Early and Progressive increase in Transverse Diffusion in White Matter Fiber Tracts of Patients at risk for Multiple Sclerosis

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Introduction: Diffusion tensor MRI (DT-MRI) has been used to quantify abnormal values in normal appearing white matter in multiple sclerosis patients. Previous analysis of normal appearing tissue in Relapsing-Remitting Multiple Sclerosis (RRMS) patients [1] with DT-MRI indicated increased diffusion transverse to white matter tracts with no change in diffusion along the tracks, a signature consistent with Wallerian degeneration observed in animal and human studies. DT-MRI of patients with clinically isolated syndromes who often go on to a diagnosis of RRMS was investigated in order to determine the earliest manifestation of changes in normal appearing tissue.

Methods: ***MR Scanning:*** Thirteen CIS patients were first imaged at 3 months post presentation and at 3 month intervals at 1.5 T on a GE SIGNA scanner with 4G/cm gradients and the standard head coil. Thirteen CIS patients were scanned at 4 time points and 10 controls were scanned with 5 at 2 time points. DTI was acquired with a 18-minute single-shot, multi-repetition echo-planar sequence and TR/TE = 7s/100ms, 9 NEX, 256 x 128 matrix, 440x220 mm FOV, and 2.1 mm slice thickness with no gap. Diffusion gradients were applied in 6 non-collinear directions with b= 2000 s/mm^2 in addition to a b=0 s/mm^2 image.

Serial DT-MRI Analysis: For each patient the b=0 scan from the first scan time point was aligned [2] to the Montreal Neurological Institute (MNI) template and this aligned scan was then used as the template for aligning subsequent scans for the patient. In the un-aligned baseline scan, cerebrospinal fluid regions were segmented based on the trace ADC values and this mask was aligned using the already obtained alignment parameters. Regions affected by partial volume averaging during the alignment procedure were removed. The normal appearing brain tissue (NABT) included only regions with FA > 55 and was further segmented into high, low, and medium anisotropy regions based on anisotropy. The means of fractional anisotropy (FA), average eigenvalue (D_{av}), and the three eigenvalues (λ_1, λ_2, λ_3) were determined in the brain and anisotropy segmented regions. The mean values of the diffusion parameters were compared to control values using Students' t-test.

Results: High anisotropy white matter (HAWM) regions correspond to coherent white matter fiber bundles. In the HAWM region the histogram mean of D_{av}, λ_2, and λ_3 increased and the fractional anisotropy decreased significantly as early as 6 months after presentation. In the NABT region, D_{av}, λ_2, and λ_3 increased as well but FA did not change significantly. The coefficients of variation for the means of the diffusion parameters in controls over time were 1 to 1.5% in the NABT region and 3 to 5% in the HAWM region.

Discussion/Conclusion: DTI fiber tracking can detect and quantify microstructural changes in normal appearing white matter of CIS patients as early as 6 months after their initial clinical symptoms. This was accomplished by using high signal to noise and high resolution DT-MRI data. These results represent the earliest manifestation of abnormal values away from lesions and are consistent with patterns of change in eigenvalues in response to Wallerian degeneration. Furthermore, the timing of this progressive increase in transverse diffusion is also consistent with that expected for Wallerian degeneration in the central nervous system [3]. While these changes were also observable in D_{av} in both HAWM and NABT, the FA changes were not significant over whole brain histograms. Furthermore, the changes in these parameters are driven solely by the increase in diffusion transverse to fiber tracts and are most sensitively detected in HAWM. Ongoing analyses include the spatial correlation of changes in transverse diffusion with DT-MRI fiber tracking from lesions, and the relationship of early diffusion changes to conversion to RRMS.

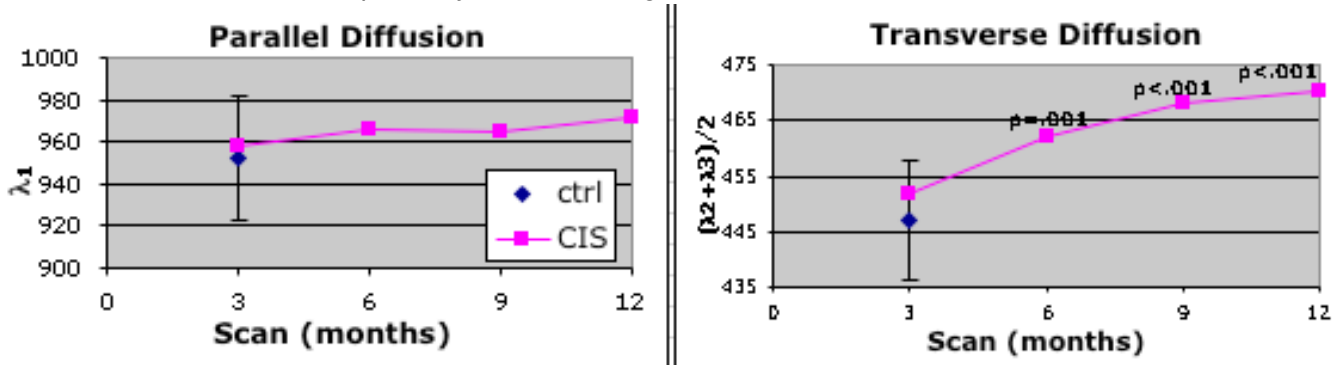

Figure: For CIS patients**,** no significant changes were found for diffusion parallel to white matter fibers in HAWM regions and significant increases ($p < .001$) in diffusion transverse to the fibers. Control means averaged over time points and standard deviations are shown.

References: 1) Henry, et al. JMRI 2003;18:420-426. 2) Woods, et al., Hum Brain Mapp. 1999;8:73-79. 3) Simon, et al., Neurology 2000;54:1155-1160. **Acknowledgements:** National Multiple Sclerosis Society RG3240A1.