Early MRI Changes and Predictors of Longitudinal Brain Atrophy Measures in Patients with Clinically Isolated Syndromes Suggestive of MS

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Introduction: Whole brain atrophy, as well as T1 relaxation and diffusion tensor imaging (DTI) abnormalities of the normal appearing white matter (NAWM), are known to occur in patients diagnosed with clinically definite multiple sclerosis (CDMS) [1-3]. The pathology reflected in these metrics and the time course for these changes, however, is not well understood. Patients with a clinically isolated syndrome (CIS) suggestive of multiple sclerosis, who often progress to a diagnosis of CDMS, were studied to monitor the earliest manifestations of abnormality in the brain. Our previous work showed strong correlations between grey matter volume and transverse diffusion in NAWM in CIS patients at presentation [4] that may reflect fiber tract degeneration associated with neuronal loss. This hypothesis is further tested in the current study in which three different techniques (volume analysis, T1 estimates, and DTI) are used to determine the metric most sensitive to early change in CIS patients, and to determine if the metrics being monitored are predictive of brain atrophy measured at 1 year.

Methods: ***Patient Scanning:*** Patients presenting with a clinical attack indicative of MS were scanned within three months following optic neuritis, myelitis, or brain stem presentation and at three month intervals thereafter. Patient groups at each time point (3, 6, 9, and 12 months post-presentation) were subgroups from a cohort of 32 patients (24 females, 8 males, mean age 37.6 years) enrolled in an ongoing MR study on CIS. Normal volunteers (10 F, 5 M, mean age 34.2 years) were scanned for comparisons. The data presented here is from the subjects for whom we have complete (T1 maps, volume measures, and DTI) data sets. All scans were performed on a 1.5 T GE SIGNA scanner with 4 G/cm gradients and the standard head coil. ***Lesion Segmentation:*** T1-lesions were manually identified on a 3D-SPGR (flip angle 40, 27/6ms TR/TE, 1 x 1 x 1.5 mm) from the first scan time point. The 3D-SPGR images from follow-up exams were aligned to the first time point using an automated affine alignment procedure [5]. The lesion ROIs from the first scan were then overlaid on the aligned images and edited for new lesions or changes in size of existent lesions. The new ROIs were then rotated back to their original space and could be overlaid on the unaligned SPGR images. ***Volumetric Analysis***: Image segmentation and volume analysis were performed on the flip 40, 3D-SPGR image using SIENAX [5]. The T1 lesion masks were used to remove lesions from the grey matter (GM), white matter (WM), and cerebral-spinal fluid (CSF) masks output by SIENAX. Normalized grey matter volume (nGM) and normalized white matter volume (nWM) were calculated by multiplying the total GM or WM volume by the scale factor obtained from registration of the patient's skull to standardized MNI space. Normalized brain parenchymal volume (nBP) is the sum of nGM and nWM. ***T1 Relaxation Estimates:*** T1 maps were calculated using the SPGR method described previously in [3] where two volumetric data sets are acquired with different flip angles. The WM mask output by SIENAX was used to segment the T1 estimate maps and histogram analysis was used to determine the T1 peak location. The peak locations were compared to normal volunteers Students' t-test. ***DTI:*** High b-value DTI was acquired with an 18-minute single-shot, multi-repetition echo-planar sequence (7000/100ms TR/TE, 9 NEX, 1.7mm in-plane, 2.1 mm thick slices, b=2000 s/mm^2, 6 directions). The diffusion parameters of the (NAWM) were isolated by resampling and aligning the WM mask output by SIENAX to the diffusion tensor images and then overlaying the aligned mask. The NAWM was further segmented into high-anisotropy regions by using histogram equalization of the NAWM and retaining the 25% of the voxels with the highest fractional anisotropy (FA). The means of the fractional anisotropy (FA), average eigenvalue (D_{av}), and primary eigenvalues (λ_1, λ_2, λ_3) were calculated in the NAWM and high anisotropy regions. These means were compared to normal volunteer values using Students' t-test.

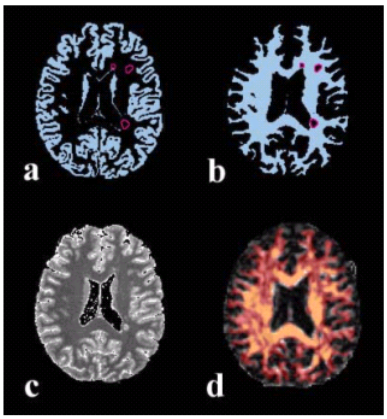

Figure: a) segmented gray matter with lesion ROIs **b)** segmented white matter with lesion ROIs **c)** T1 relaxation map **d)** FA map with NAWM (red) and high anisotropy (orange) regions highlighted.

Results: ***Time Course of Change:*** The NAWM T1 peak location is significantly higher in patients than in controls beginning with the first scan at 3 months post presentation ($p<0.05$), and persisting at each time point ($p<0.05$, 6, 9 months) through the scan at one year ($p<0.01$). DTI in the high anisotropy NAWM was able to distinguish cross sectional differences between patient and control groups at 6 months post-presentation using transverse diffusion (evt = $(\lambda_2 + \lambda_3)/ 2$; $p<0.05$), at 9 months (evt, $D_{av;\ p}$; $p<0.05$), and at 12 months post presentation (evt, FA; $p<0.01$, $D_{av;}$ $p<0.05$). DTI in the whole brain NAWM was able to distinguish a difference only at 12 months post presentation (evt, FA, D_{av}; $p<0.05$). The nGM and nBP were significantly different from controls 6 months ($p<0.01$) and 12 months post presentation ($p<0.05$), however nWM was not significantly different from normal volunteers. ***Predictability:*** T1 estimate values at the first scan time point did not correlate with nWM, nGM, or nBP change measured over one year. Transverse diffusion values from the whole brain NAWM at the first scan correlated significantly with only change in nBP over the span of one year (Spearman rank correlation coefficient = -0.62, $p<0.05$), and trended towards predicting both nGM and nWM changes (Spearman rank correlation coefficient = -0.51, $p=0.1$).

Discussion and Conclusions: In this study, the T1 relaxation estimates are the metric most sensitive to the early changes that occur in the brains of CIS patients; however, these abnormalities do not predict long-term brain volume loss. The DTI parameters have a slower time course before showing significant differences, but are indicative of brain volume change that is observed over the course of a year.

References: [1] Chard DT, et al. Brain 2002; 125(2):327-37. [2] Henry RG, et al. JMRI 2003; 18:420-426. [3] Srinivasan R, et al. AJNR 2003; 24:58-67. [4] Henry RG, et al. ISMRM 2004. [5] Image Analysis Group, FMRIB, Oxford, UK.

Acknowledgements: National Multiple Sclerosis Society RG3240A1.