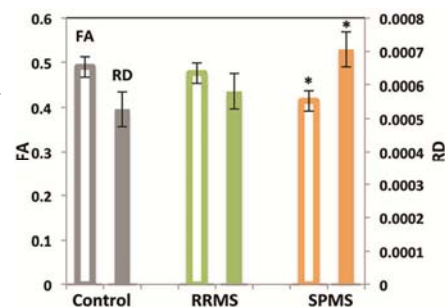
RESULTS: We found a smaller whole brain volume in SPMS than in RRMS patients, which was dominated by smaller white matter volume (p<0.01, Fig. 2), not whole gray matter or cortex volumes. T2 lesion load was not different (p=0.1) between SPMS and RRMS. In TBSS, we found corpus callosum being the major site of damage in MS patients (Fig. 1). In this structure, we also observed significantly higher RD, AD, MD and lower FA in SPMS patients (Fig. 3) than in controls, and than in RRMS patients in all indices but AD and MD. The area of corpus callosum showed the same trend but its length was similar across groups. There was no difference in any measures between RRMS and control subjects.

Fig. 3. FA and RD of the corpus callosum. Both measures are compromised (*) in SPMS compared to RRMS and control subjects (p<0.01).

DISCUSSION: We observed greater tissue injury and loss in the corpus callosum of SPMS patients, suggesting greater demyelination and axonal damage than of RRMS patients[4]. As the largest interhemispheric normal appearing white matter (NAWM), corpus callosum involves in numerous neurological and cognitive functions[5]; therefore, increased damage may lead to advanced disability in our SPMS cohort. In addition, greater white matter atrophy without larger lesion volume in SPMS may also suggest greater NAWM damage in other parts of the brain besides corpus callosum than in RRMS. Compared to controls, however, we did not found increased damage in the NAWM in our mild RRMS group. This may indicate a time window for diffuse tissue damage to evolve in RRMS and the likelihood for early intervention.

CONCLUSION: The major substrate for advanced disability in SPMS appears to be the NAWM, especially the corpus callosum. Neuroprotective treatments applied within 5 years of mild RRMS may help rescue the patients from developing progressive disability.

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