Diffusion tensor imaging and contrast-enhanced MRI of the eye and the central visual pathway in streptozotocin-induced diabetes

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TARGET AUDIENCE: Clinicians and researchers interested in employing microstructural and contrast-enhanced MR imaging modalities to evaluate the effects of diabetic retinopathy on the visual pathway.

PURPOSE: Diabetic retinopathy is a leading cause of acquired blindness. However, visual function may be deteriorated in diabetic patients even before the onset of retinopathy. This leads to the hypothesis suggesting that the distal visual pathway in the brain may be altered before the retina in diabetes[1]. In this study, diffusion tensor imaging (DTI) was employed to assess the microstructural integrity of the visual pathway in early experimental diabetes using streptozotocin (STZ)-induced type 1 diabetic rats. In addition, chromium-enhanced MRI (CrMRI) of the retina and manganese-enhanced MRI (MnMRI) of anterograde axonal transport were employed to investigate the initial structures compromised in visual system.

METHODS: **Animal preparation**: Ten-week old Sprague-Dawley female rats (N=10) were randomized into 2 groups. 5 rats underwent 1 day of fasting followed by intraperitoneal injection of streptozotocin (STZ) at 65 mg/kg in 0.01M citric acid. The other 5 rats were injected with citric acid only and acted as a control (CTRL). MRI was performed 1 month after drug injection. After DTI, Cr(VI) (3μL, 10mM) was intravitreally injected into the left eye, and CrMRI was performed 1 day later. $MnCl_2$ solution (3μL, 50mM) was injected intravitreally into the right eye after CrMRI, and MnMRI was performed 1 day later. **MRI Protocol**: All MRI measurements were acquired utilizing a 7 T Bruker scanner. Under inhaled isoflurane anesthesia, animals were imaged using a receive-only surface coil under circulating warm water. For DTI, multi-shot SE-EPI diffusion weighted images were acquired with TR/TE = 3000/30ms, in-plane resolution = 250x250μm^2, slice thickness = 1 mm, b = 0 and 1000 s/mm^2, 4 shots and 30 diffusion directions. T1-weighted MRI was performed covering the whole brain for both CrMRI and MnMRI using the 2D RARE sequence with TR/TE=475/8.8ms and spatial resolution = 125x125x800μm^3. DTI parametric values including fractional anisotropy (FA), axial diffusivity ($\lambda_{//}$) and radial diffusivity ($\lambda_{\perp}$) were extracted from the prechiasmatic optic nerve and the optic tract using DTIStudio and ImageJ. T1-weighted signal intensities were measured bilaterally in the retina in CrMRI and the subcortical visual nuclei in MnMRI. DTI parametric values and Cr and Mn enhancement were compared between STZ and CTRL rats using two-tailed unpaired t-tests. Results were considered significant when $p<0.05$.

RESULTS: STZ-induced diabetic rats showed a significantly smaller weight gain than CTRL rats throughout the 1-month experimental period (Fig. 1). The blood glucose level was also significantly higher in STZ than CTRL rats before MRI experiments (Fig. 2). DTI revealed statistically significant FA decrease and $\lambda_{\perp}$ increase in the prechiasmatic optic nerves of both hemispheres in the STZ rats compared to CTRL rats (Figs. 3 and 4). There was no statistically significant difference between STZ and CTRL groups in Cr enhancement in the retina (131%±52% vs 119%±26%; $p>0.05$) (Fig. 5). Mn enhancement in the lateral geniculate nucleus (41%±15% vs 55%±20%) or superior colliculus (60%±16% vs 62%±21%) also showed no significant difference between STZ and CTRL groups ($p>0.05$) (Fig. 6).

DISCUSSION AND CONCLUSIONS: Recent evidence suggested that at 6 weeks after STZ injection to adult rats, astroglial alterations occurred at the distal but not proximal portion of the optic nerve before retinal ganglion cell loss or substantial alterations in the superior colliculus[1]. Consistent with this observation, our DTI study showed significantly decreased FA and increased $\lambda_{\perp}$ in the prechiasmatic optic nerve as early as 4 weeks after STZ injection. This suggested that FA and $\lambda_{\perp}$ may be early DTI biomarkers to detect compromise in regional visual pathway integrity in early experimental diabetes. Although previous studies showed the deficits in anterograde transport from the retina to the superior colliculus at 6 weeks after STZ injection[1,2], Our MnMRI data did not appear to detect such anterograde Mn transport alteration if there was any at 4 weeks after STZ injection. While CrMRI may enhance oxidizable lipids in retina and the brain[3], and lipid contents may be altered in the retina of STZ rats[4,5], CrMRI did not detect significant difference in retinal enhancement between STZ and CTRL rats. Overall, our results suggest that STZ-induced type 1 diabetes first leads to structural changes in the distal optic nerve before MRI-detectable changes in retina, optic tract, superior colliculus or lateral geniculate among DTI, CrMRI and MnMRI modalities at 7 Tesla. Further studies may elucidate if and when MRI-detectable changes may begin to occur in these structures.

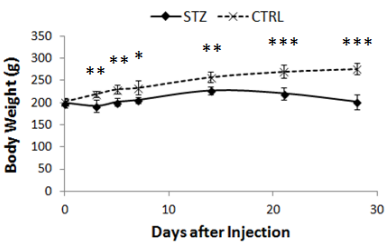

Fig. 1: Body weight of STZ and CTRL rats. (Two-tailed unpaired t-tests, *p<0.05; **p<0.01; ***p<0.001)

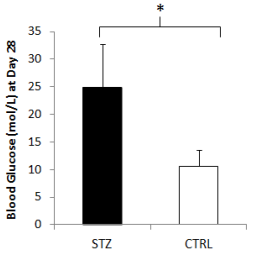

Fig. 2: Blood glucose level at 1 month after STZ or citric acid injection (Two-tailed unpaired t-test, *p<0.05)

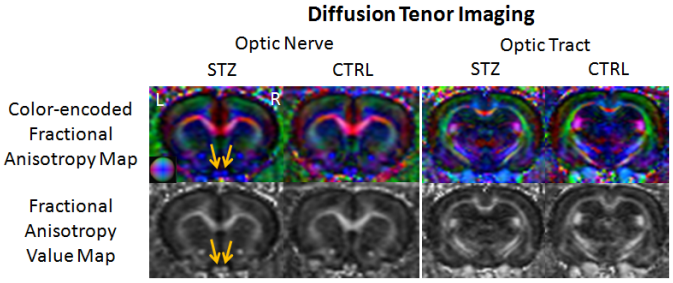

Fig. 3: Color-encoded fractional anisotropy (FA) maps (top row), and FA value maps (bottom row) at the level of the prechiasmatic optic nerve and the optic tract. Note the lower FA in STZ rats compared to CTRL rats (arrows). (blue: caudal-rostral; red: left-right; and green: dorsal-ventral)

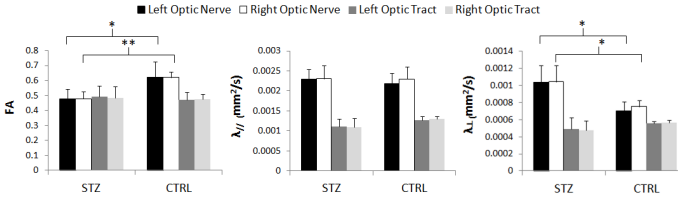

Fig. 4: Fractional anisotropy (FA) (left), axial diffusivity ($\lambda_{//}$) (middle) and radial diffusivity ($\lambda_{\perp}$) (right) of the bilateral optic nerves and the optic tracts between STZ and CTRL rats. (Two-tailed unpaired t-tests, *p<0.05; **p<0.01)

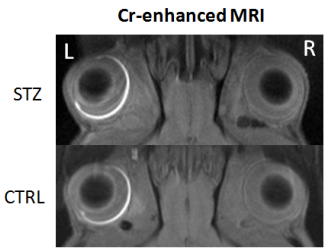

Fig. 5: Cr-enhanced MRI of the retina at 1 day after Cr injection into left eye and 1 month after STZ or citric acid (CTRL) injection.

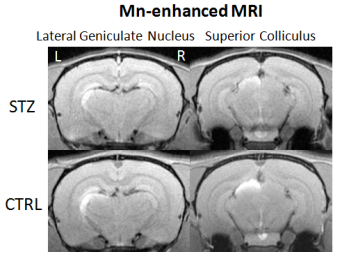

Fig. 6: Mn-enhanced MRI of the subcortical visual nuclei at 1 day after Mn injection into right eye and 1 month after STZ or citric acid injection..

REFERENCES: [1] Fernandez DC, Am J Pathol. 2012;180(1):303-313. [2] Fernandez DC, PLoS One. 2012;7(12):e51966. [3] Chan KC Magn Reson Med. 2012 Oct;68(4):1202-10. [4] Obrosova IG, Eur J Pharmacol. 2000 Jun 9;398(1):139-46. [5] Colantuoni A, Diabetologia. 2002;45(1):121-124.