

Axonal and Myelin Damage to Optic Nerve and Optic Tract in EAE Mice Characterized by DTI

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Introduction

Experimental autoimmune encephalomyelitis (EAE) is a widely used animal model of human multiple sclerosis (MS). The pathology of EAE and MS involves both myelin and axon destruction in white matter. However, a non-invasive means to accurately characterize the pathology in EAE or MS is still lacking, making longitudinal investigation difficult. Diffusion tensor imaging (DTI) has shown great sensitivity and specificity in quantifying micro-structural changes in cerebral white matter development and pathology. It has been proposed and demonstrated that reduced λ_{\parallel} and the increases λ_{\perp} can serve as surrogate markers of axonal injury, and demyelination respectively (1). In this study, DTI was employed to detect CNS white matter lesions in mice affected with EAE.

Materials and Methods

Four 8-week-old female C57BL/6 mice were immunized with myelin oligodendrocyte glycoprotein (MOG) amino acids 35-55 emulsified in complete Freund's adjuvant (CFA). Pertussis toxin (PTX) was injected intravenously on the day of immunization and three days later. At 3 months after immunization, when the mice were chronically affected, *in vivo* DTI of brains was performed. Four age-matched female C57BL/6 mice served as controls. For acquisition of *in vivo* DTI, a conventional spin-echo imaging sequence modified by adding the Stejskal-Tanner diffusion sensitizing gradient pair was employed. The imaging parameters were TR 1.5 sec, TE 50 msec, Δ 25 msec, δ 10 msec, NEX 8, slice thickness 0.5 mm, field-of-view 3 cm, and data matrix 256x256 (zero filled to 512x512). Diffusion sensitizing gradients were applied along six directions: $[G_x, G_y, G_z] = [1, 1, 0], [1, 0, 1], [0, 1, 1], [-1, 1, 0], [0, -1, 1],$ and $[1, 0, -1]$. Two diffusion sensitizing factors or b-values (0 and 0.768 ms/ μm^2) were used. Three quantitative indices including RA, axial diffusivity ($\lambda_{\parallel} = \lambda_1$), and radial diffusivity ($\lambda_{\perp} = (\lambda_2 + \lambda_3)/2$) were measured in the white matter tracts including anterior commissure (AC), corpus callosum (CC), cerebral peduncle (CP), external capsule (EC), optic nerve (ON), and optic tract (OT).

Results

Representative DTI index maps were shown in Fig. 1. Relative anisotropy provided good image contrast to for ON (marked by green circles) and OT (marked by green arrows) as shown in Figs. 1a and b.

Data obtained from 4 EAE mice and 4 age-matched control mice were shown in Fig. 2. In the white matter tracts of CC, AC, EC, and CP, no significant differences were detected in RA, λ_{\parallel} , and λ_{\perp} . However, significant changes were observed in optic nerve and tracts (ON and OT). In EAE-affected mice, RA was decreased by 45.5% and 40.8%, λ_{\parallel} decreased by 16.9% and 22.5%, and λ_{\perp} increased by 226.9% and 113.2% for ON and OT respectively when comparing with the control.

Discussion and Conclusions

Optic neuritis is a common clinical manifestation in patients with MS (2). It is also frequently observed in the EAE model (3). In both MS and EAE, inflammation, demyelination and axon damage occur in CNS white matter. In this study, the distinct and selective injuries to optic nerve and optic tract were confirmed by comprehensively surveying the white matter in whole brain data acquired using DTI. According to our previous study (1), decreased λ_{\parallel} and increased λ_{\perp} strongly suggest axon damage and demyelination taking place in ON and OT in mice with chronic EAE. Our results, acquired non-invasively, are consistent with the known pathology to optic nerve and optic tract in EAE. This study demonstrated the feasibility of DTI as a sensitive tool to detect white matter lesions in living EAE mice. DTI would be useful for studying the pathology of EAE and perhaps MS longitudinally.

Reference

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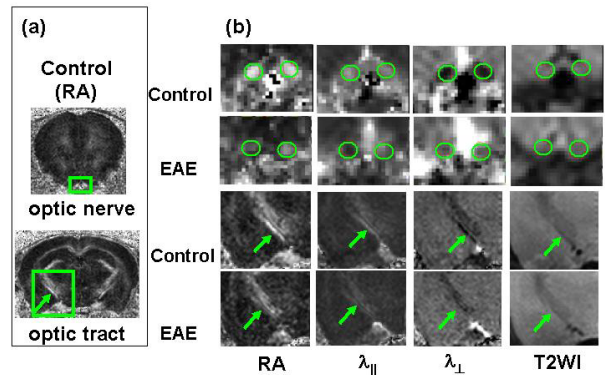


Fig. 1

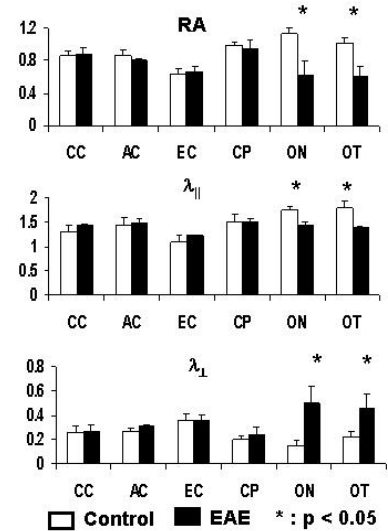


Fig. 2