Understanding white matter pathology through correlating longitudinal and quantitative MRI metrics weekly in the cuprizone mouse model of demyelination

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INTRODUCTION: MRI methods such as diffusion tensor imaging (DTI)1, quantitative magnetization transfer imaging (qMTI)2, and multicomponent T2 relaxometry3 might help quantify changes related to demyelination. To understand the interplay different MRI methods have as white matter changes longitudinally in the cuprizone mouse model, in vivo T2-weighted (T2w) and magnetization transfer images (MTI) were acquired weekly in control (CTL) (n=18) and cuprizone-fed (CPZ) (n=18) mice. As well, weekly DTI, qMTI, T1/T2 relaxometry, T2w imaging, and electron microscopy (EM) were used to analyze ex vivo tissue after each week of cuprizone delivery (n=3 per group each week). Correlation between both longitudinal and quantitative datasets was measured with a focus on the corpus callosum (CC) and external capsule (EC). A previous study examined correlations between MR metrics and EM measures after 6 weeks of feeding4. The addition of weekly ex vivo tissue analysis allows for a more complete understanding of the correlations between MR metrics and EM measures of tissue pathology.

METHODS: Mouse Model C57BL/6 mice were fed 0.3% cuprizone (w/w) starting at 8 weeks of age. After each week of feeding, a subset of mice was perfused with 10 ml of 0.1M phosphate buffered saline (PBS) for ~2 min followed by 0.5% glutaraldehyde and 2% paraformaldehyde (PFA) for ~10 min. This was followed by another 10 ml of 0.1M PBS to flush out any remaining fixative. All tissue external to the skull was removed and the mouse head was stored in PBS prior to overnight imaging. All experiments were approved by the university’s animal care committee. MRI Experiments were performed on a 7T Bruker Avance III NMR system. Mice were anesthetized using 1.5% isoflurane in O2/N2O. Respiration and external body temperature were monitored during imaging. In order to reduce volume averaging effects, coronal slices were selected in each mouse perpendicular to the rostral region of the CC. Initially, 18 CTL and 18 CPZ mice underwent in vivo T2w imaging and MTI on the day the treatment began (week 0) and one week later (week 1). Starting on week 1, 6 animals (3 CTL, 3 CPZ) were sacrificed each week for ex vivo analysis. After sacrifice, additional high-resolution T2w, DTI, qMTI, and T1/T2 relaxometry datasets were acquired. In vivo T2w and MT images were aligned using manual and mutual information image registration5. Regions of interest representing both the CC and the EC as well as the cerebral cortex were selected in the in vivo MT contrast images and ex vivo DTI directionality encoded color maps and applied to analysis of all MR methods. All images were acquired on the same 3 coronal slices with 1.25 mm inter-slice spacing and 98x98x750 μm3 resolution. FOV/matrix size was (2.5 cm)2/256x256 in vivo and (1.25 cm)2/128x128 ex vivo. In vivo T2w RARE, 12 averages, effective TE/TR = 80/1640 ms, RARE factor 8; 10 minutes. In vivo MTI FLASH, 48 averages, effective TE/TR = 6/70 ms, 10° flip angle. In order to calculate the magnetization transfer ratio (MTI), images were acquired with an MT saturation pulse (Gaussian, 10.25 ms, 10 Hz offset resonance) and without an MT saturation pulse, 2x14 minutes. Ex vivo T1/T2 Relaxometry Fit to a series of RARE images, effective TE = 11, 33, 55, 77, 99 ms; TR = 5000, 3000, 1500, 800, 400, 353 ms; RARE factor 2; 8 averages; 71 minutes. Ex vivo qMTI 1 proton density image + 18 MT images acquired with irradiation powers of 5, 10, and 20 mT and frequency offsets at each power of 1000, 2000, 4000, 6000, 10000, and 30000 Hz, 64 averages 9.6 min/image x 19 images. Ex vivo DTI PGSE, tetraorthogonal gradient-encoding scheme (7-directions), b-value = 1000 s/mm2 (b = 6 ms, Δ = 14 ms), 1 slice, 6 averages, TE/TR = 26/5000 ms, 5 hours. Ex vivo T2w RARE, 1 slice, 36 averages, effective TE/TR = 80/1640 ms, RARE factor 8, 31 minutes. Presented here are in vivo and ex vivo MR data from weeks 0-2.

RESULTS

DISCUSSION AND CONCLUSION: Changes in white matter pathology are expected to begin at week 3. EM analysis of the tissue still needs to be done for correlations with white matter pathology. Weekly imaging out to week 6 is currently underway. The addition of the weekly ex vivo tissue analysis allows for a more complete understanding of the correlations between MR metrics and EM measures of tissue pathology.