In vivo MRI Quantification of Mouse Spinal Cord with Relapsing Remitting EAE: Disability and imaging correlates

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Introduction

Spinal cord pathology is common in multiple sclerosis (MS), and contributes substantially to locomotor disability[1]. Diffuse pathology within spinal cord, including inflammation, edema and gliosis, may also cause cord volume change. However, investigation of spinal cord pathology using quantitative MRI, in relation to clinical outcome in MS, has been limited[2]. Nevertheless, quantitative MRI measurement of spinal cord pathology may provide a more detailed understanding of the disease process. Ultra Small particle iron oxide (USPIO) loaded macrophages cause magnetic susceptibility, which in turn shortens T2 relaxation time (T2 RT) in MR imaging. Consequently, active inflammation with USPIO loaded macrophages, can be detected *in vivo*[3]. Our goal is to examine the relationship between disability and quantitative MRI of cord volume and USPIO loaded macrophages in the spinal cord of a mouse relapsing-remitting EAE model (RREAE).

Methods

RREAE was induced in six strain-129 mice by immunization with MOG peptide, Mycobacterium in complete Freund's adjuvant, and Pertussis toxin. Immunized mice were observed daily and assigned a neurological score from 0 (normal) to 11 (death from EAE). Groups of two mice were imaged separately during: a) first remission (mean score 2.5, symptoms on 8 - 10 days post-immunization); b) second relapse (mean score 8.3, symptoms on days 13 - 17); and, c) second remission (mean score 1.8, symptoms on days 23 - 27). Mice were sacrificed within 24 hours after imaging for histological processing.

Each mouse with EAE was administered AMI-228 USPIO (at a dose of 30mg Fe/kg) 24 hours before MR imaging. Imaging occurred on a 7T Bruker scanner using an 8-echo T2-weighted pulse sequence (TR/TE = 2540ms/26.79ms, matrix size = 256 x 256, FOV = 2.5 x 2.5 cm^2, NEX = 4, slice thickness/gap = 0.75 mm). Multi-echo imaging was acquired in each mouse from 12 interleaved slices covering the spinal cord from L2 to the sacral segment. For comparison, two control mice from the same strain were also imaged (three scans per mouse, separated by one or more days) using the same protocol.

LiveWire segmentation[4] was applied to segment the spinal cord and measure its volume in the first eight MR slices (Fig. 1). The erector spinae muscle was also segmented and measured in the first two slices. Total cord volume for each mouse was obtained by summing volumes from each slice. Cord volume was normalized in each mouse by dividing by the erector spinae muscle volume. T2 maps for each slice were calculated from the multi-echo imaging using a 1-D fitting algorithm. The final T2 RT for each mouse was obtained by averaging the mean T2 RT from the first eight slices. The same process was repeated for each EAE and control mouse.

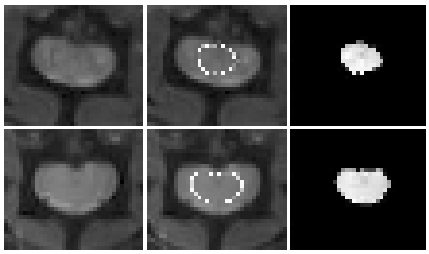

Fig.1: 7 T MRI of control (top row) and EAE (bottom row) cord and its segmentation by LiveWire algorithm (middle and right column). EAE cord is larger and less distinct than control cord.

Results

The grand mean normalized spinal cord volume from all the mice with RREAE was significantly larger ($p < 0.05$) than that from control mice. The cord boundary from surrounding CSF was less clear in EAE mice compared to normal mice (Fig. 1). No significant difference was found in grand mean whole cord T2 RT between EAE and control mice. However, within EAE mice, both the mean normalized cord volume ($r = -0.9$, $p < 0.01$) and the mean cord T2 RT ($r = -0.7$, $p < 0.01$) were significantly correlated with mean disability score in each group of mice (1st remission; 2nd relapse; 2nd remission) (Fig. 2). EAE mice during the 2nd relapse had larger normalized cord volume ($p < 0.05$) and shorter T2 RT ($p < 0.05$) than the other groups. Mice in 1st or 2nd remission had significantly larger normalized cord volume than control mice ($p < 0.05$).

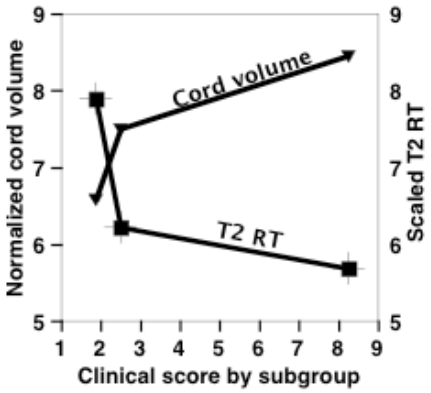

Fig.2: Normalized cord volume and T2 RT vs mice clinical score in each subgroup. Cord volume is positively, T2 RT is negatively correlated with mice score in RREAE.

Discussions and Conclusions

The spinal cord volume and T2 RT in mice with RREAE correlated with disability. In mice with lower clinical score (remission), cord enlargement was the dominant change. When disability increased (relapse), both cord enlargement and macrophage infiltration (T2 RT shortening) occurred. The insignificant difference of MR measurements between first and second remission suggests that EAE cord abnormality depends more on mice disability scores, than disease course and duration. Normalized spinal cord volume increased at very low disability scores, suggesting that cord volume may be a sensitive measurement of disease severity in spinal cord EAE. Further study is needed to verify these results in EAE mice and patients with early MS.

References

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