Evaluation of Demyelination and Remyelination in Mouse Spinal Cord using Multiexponential T2 and Magnetization Transfer Ratio

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INTRODUCTION: Evaluation of various treatments of multiple sclerosis involves identification of demyelination and remyelination. Microinjection of lysolecithin into the spinal cord of mice provides a model of demyelination with spontaneous remyelination [1,2]. Both multiexponential T2 analysis and magnetization transfer ratio imaging (MTR) reflect myelin content, although MTR is also influenced by inflammation and axonal density [3-5]. The aim of this study was to use multiexponential T2 and MTR to study the time course of changes in myelin in a lysolecithin model of demyelination/remyelination.

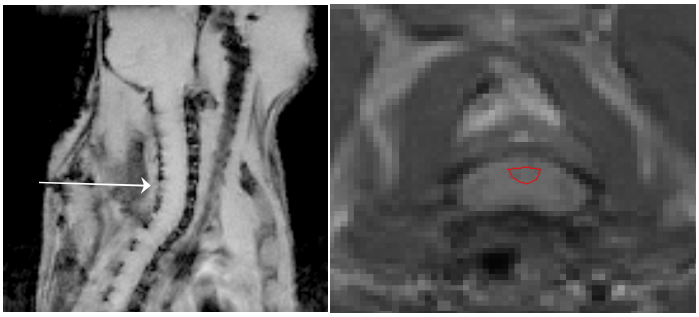

Figure 1. Sagittal and axial views of myelin damage location. Arrow indicates the site of injection. An example of an ROI (red) outlining the dorsal column is shown on the axial image (TR/TE=3s/15ms).

METHODS: Male mice (C57/Bl6) were anaesthetized and microinjected with 1μL of 1% lysolecithin into the spinal cord dorsal funiculi between cervical vertebrae 5 and 6. Multi-echo spin echo (SE) images (TR/TE=3000/5 ms, inter-echo spacing = 5ms, 64 echoes, NA=4, FOV = 1.92x1.92 cm, matrix=128x128, slice=0.75mm, resolution=150μm) were acquired on a 9.4T Bruker Avance system once a week for 4 wk following injection. SE images with and without off-resonance pulses were also acquired for calculation of the magnetization transfer ratio (TR/TE=4000/15 ms with 40-4μT pulses applied 2kHz off-resonance, NA=2, FOV=2x2 cm, matrix=256x128, slice=0.75mm, resolution=78x156μm). A region of interest (ROI) was drawn outlining the dorsal funiculus to select signals for T2 and MTR analyses for the same slice in each animal (Figure 1). The signal intensity decay curves were fit with a regularized NNLS algorithm [6]. The T2 distributions were separated into 3 regions: myelin water fraction (MWF) 7.5-25ms, intra/extracellular water fraction (IEWF) 25-90ms, and long T2 fraction 90-640ms. Geometric mean T2 (gmT2) and the peak areas were determined for each region. MTR was calculated as the difference between signal intensity without and with saturation pulses and expressed as a percentage of the signal intensity without saturation pulses. ANOVA with SNK post-hoc tests was used to compare time points.

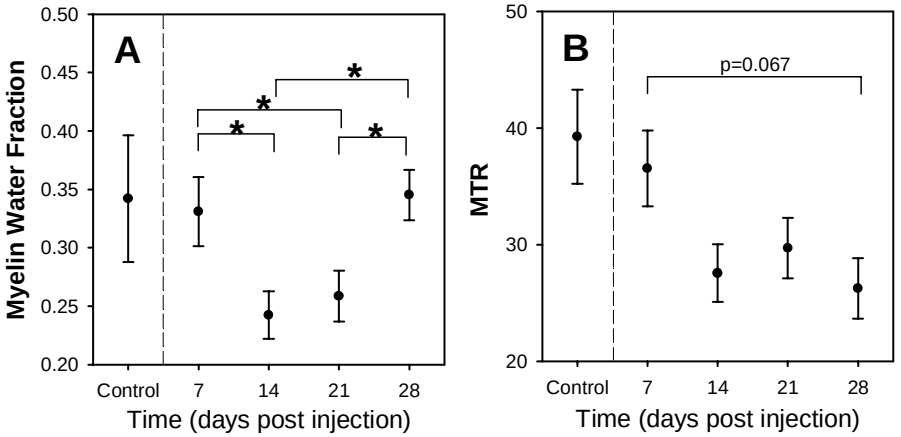

Figure 2. Time course changes in myelin water faction (A) and MTR (B). Mean values (±StError) are shown for control (n=3) and lysolecithin-treated mice (n=7). Significantly different groups are indicated by an asterisk (p<0.05).

RESULTS: The MWF significantly decreased by 14 days post injection (dpi) and showed recovery by 28 dpi (Figure 2A). Conversely, the IEWF increased significantly at 14 and 21 dpi and showed a decrease in gmT2 values (±StDev) from 52±4ms (control and 7 dpi) to 46±3ms (14 and 21 dpi) returning to 49±4ms by 28 dpi. No significant changes in the MWF gmT2 values or in the long gmT2 component were detected, although the variance in the long component fraction nearly doubled in the 14dpi group. MTR values decreased by 14 dpi and remained low. However, this change did not reach significance (Figure 2B).

DISCUSSION: Evidence of remyelination in our lysolecithin model was indicated by an increase in the MWF by 28 dpi which was not apparent in MTR that remained decreased over the time course studied. These results are consistent with prior studies showing that although MWF and MTR are both related myelin content, they are independent measures [3-5]. The decreased MTR after 28 dpi may be related to the presence of inflammation needed for remyelination [4, 7]. It may be possible to differentiate early remyelination from normal white matter by the return of MWF to near control values while the MTR remains decreased.

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