Using MRI to Quantify Optic Nerve Injury in Monkeys with Experimental Glaucoma: Atrophy and Diffusivity Effects

A. Coimbra[1], M. Ogidigben[2], R. Peiffer[2], L. O'Neil-Davis[2], M. Holahan[1], J. Cook[1], and D. Williams[1]

[1]Imaging, Merck Research Laboratories, West Point, PA, United States, [2]Ophthalmic Research, Merck Research Laboratories, West Point, PA, United States

Introduction: Glaucoma is a blinding disease of the optic nerve (ON) whose pathophysiology is poorly understood and clinical management is currently limited to intraocular pressure reduction strategy. In spite of evidence suggesting that glaucomatous optic neuropathy affects intraocular (ON head) and extraocular (CNS) structures, diagnosis and treatment are mostly limited to observations and events in the eye. Current methods for examining ON degeneration in glaucoma are ex-vivo preclinical studies and in-vivo imaging of nerve fiber layer in the periphery of the ON head. There are no in-vivo methods for measuring ON damage beyond the ON head. The present study accesses the ability of MRI to quantify degeneration of the ON in the retroorbital space of laser-induced glaucoma monkeys. Current methods relying on post-morten histology[1] show reduction of ON axonal counts to levels as low as 10% of normal in this model. We used high resolution, high tissue contrast anatomical MRIs to assess morphological abnormalities, and diffusion tensor imaging (DTI) to assess integrity of myelin structure in the ON. Neurodegeneration of the ON should be associated with morphological atrophy and reduction of the cross sectional area of the ON. Additionally, loss of axons and demyelination in the ON should induce changes in water diffusivity as measured by DTI. In particular, demyelination should induce noticeable increase in radial diffusivity (radial with respect to the nerve's main axis).

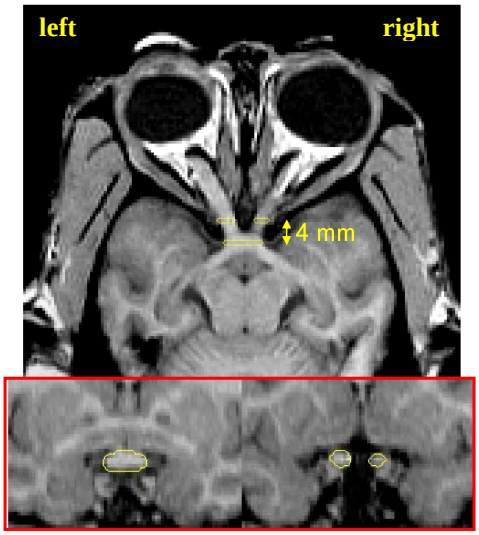


Figure 1: typical horizontal (top) and coronal (bottom) views of the chiasm and ON delineated by yellow contours.

Materials & Methods: Experiments were conducted in 8 cynomolgus monkeys (10-11 yrs) scanned ~2 years after photocoagulation of the right eye trabecular meshwork to induce increase of intraocular pressure. Animals were scanned on a Siemens Trio 3T magnet. T1 weighted MPRAGE pulse sequence (TR/TE/TI/FA = 1.47/4.38/870/12) was used to obtain high resolution images (0.5x0.5x0.8 mm^3) of the animals' whole heads. Diffusion tensor imaging (DTI) scans were also performed to assess integrity of the ON (TR/TE/TI=11.4s/118ms/2.2s; beta=0, 1000 s/mm^2, 30 diffusion sensitizing gradient directions, image resolution 1.5x1.5x1.5 mm^3). Parametric maps of diffusivity and diffusion anisotropy were extracted from the DTI data. Reconstructed images and parametric maps were re-oriented to standard position such that the brain anterior and posterior commissures lay in the same horizontal plane. The chiasms were identified and cross-sectional areas (CAs) were estimated on the chiasm central coronal planes. CAs of left and right ONs were computed 4 mm anterior to the chiasm plane (figure 1). Four DTI parameters were analyzed: axial and radial diffusivity; fractional anisotropy (FA), and apparent diffusion coefficient (ADC). Intraocular pressure (IOP) was measured in all 16 eyes. However, data from one eye was dropped because of failure to obtain a reliable IOP measurement. Comparative statistical analysis was performed between ON MRI parameters of normotensive and hypertensive eyes. Correlation between ON parameters and IOPs was also assessed.

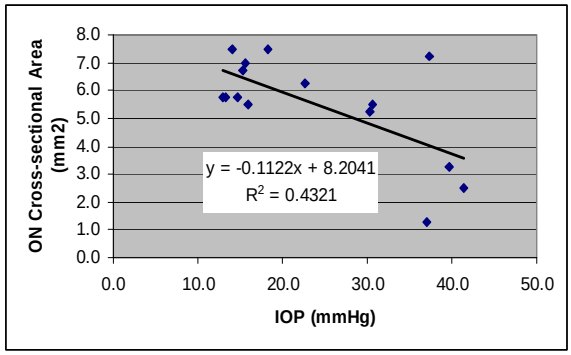
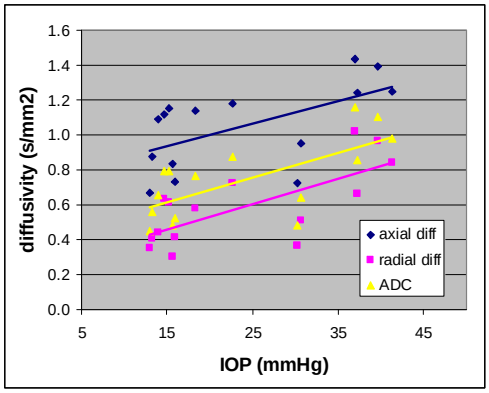


Figure 2: ON atrophy and IOP. Scatter plot showing relationship between intraocular pressure and cross-sectional area of the optic nerve of corresponding eye in monkeys with experimental glaucoma. Cross-sectional area of the ON is reduced as a linear function of IOP.

Results & Discussion : In normotensive eyes, IOP was 15.0±1.7 mmHg (mean±S.D.) and ON area was 6.4±0.8 mm^2. In contrast, IOP in hypertensive eyes was 34.1±6.6 mmHg and ON area was 4.5±4.7 mm^2 (single-sided t-test, p=0.027). ON CAs correlated with IOPs (figure 2, Pearson's r=0.66, p=0.008). DTI diffusivity parameters in ON of normotensive eyes were 1.16±0.2 and 0.71±0.23 s/mm^2 for axial and radial diffusivity, respectively. In the ON of hypertensive eyes those parameters were 0.95±0.19 and 0.47±0.12 s/mm^2, respectively (p=0.034 for axial and p=0.013 for radial diffusivity). Fractional anisotropy was also lower in the ON of the hypertensive eye (0.35±0.09) when compared to the normotensive eye (0.45±0.07, single-sided t-test p=0.0167). Finally, the overall ADC in the ON of the hypertensive eye was larger (0.86±0.23 s/mm2) than in the normotensive eye (0.63±0.14 s/mm2, p=0.017). Pearson correlation coefficients between IOP and Axial and Radial diffusivity, FA and ADC were 0.58 (p=0.02), 0.71 (p=0.003), -0.59 (p=0.02) and 0.67 (p=0.006) respectively (Figure 3).

Conclusion : This study shows that MRI may be used to study ON degeneration induced by increased IOP in vivo. Longitudinal studies will be required to determine the onset and rate of optic nerve degeneration to confirm the suitability of this MRI methodology to delineate surrogate markers for disease progression and address potential benefit of novel therapies to glaucoma patients.



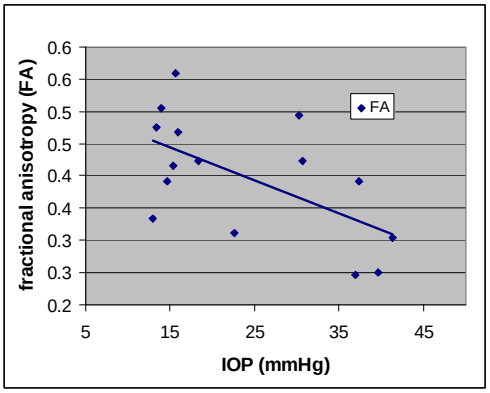


Figure 3 : Correlation between diffusivity and IOP. Scatter plots showing relationship between intraocular pressure and diffusivity parameters axial and radial diffusivity and ADC (left panel) and fractional anisotropy (right panel) of the optic nerve. All diffusivity parameters of the ON increased as a linear function of IOP. Fractional anisotropy decreased with increasing IOP.

References[1]Radius and Pederson. Arch Ophthalmol. 1984.