

In vivo DTI-derived axial diffusivity correlates with neurological assessments in EAE-affected mice

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Introduction

Multiple sclerosis (MS) is an inflammatory demyelinating disease characterized by inflammation, demyelination, and axonal/neuronal dysfunction (1). Experimental autoimmune encephalomyelitis (EAE)-affected mice display these MS pathologies. In this study, we employed diffusion tensor imaging (DTI) to evaluate the EAE-affected spinal cord white matter integrity and to correlate it with various neurological assessments. Results showed 1) a statistically significant decrease in axial diffusivity ($\lambda_{||}$) in EAE-affected spinal cord white matter compared with that in normal control mice, and 2) the $\lambda_{||}$ defined axonal injury severity correlated with neurological dysfunction.

Methods

Control and EAE mice underwent in vivo DTI examination on a 4.7 T scanner. A respiratory gated spin-echo diffusion-weighted sequence was employed with actively decoupled volume (6-cm inner diameter, RF excitation) and surface coil (16 mm x 9mm,

signal receiver). The overall set up is similar to that described previously (2). All images were obtained with acquisition parameters of TR 1.2 sec (gated acquisition), TE 38 ms, Δ 18 ms, δ 7 ms, slice thickness 1.0 mm, zero filled spatial resolution (38 μ m x 38 μ m), total data acquisition time ~ 1.0 hr, (Gx,Gy,Gz) = (1,1,0), (1,0,1), (0,1,1), (-1,1,0), (0,-1,1), and (1,0,-1), and b = 0 and 1.0 ms/ μ m². Neurological function was assessed with clinical score (CS) (3), Basso Mouse Scale (BMS) (4), and Gait Analysis (5). All measurements were performed at the end point of longitudinal CS evaluation.

Results and Discussion

The disease was longitudinally examined with CS (Fig. 1). Representative *in vivo* DTI derived $\lambda_{||}$ maps of the spinal cord at the lumbar cord level are shown with the $\lambda_{||}$ -threshold segmented white matter lesions, indicated in red (Fig. 2). Minor abnormal $\lambda_{||}$ regions were also seen in the control cord (Fig. 2a) since the threshold is set at 95% confidence interval of $\lambda_{||}$ from the averaged control white matter. The extent of abnormal white matter correlated with the four neurological assessments (Fig. 3). Interestingly, some mice induced to develop EAE, but with CS = 0 (Fig. 2b) had mildly abnormal $\lambda_{||}$ which correlated with mild dysfunction on more sensitive clinical tests (BMS, gait analysis). Other mice with CS=0 had normal $\lambda_{||}$ and also normal BMS and gait analyses. (Fig. 3, dotted box). The neurological function assessed by gait analysis with linear and continuous scale, i.e., maximum speed and foot base, correlated in linear fashion with $\lambda_{||}$ defined white matter lesions (Fig. 3c and d). Both open-field behavior ordinal scale assessments showed a 2nd order correlation with DTI findings (Fig 3a and b).

Conclusion

The statistically significant correlation between DTI defined white matter abnormalities in spinal cord and neurological outcome strongly suggest that DTI may be used as a noninvasive, quantitative assay for therapeutic efficacy and outcome prediction in EAE.

References

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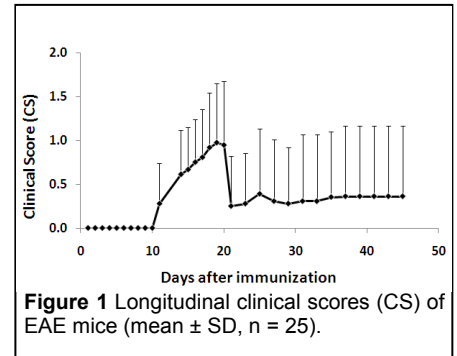


Figure 1 Longitudinal clinical scores (CS) of EAE mice (mean \pm SD, n = 25).

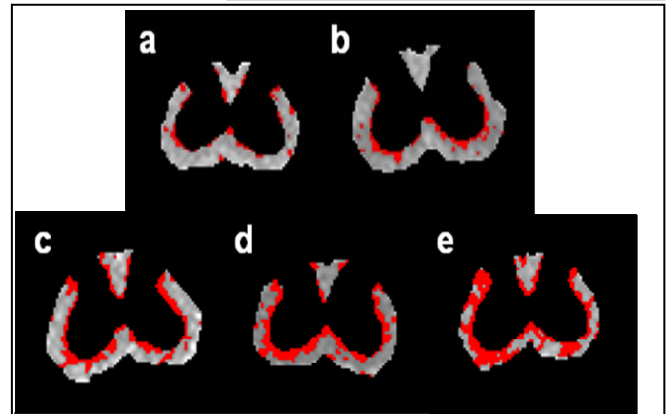


Figure 2 In vivo $\lambda_{||}$ threshold segmented white matter lesions (in red). Compared to control (a), EAE mice of CS = 0, 1, and 2 (c, d, and e) exhibit significantly higher content of white matter lesions. Some EAE mice with CS = 0 (b) have negligible extent of abnormal white matter compared to control.

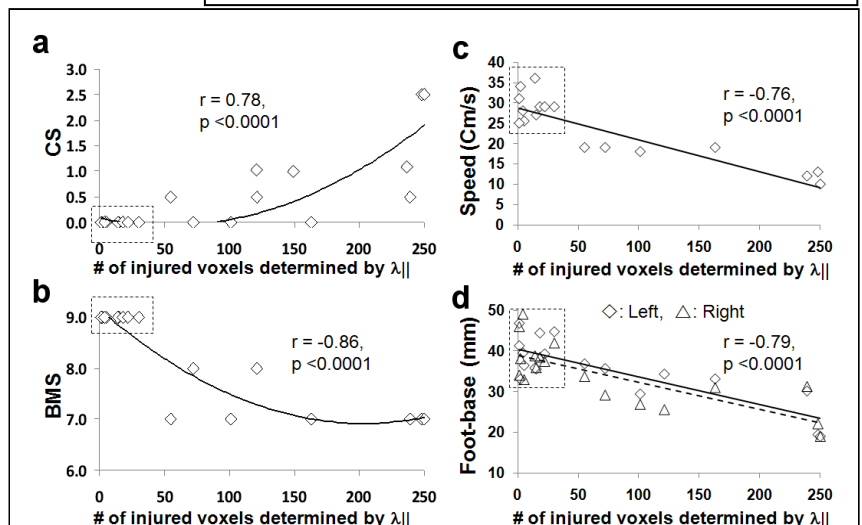


Figure 3 The correlation between $\lambda_{||}$ -threshold segmented lesion white matter extent and neurological assessments including CS (a), BMS (b), and gait analysis[(maximum speed (c) and Foot-base (d)]. DTI determined white matter lesion extent correlates with neurological assessments.