Evaluating Wallerian Degeneration in Visual Pathway of EAE Mice

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Introduction Although multiple sclerosis (MS) is the typical inflammatory demyelinating disease of the central nervous system (CNS), increasing evidence has suggested that the axonal and neuronal loss is the pathological correlate of the irreversible neurological impairment in patients with MS. Recent neuropathology studies suggested that axonal loss could occur both locally within the lesion and more distantly as a result of Wallerian degeneration. Time course studies characterizing the relation between myelin and axonal damage will shed lights on the complicated mechanisms of disease progression in MS. Specifically, the initial insult may involve myelin damage (followed by axonal damage); the secondary degeneration may cause axonal damage (followed by myelin damage) distant from the initial insult. Derived from diffusion tensor imaging (DTI), decreased $\lambda_{\parallel}$ and increased $\lambda_{\perp}$ have demonstrated correlations with axonal and myelin damage respectively (1). In the chronic stage of mice affected by experimental autoimmune encephalomyelitis (EAE), an animal model of human MS, consistent and severe damages in visual pathway have been demonstrated by DTI and immunohistochemistry (1). In this study, the temporal and spatial evolution of damage of the visual pathway from EAE mice was conducted using DTI.

Materials and Methods Four C57BL/6 (Wild-type) and four C57BL/wlds (Wlds) female mice, 8 weeks old, were immunized with myelin oligodendrocyte glycoprotein (MOG) to generate EAE. DTI was acquired in one week before and 1, 2, and 3 months after the immunization. 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 optic nerve (ON) and optic tract (OT).

Results In ON, decreased $\lambda_{\parallel}$ and increased $\lambda_{\perp}$ have been observed in both Wild-type EAE and Wlds EAE at 1 month with increasing severity of damages at 2 and 3 months after immunization. In OT, similar trend of decreased $\lambda_{\parallel}$ was observed in the Wild-type EAE with the increased $\lambda_{\perp}$ seen at 2 and 3 months, i.e., a delayed demyelination in OT. Interestingly, Wlds EAE did not show any damage in OT at 1 month. The decreased $\lambda_{\parallel}$ was observed at 2 months followed by the increased $\lambda_{\perp}$ at 3 months after immunization. An example of DTI maps from Wlds EAE were shown in Fig. 2. At 2 months, decreased $\lambda_{\parallel}$ and increased $\lambda_{\perp}$ were seen in ON while OT showed only decreased $\lambda_{\parallel}$ with no changes in $\lambda_{\perp}$.

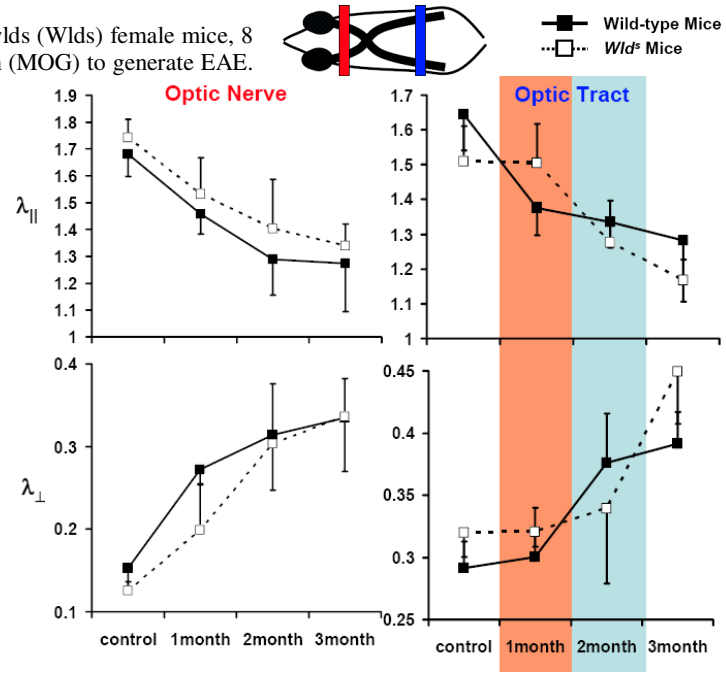

Fig. 1, Time courses of $\lambda_{\parallel}$ and $\lambda_{\perp}$ in ON and OT from wild-type EAE and Wlds EAE.

Discussions and Conclusions In this study, the feasibility of using $\lambda_{\parallel}$ and $\lambda_{\perp}$ in characterizing the primary and secondary axonal damage of EAE mice was evaluated. Specifically, based on the time course of DTI, the decreased $\lambda_{\parallel}$ followed by increased $\lambda_{\perp}$ in OT from the Wild-type EAE suggested that OT was likely damaged by the Wallerian degeneration. Since Wallerian degeneration can be delayed in Wlds EAE, the delayed damage of OT in Wlds mice, i.e., one month later than the damage to ON, supported that OT damage is a secondary degeneration originating from the initial ON damage. In Wlds EAE, the ON damage was not different from the ON damage in Wild-type EAE, suggestive of primary injury of ON in EAE not protected by Wlds. The current findings demonstrate the utility of *in vivo* DTI derived $\lambda_{\parallel}$ and $\lambda_{\perp}$ as the biomarkers for evaluating the progression of axonal damage and the nature of the injury.

References

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

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Fig. 2, DTI of Optic Nerve and Optic Tract from a Wlds EAE (2 months) and a normal Wlds mouse.