Assessment of demyelination and remyelination in acute MS lesions: magnetization transfer ratio imaging versus quantitative magnetization transfer imaging

P. S. Giacomini[1], I. R. Levesque[2], L. T. Ribeiro[1], S. Narayanan[1], G. B. Pike[2], and D. L. Arnold[1]

[1]Neurology and Neurosurgery, McGill University, Montreal, Quebec, Canada, [2]Biomedical Engineering, McGill University, Montreal, Quebec, Canada

Introduction: Changes in the magnetization transfer ratio (MTR) values observed in multiple sclerosis (MS) correlate with changes in myelin content in the white matter[1, 2]. However, the MTR change can also be affected by changes not specific to myelin, such as increased water content and inflammation[3, 4], potentially complicating the interpretation of MTR changes in the context of acute gadolinium enhancing lesions. Quantitative magnetization transfer imaging (qMTI) provides a more complete description of the MT phenomenon and overcomes some of the limitations of MTR[5-7]. In this study, we explore the relationships between changes in the size of the restricted pool proton density (PDR), which should be insensitive to edema, and MTR changes in acute contrast-enhancing lesions of MS, to determine whether MTR can be used as a marker of myelin content in these lesions.

Methods: We studied six patients with acute gadolinium enhancing lesions serially using qMTI and compared these estimates with MTR measures. The qMT parameter F is directly estimated as part of the binary spin bath model and represents the ratio of proton densities of the restricted and free pools (PDR/PDF); hence it is sensitive to changes in both.

In the absence of an external standard, the PDF can be computed relative to a specific region-of-interest within the brain that, while not an absolute indicator of proton density, can provide an index of relative changes in liquid content. In this study, we have computed the relative PDF (rPDF) in lesions relative to a region of homologous normal-appearing white matter (NAWM) contralateral to the lesion. Thus, the contralateral region has an rPDF of 1, by definition. Increases of water in the lesion therefore result in rPDF > 1. By extension, we can define the relative PDR (rPDR) as the product F x rPDF. rPDR thus should more accurately reflect changes in the restricted pool size, and should not be influenced by changes in lesion water content. In turn, decreases in rPDR should provide a more accurate estimate of demyelination, with less influence from water increases that accompany acute lesions with edema.

MT and relaxometry data were acquired in a single oblique 7-mm section in six patients with multiple sclerosis (gender/age at entry: F/25, F/43, F/56, F/42, F/50, F/49) at monthly time points over of a period of one year, using the qMTI protocol described by Sled and Pike [8] and a CPMG sequence with 32 echoes and 10-ms spacing. Patients were selected based on the presence of an active lesion as defined by gadolinium (Gd) enhancement. All data were acquired on a 1.5 T Siemens Sonata. Data were analyzed, including corrections for static and RF transmit field inhomogeneities, on a voxel-by-voxel basis to produce parametric maps of the binary spin-bath model. The enhancing regions of the acute lesions were labeled on a high-resolution post-gadolinium scan at the first time point. These labels were automatically propagated to subsequent time points, resampled to the lower resolution of the QMTI scans, and thresholded to 80% purity to limit partial volume contamination by peri-lesional tissue. Control regions of normal-appearing white matter (NAWM) were defined contralateral to the lesions in homologous regions free of any visible pathology. All measures of MTR, F, rPDR and rPDF values from the lesions were normalized to contralateral, homologous NAWM at each time point to yield relative measures of MTR, F, rPDR and rPDF.

Results: The baseline normalized MTR in Gd-enhancing voxels was 0.75 ± 0.05 (mean ± st dev) at the time of gadolinium enhancement. The value rose to 0.84 ± 0.09 after one month and to 0.86 ± 0.07 by the second month post-enhancement. The normalized rPDR was 0.46 ± .10 (mean ± st dev) at baseline. It increased to 0.74 ± 0.24 the first month and 0.80 ± 0.13 the second month post-enhancement. See Figure 1. Changes in F closely tracked rPDR.The differences in normalized MTR, and rPDR were statistically significant between baseline and the timepoints from month 2 post-enhancement onward for all measures (p-values < 0.01). The normalized MTR and rPDR were highly correlated (R square 0.70, p-value <0.0001). See Figure 2.

Discussion: MTR is a practical imaging technique that is widely available and is sensitive to changes in myelin content in cerebral white matter [1, 2, 9, 10]. However, it is also sensitive to changes in water content and T1 relaxation time of the tissue [3, 4]. In the context of an acute multiple sclerosis lesion, where there is inflammation and edema, there is concern that multiple microstructural changes may affect the specificity of MTR. The normalized rPDR value in acute lesions is substantially lower at baseline compared to the normalized MTR (0.46 vs. 0.75), likely because increased fluid content in the acute lesion attenuates the MTR decrease. Thus, MTR may underestimate the degree of demyelination in acute lesions. Nevertheless, there was still a strong correlation between the normalized MTR and rPDR (R^2 of 0.70, $p < 0.0001$), and the evolution seen in the rPDR tracks that seen in MTR. In conclusion, despite some attenuation of MTR in acute lesions due to dilution and T1 relaxation time changes, the results from this study support the notion that the MTR is a useful, practical marker of myelin changes, even in acute lesions.

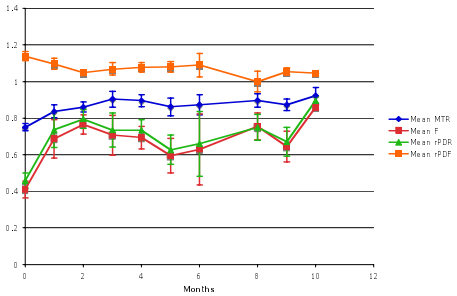

Figure 1: Ratios of mean MTR, F, rPDR and rPDF (± Standard Error of Mean) of Gd-enhancing voxels to mean MTR, F, rPDR and rPDF in a contralateral NAWM region of interest vs. time (months)

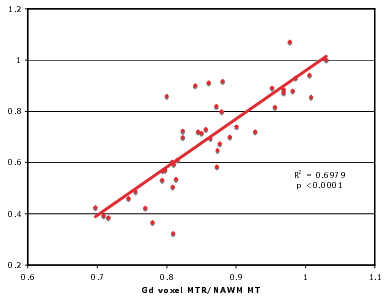

Figure 2: Correlation of mean normalized MTR and mean normalized rPDR in Gd-enhancing enhancing voxels

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