Measuring the potential for remyelination and demyelination in multiple sclerosis lesions

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Abstract: Lesions in multiple sclerosis (MS) show differing degrees of demyelination. The magnetization transfer ratio (MTR) is a marker of myelin content, however, there is no method to quantify remyelination potential. We hypothesized that remyelination or demyelination of lesions, measured by the change in MTR over time, would be related to baseline lesion MTR signal inhomogeneity. Studying 6 subjects at baseline and after 2 months, we found that lesion voxels which significantly decreased in MTR on follow-up, had a significantly higher MTR signal inhomogeneity at baseline (372±71au) compared to lesion voxels which increased in MTR (111±73au), $p<0.001$. This suggests that local MTR signal inhomogeneity provides a method for quantifying lesion remyelination potential.

Introduction: Demyelination is associated with acute axonal transection and possibly also with pre-programmed cell death of chronically demyelinated axons. Histopathology shows that early active demyelinating lesions have the highest degree of axonal damage, and less axonal damage is found in remyelinated compared to demyelinated lesions [1]. The MTR of remyelinated lesions has been shown to be higher than that of demyelinated lesions, and lower than normal-appearing white-matter (NAWM) [2]. Our objective was to quantify remyelination potential in MS lesions.

Methods: Patients were recruited at the Ottawa Hospital-General Campus, scanned twice with a 2-month interval, as part of the baseline evaluation of a phase II trial of complete immunoablation followed by autologous stem cell transplantation. All patients had secondary-progressive MS and evidence of disease activity. Scans were performed on a 1.5T Siemens Magnetom Symphony (Siemens AG Medical Solutions, Erlangen, Germany) and included the following sequences: PD/T_2-weighted (TR=2070ms; TE=12, 86ms; thickness=3mm; 192x256); MT with (Sat) and without (NoSat) a saturation pulse (TR=30ms, TE=11ms); T_1-weighted pre and post gadolinium (TR=28ms, TE=11ms).

MRI analysis: **MTR calculation:** The MT Sat image was linearly registered to the MT NoSat image prior to MTR image volume calculation (100*(NoSat-Sat)/NoSat). **Lesion masks:** Maps of T_2-weighted lesions (baseline and follow-up) were transformed to post-gadolinium baseline time-point space, and combined to form a binary mask of all tissue classified as lesion on either scan. **ΔMTR in lesion:** MTR volumes for baseline and follow-up time-points were transformed to post-gadolinium baseline time-point space. Baseline MTR was subtracted from MTR at follow-up, and the lesion mask was applied to mask the change in MTR values in the lesions. **Lesion MTR signal inhomogeneity:** The baseline MTR volume was blurred using a 3-D gaussian kernel (standard deviation=0.25mm). The blurred image was subtracted from the baseline MTR image, and the absolute value was calculated, to yield a measure of baseline local MTR signal inhomogeneity. The lesion mask was applied to yield a map of the baseline lesion MTR signal inhomogeneity. **Threshold of ΔMTR in lesion:** A region-of-interest (ROI) analysis was performed on the baseline NAWM of all patients. Six white-matter ROIs were sampled, and the median value for each ROI was calculated for each patient. MTR_{min} was the minimum NAWM ROI median MTR value, and MTR_{max} was the maximum NAWM ROI median MTR value, over all regions and all patients. A voxel was defined as having significantly decreased in MTR if $\Delta MTR<-2*(MTR_{max}-MTR_{min})$, or significantly increased in MTR if $\Delta MTR>2*(MTR_{max}-MTR_{min})$.

Results:

Figure 1

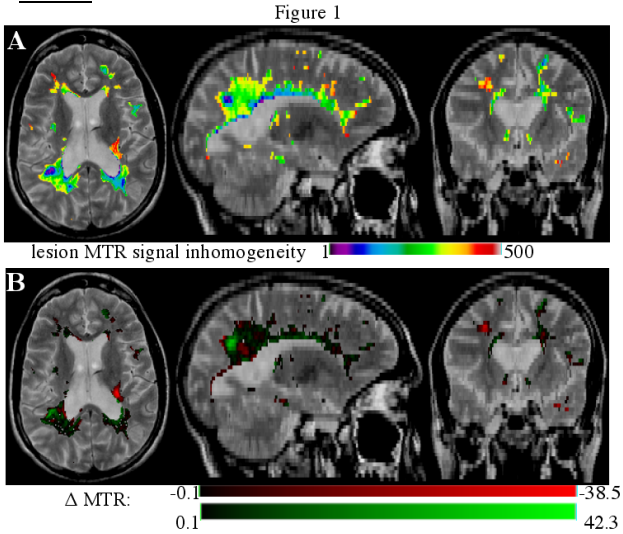


Figure 2

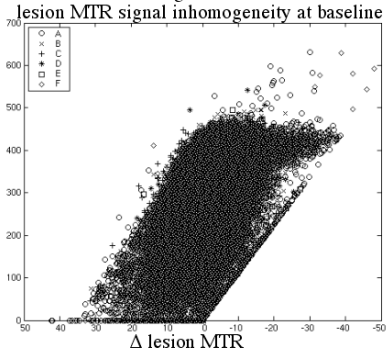
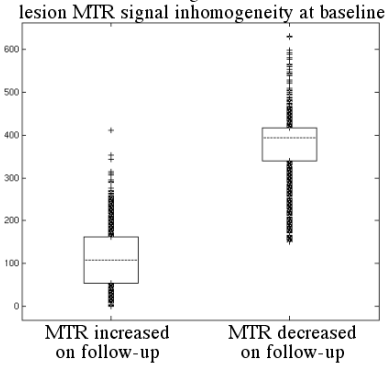


Figure 3



Examples of lesion MTR signal inhomogeneity at baseline (Fig. 1A), and change in lesion MTR ($\Delta MTR=MTR_{follow-up}-MTR_{baseline}$) (Fig. 1B), superimposed on a baseline T_2-weighted image. Notice that the regions with high MTR signal inhomogeneity (red in Fig. 1A) have decreased in MTR on follow-up (red, Fig. 1B); and regions with low MTR signal inhomogeneity at baseline (blue, Fig. 1A) have increased in MTR on follow-up (green, Fig. 1B).

In Fig.2 we show a plot of the data from all patients (labeled A→F), where each symbol represents a patient, and each data point represents a lesion voxel. The bottom limit on the value of MTR signal inhomogeneity for a given ΔMTR, results from its calculation in voxels where the baseline MTR=0. We defined a lesion voxel as significantly decreased in MTR if ΔMTR<-13.3, and increased in MTR if ΔMTR>13.3 (see Methods). We found that the lesion voxels which decreased in MTR on follow-up had a significantly higher lesion MTR signal inhomogeneity (371±71 au) at baseline compared to those which increased in MTR (111±73 au), $p<0.001$, (Fig. 3).

Discussion: We have found an association between lesion MTR signal inhomogeneity on baseline and change in lesion MTR 2 months later. This association was valid over a large range of ΔMTR (-32.5→29.4%), which is not likely to be due to the effects of edema alone, estimated at 5→8% [3]. Therefore the MTR changes and the related baseline lesion MTR signal inhomogeneity likely reflect the state of remyelination and demyelination.

Conclusions: Remyelination is of importance in MS, as demyelination is associated with axonal loss, which is the substrate for chronic disability. Our results suggest that measuring the lesion MTR signal inhomogeneity can provide a method for quantifying remyelination potential of MS lesions. This new approach to assessing demyelination and remyelination could provide an important new metric for monitoring and assessing the efficacy of therapies targeting remyelination in MS.

References: [1] Kuhlmann T et al, Brain, 125:2202, 2002; [2] Barkhof F et al, Arch Neurol, 60:1073, 2003; [3] Dousset V et al, Radiology, 182:483, 1992.