Evaluation of Diffusion Tensor Imaging derived Disease Markers for Multiple Sclerosis: EDSS and the MSFC

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Synopsis
Diffusion tensor studies are known to be sensitive to the pathobiology of MS. To evaluate possible surrogate markers, we studied global histogram-derived metrics from mean diffusivity (D) and FA maps in MS patients and controls and tested for correlations with the Expanded Disability Status Scale and the MS Functional Composite score. We confirmed abnormal DT characteristics in MS and found interrelations with both scores, the strongest correlations were between variance and asymmetry of D and MSFC global and PASAT z-scores. Thus, global diffusivity histograms reflect the burden of disease and global CNS functioning may provide useful MS surrogate markers.

Introduction
In recent years, numerous studies attempted to use quantitative MRI and MRS to establish surrogate markers in CNS diseases. This was particularly successful in MS, with widely accepted surrogate markers of the inflammatory disease activity and the final brain atrophy. Diffusion tensor studies may, however, be better suited to depict and quantify the demyelinating and inflammatory pathology in MS.1-3 To evaluate global histogram-derived potential surrogate markers from DT studies, we studied how abnormal these measures are in patients with clinical definite MS and correlated the variables with symptom severity assessed by the Expanded Disability Status Scale (EDSS) and the MS Functional Composite (MSFC).4-5 We hypothesized that the MSFC would better correlate with a global measure of disease since it is posited to better reflect overall mental and motor functions.

Material and Methods
Thirty-one patients (20 women, 11 men, mean age=39.2 yrs, SD=11.8 yrs) with clinically definite multiple sclerosis of the relapsing remitting (RR, n=22), secondary progressive (n=7) and primary progressive (n=2) course and 22 controls (13 women, 9 men, mean age=37.5 yrs, SD=14.3 yrs) were included in this study. At the time of MRI patients were clinically stable and were scored using the Extended Disability Status Scale (EDSS) and the MS Functional Composite (MSFC) within one month. For diffusion measurements, a spin echo echoplanar diffusion tensor sequence (TR=2500, TE=80, with six non collinear gradient directions and b = 880 s/mm² [3 averages] was used (24 slices, 1.9x1.9x3mm³, gap=1mm). Postprocessing was done with inhouse software to calculate the diffusion tensor, mean diffusivity (D) and fractional anisotropy (FA). To extract brain tissue, a region-growing algorithm was used and manually corrected where needed. We then calculated histograms for global brain tissue including CSF and derived peak positions, mean values, variance (VAR) and asymmetry. These measures were subjected to multivariate analysis comparing patients and controls and correlation analysis was performed with EDSS and z-transformed total and subtests (Timed 25-Foot Walk, Nine-Hole Peg Test and Paced Auditory Serial Addition Test (PASAT)) of the MSFC.

Results
Patients differed significantly from controls (Wilks test, F=2.67, p=0.018) with both age and gender exerting a significant covariate effect. Subsequent univariate-tests showed that elevated mean D, decreased FA and elevated variance of FA contributed most to the disease effect, but also FA peak, D asymmetry and D VAR being significantly abnormal in MS patients. Age was significantly covaried with FA variance, D mean, FA peak, FA asymmetry, and marginally FA mean. Gender had a trend effect on FA peak. In patients, EDSS was positively correlated with D VAR (Spearman rho=0.528, p=0.001) and trends for positive and negative correlations with D mean and FA resp. Pearson’s correlation analysis for the MSFC revealed a strong negative association for D VAR and the global score (r=-0.712, p<0.001) and a marginal positive correlation with D asymmetry (r=0.423, p=0.05). All individual tests were significantly correlated with D VAR (p<0.005) and for the PASAT also a positive correlation was found with D asymmetry (r=0.633, p=0.002). Restricting the analysis to RR-MS patients, EDSS was negatively correlated with FA-mean (r=-0.478, p=0.028) and for the MSFC, only D asymmetry remained positively correlated with PASAT (r=0.631, p=0.012).

Conclusion
This study confirms that DT studies are sensitive to depict MS pathology. MSFC was indeed more closely associated with some of the variables compared to EDSS. In this patient sample, variance and asymmetry of the global DT histograms indicated best the overall CNS functioning in MS patients and may thus be a valuable candidate surrogate marker. D and FA-threshold-based segmentation of CSF, GM and WM will be needed to explain which of these compartments contribute most to the observed interrelations.

References

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