Longitudinal MR frequency shift imaging in patients with clinically isolated syndrome

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Target Audience: MR Physicists, Neurologists, Radiologists and Clinicians

Introduction: Recent studies utilizing MR frequency shift (FS) imaging demonstrated the technique's potential to quantitatively assess tissue damage due to multiple sclerosis (MS) lesion formation[1-3]. Observed differences in MR FS within lesion subtypes suggest great sensitivity in describing lesion heterogeneity, reflective of variable degrees of demyelination and tissue matrix destruction[2]. The frequency signal changes due to either varying magnetic susceptibility within a voxel or alterations in the tissue's microarchitecture[1, 2]. Both occur during the formation and evolution of new MS lesions[3]. Clinically isolated syndrome (CIS) patients experience demyelinating events suggestive of MS, but do not yet fulfill the criteria for definite MS. Assessing white matter integrity with MR FS longitudinally in this pre-MS cohort may help to illuminate the time line of axonal loss and demyelination in new MS lesions.

Methods: 73 patients with CIS were enrolled into a randomized, placebo-controlled, double-blind Minocycline therapeutic trial and received an MRI at baseline. Following treatment initiation, patients received 5 follow-up MRI over 2 years (month 3,6,12,24). As per study design, patients were discontinued from the study if they converted to definite MS, according to the 2005 McDonald criteria. Multi-gradient echo (GRE), proton density (PD), FLAIR and contrast-enhanced SE T_1-weighted images were acquired at 3T (Philips Achieva) using an eight-channel head coil. GRE acquisition parameters were: 5 echoes, TR/TE/ΔTE=48/20/6ms, FOV=220x167x80 mm^3, reco. voxelsize=0.38x0.38x1.2 mm^3. Gadolinium (Gd)-enhanced and T_1-hypointense lesions were identified on T_1-Gd scans. Lesions that appeared without Gd-enhancement but at subsequent FLAIR scans were classified as *new* lesions. Normal appearing white matter (NAWM) and diffusely abnormal white matter (DAWM) were defined on PD images. All regions of interest were segmented with in-house developed software. MR frequency maps were computed from the GRE phase by homodyne filtering and scaling of the image intensities to the Larmor frequency at 3T. Average frequency shifts for each region were estimated at TE=23ms and statistical analysis was performed in R applying a linear mixed-effects model.

Results: 11/73 subjects received MRI at all time points. 30 Gd-enhancing lesions in 9 subjects and 19 *new* lesions in 8 subjects appeared over the course of the study. The frequency shift of all 49 lesions is displayed in Fig. 1 in comparison to the frequency shifts observed in NAWM, DAWM and chronic black holes. The lesions' frequency increases significantly (p=0.0001) in between 6 months prior to enhancement up to 3 month post-enhancement, with a rapid increase close to the time of enhancement. The frequency within lesion tissue remained elevated but exhibited no significant changes beyond 3 month post-enhancement. Frequency shifts in non-lesion tissue and in black holes remained constant (Fig. 1, p>0.4). The average frequency shifts were 0.73±0.31 ppb in black holes, -0.005±0.025 ppb in DAWM and -0.715±0.140 ppb in NAWM.

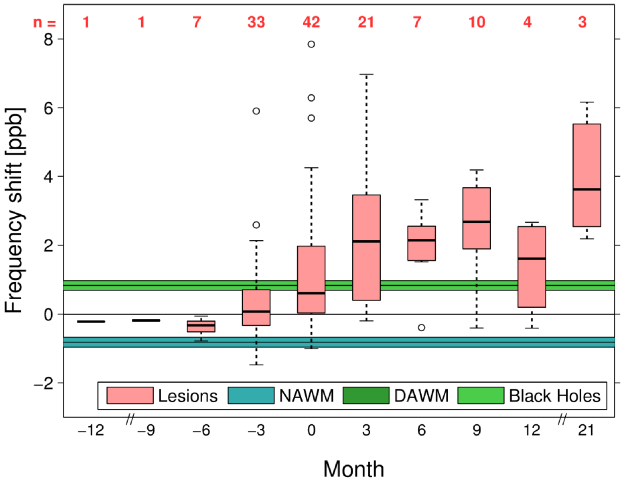

Figure 1: MR frequency shifts in new MS lesions increase rapidly at the time of lesion appearance (Month 0), while no changes over 2 years are observed in NAWM, DAWM and black holes.

Discussion: The present results confirm and extend findings of an earlier non-treatment study in 20 patients with relapsing-remitting MS (RRMS) over 6 months[3] and demonstrate that the frequency in new MS lesions remains elevated for up to 12 months. Beyond 12 months the small number of lesions precludes definite conclusions. In contrast to another study of RRMS patients showing normalization of MR frequency 5 years after lesion appearance[4], our results indicate that this normalization does not occur within the first 12 month after lesion formation.

Conclusion: Lesion formation in CIS leads to increases in the MR resonance frequency signal that persist for at least 12 months after lesion appearance.

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References: [1] He and Yablonskiy, PNAS 2009 [2] Yablonskiy et al., PNAS 2012 [3] Wiggermann et al., Neurology 2013 [4] Wiggermann et al., ISMRM 2014, #0892