Longitudinal imaging of myelin repair and axonal loss in multiple sclerosis

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Objectives: Evaluate the long-term changes in diffusion tensor imaging (DTI) in multiple sclerosis (MS) patients starting highly effective anti-inflammatory therapy.

Background: DTI is an MRI measure of brain tissue integrity and is an attractive metric for use in clinical trials evaluating neuroprotective agents. Pathology-imaging correlation studies suggest that longitudinal diffusivity (parallel to fiber tracts, $\lambda_{\parallel}$) represents axonal integrity, while transverse diffusivity (across fiber tracts, $\lambda_{\perp}$) represents myelin integrity.[1,2] Little is known about the responsiveness of DTI metrics to anti-inflammatory MS therapies.

Design/Methods: Nineteen MS patients starting natalizumab were imaged serially for 1 year. Imaging was performed on a 3T Siemens Trio. Diffusion-weighted imaging used 71 non-collinear diffusion-weighting gradients (2.5 x 2.5 x 2.5mm voxels, b=2000sec/mm^2, 8 b=0 acquisitions). Anatomical imaging was performed for lesion detection and co-registration. Gad lesions and 20 normal-appearing white matter tissue (NAWM) regions of interest (ROIs, Figure 1) were outlined on each baseline image set. ROIs were followed using FSL [3] and AFNI [4] software. Average values within each ROI were derived for fractional anistotropy (FA), mean diffusivity (MD), $\lambda_{\parallel}$, and $\lambda_{\perp}$. Analysis was performed using mixed model regression analysis.

Results: At baseline, eleven of nineteen patients demonstrated a total of 60 (median = 5) gadolinium-enhancing lesions. Over 1 year (Figure 1), FA increased in gad lesions (2.10/month), but decreased in NAWM (-1.01/ month; p<0.0001 for both). Changes in FA were driven by decreased $\lambda_{\perp}$ in gad lesions (-1.95 10^{-6} mm^2/sec/month, p<0.001; NAWM was n.s.), but decreased $\lambda_{\parallel}$ in NAWM (-2.13 10^{-6} mm^2/sec/month, p<0.0001; gad lesions was n.s.). MD decreased in both gad lesions (-1.11 10^{-6} mm^2/sec/month, p=0.03) and NAWM (-0.54 10^{-6} mm^2/sec/month p=0.01), but was greater in gad lesions (p=0.003).

Conclusions: The results are consistent with short-term remyelination within acute lesions and long-term axonal degeneration in normal appearing white matter. These results also suggest that DTI may provide pathology-specific insights into MS. 2-year follow-up is underway.

Support: K23NS47211 and NMSS RG3548 to RJF.

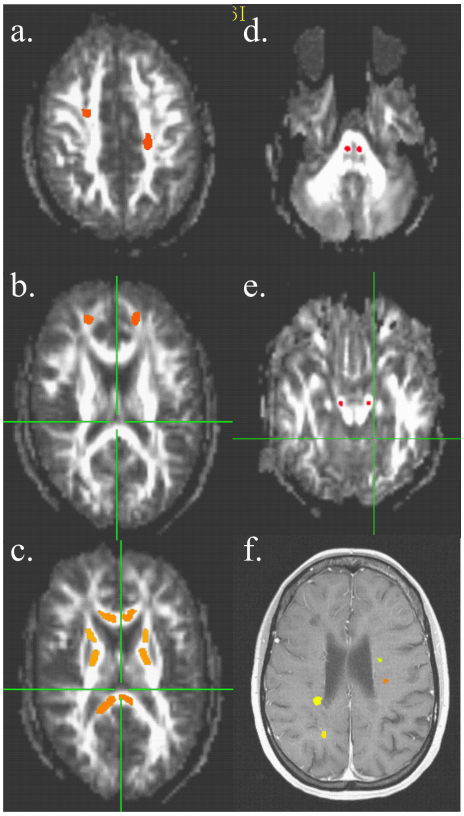

Figure 1. (a.-e.) Locations of normal-appearing white matter ROIs. (f.) Example ROIs of enhancing lesions

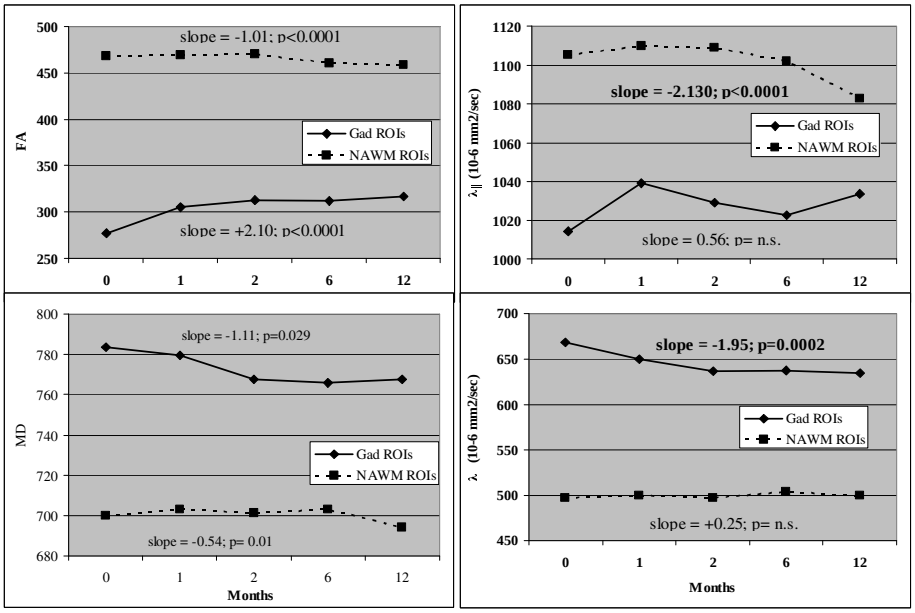

Figure 2. Changes in DTI measures over 12 months in MS patients starting highly-effective long-term anti-inflammatory therapy (natalizumab).

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