Optic nerve damage of EAE mice detected by DTI but not by MEMRI

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Introduction Manganese (Mn) is currently the only MRI-sensitive marker for in vivo tract tracing in the central nervous system (CNS). Thus, Mn-enhanced MRI (MEMRI) has provided exciting findings of tracing neuronal circuits in living animals. Several literatures have supported that Mn2+ enters cells via L-type voltage gated calcium channels and transport along microtubules (1,2). Thus, it is possible axonal damage would manifest as decreased enhancement seen by in vivo MEMRI. To test this hypothesis, Eye-Drop MEMRI, noninvasive loading of Mn2+ by eye drop for MEMRI, was conducted on the mice affected by experimental autoimmune encephalomyelitis (EAE), an animal model for human MS (3). In the chronic stage of EAE mice, axonal and myelin injuries in optic nerve and tract have been documented by $\lambda_{\parallel}$ and $\lambda_{\perp}$ derived from diffusion tensor imaging (DTI) and histology. In this study, both DTI and Eye-Drop MEMRI were employed to evaluate the damage of optic nerve (ON) in EAE mice.

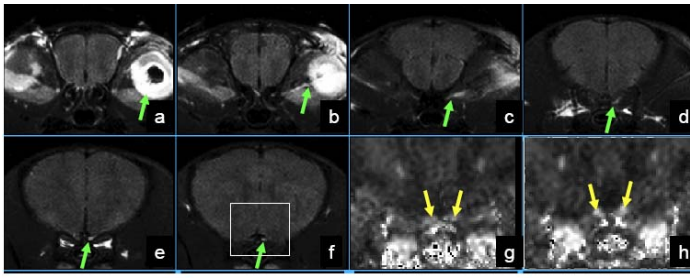

Fig. 1, Partial slices of Eye-Drop MEMRI from an EAE mouse (a-f, arrows: enhanced visual pathway). From the rectangle in f, reduced RA indicated the damage of optic nerve in EAE (g) comparing to control (h).

Materials and Methods Five 8-week-old female C57BL/6 mice were immunized with myelin oligodendrocyte glycoprotein (MOG) to generate EAE. Five age-matched female C57BL/6 mice served as controls. At 3 months after immunization, mice were examined using DTI and Eye-Drop MEMRI. The DTI was acquired with TR 1.5 s, TE 50 ms, Δ 25 ms, δ 10 ms, NEX 4, slice thickness 0.5 mm, FOV 3 cm, and data matrix 256×256 (zero filled to 512×512). Diffusion sensitizing gradients were applied along six directions with b-values of 0 and 0.85 ms/μm^2. Three quantitative indices including RA, $\lambda_{\parallel}$, and $\lambda_{\perp}$ were measured in ON. In 3 days after DTI, Mn2+ was loaded to the mouse eye by eye drop (about 10μl) containing 0.5 M $MnCl_2$ under anesthetization. Body temperature was maintained using an electric heating pad. After 1 hour, the remaining solution was carefully removed by a lint free tissue (Kimwipes) without touching the eye. Mice were returned to the original cages followed by T1-weighted imaging (T_1WI) conducted 1 day after the loading with TR 0.4 s, TE 23 ms, NEX 8, slice thickness 0.5 mm, field-of-view 3 cm, and data matrix 256 × 256 (zero filled to 512 × 512). In addition to T_1WI, T2-weighted images (T_2WI) with TR 1 s, TE 70ms, NEX 4, were also collected. The regions of interest (ROI), including left and right optic nerves (ON), optic tracts (OT), optic radiations (Rad), and visual cortex (Cort), were selected on T_2WI. As the mouse is a monocular specie, the ROI of Mn2+ enhancements were measured following the visual system starting from the right ON, left OT, left Rad, and reaching the left Cort. The corresponding control was measured at the same anatomical structures from the opposite hemisphere. The enhancement was quantified as (intensity-Mn2+ – intensity-control) / intensity-control.

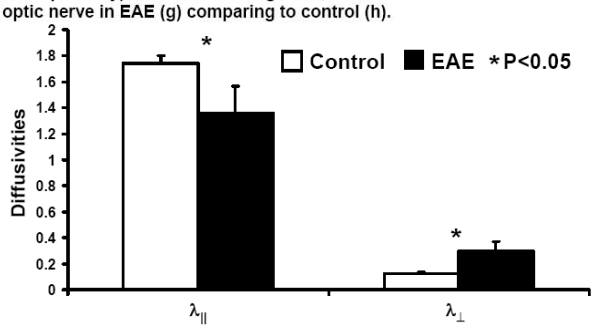

Fig. 2, Decreased $\lambda_{\parallel}$ and increased $\lambda_{\perp}$ in EAE ON.

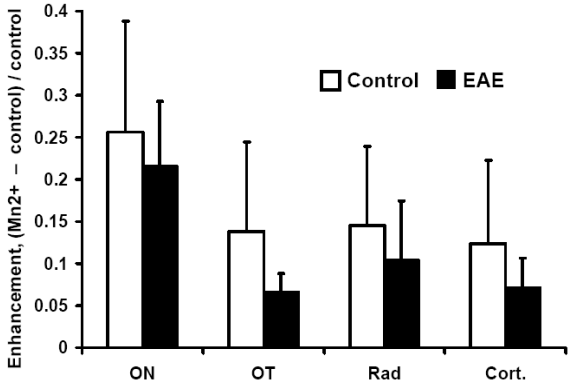

Fig. 3, Significant enhancement was found in Control and EAE visual pathway at 1 day after Eye-Drop MEMRI.

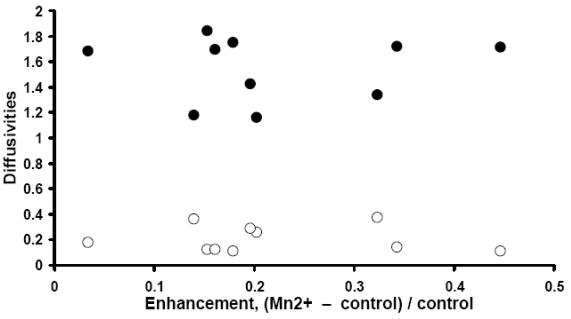

Fig. 4, Scatter plots of diffusivities, $\lambda_{\parallel}$ (•) and $\lambda_{\perp}$ (o), vs. Enhancement of Eye-Drop MEMRI in mouse optic nerves.

Results The significant 22% decrease in $\lambda_{\parallel}$ and 140% increase in $\lambda_{\perp}$ were observed in ON from EAE mice (Figs. 1 and 2) suggestive of axonal and myelin damage. Both control and EAE mice showed significant enhancement in Eye-Drop MEMRI (Fig. 3). The correlation analysis showed that there was no significant correlation between DTI changes and the enhancement measured by Eye-Drop MEMRI (Fig. 4).

Discussions and Conclusions In this study, the damage of ON induced by EAE was evaluated by DTI and Eye-Drop MEMRI. Although the damage resulted in significantly decreased $\lambda_{\parallel}$ and increased $\lambda_{\perp}$ derived from DTI, Eye-Drop MEMRI showed no significant difference between EAE and control mice. Both control and EAE ON showed significant enhancement by Eye-Drop MEMRI. Thus, MEMRI may be less sensitive to detect axonal injury resulting from EAE. Since the Mn+ uptake is complicated, i.e., dependent on activity (4), it is possible that the change in Ca2+ channel activity and the remaining unaffected axons in ON from the EAE mice may compensate the lost axons to maintain the sufficient amounts of Mn2+ transported after loading.

References

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(3) Sun et al., Neurobiology of Disease 2007; 28: 30-38.

(4) Bilgen et al, J Neurosci Methods 2006;156(1-2):17-22.

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