All enhancing voxels are not equal: quantifying destruction and repair within gadolinium-enhancing lesions in multiple sclerosis

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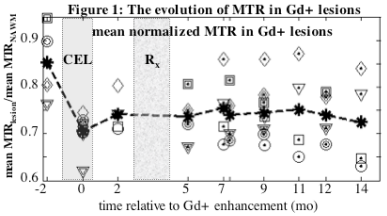
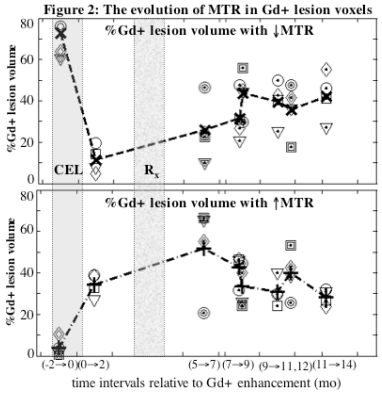
Abstract: The objective of this study was to develop methods to study the evolution of magnetization transfer ratio (MTR) changes in gadolinium (Gd) contrast-enhancing lesions (CEL) of patients with secondary progressive multiple sclerosis (MS) treated by immunoablation and autologous stem-cell transplantation (ASCT). On average, MTR decreased in CEL, partially recovered over the subsequent 2 mo, and did not change significantly after that up to 14 mo. Voxel-based analysis, however, showed that averaging over all lesion voxels hid significant heterogeneity. At the time of Gd-enhancement, 73% of the Gd-enhancing lesion voxels had decreased their MTR consistent with demyelination. The proportion of demyelinating voxels subsequently decreased, but demyelination continued over the next year affecting 42% of voxels. Remyelination, as measured by increased MTR, was active 1 month after Gd-enhancement (affecting 34% voxels), but did not peak until 6 months (52% of voxels). Remyelination was still ongoing in a smaller proportion of voxels 1 year later.

Introduction: Studies of MTR changes in Gd-enhancing lesions have shown that, on average, normalized lesion MTR decreases with the appearance of a CEL, and subsequently recovers partially within 2 mo [1]. This approach assumes that all regions of individual CELs, and all CELs in all subjects, evolve similarly. To refine this analysis, we developed methods to study the evolution of MTR changes in individual voxels of Gd-enhancing lesions. We used these methods to assess demyelination and remyelination in CEL voxels of MS patients undergoing therapy with immunoablation and ASCT.

Methods: We studied CELs in 4 secondary-progressive patients with active MS who were studied as part of the Canadian Bone Marrow Transplant trial. MRI scans, which included sequences to measure MTR, were obtained at months -2.5, -0.5, 2, 4, 6, 9 with respect to the immunoablation and ASCT. CELs were segmented manually. Two populations of CELs were followed: *i)* lesions that enhanced on the first baseline scan obtained at -2.5 mo (B1-CEL), and *ii)* lesions that enhanced on the second baseline scan obtained at -0.5 mo (B2-CEL). None of the follow-up scans showed Gd-enhancement. ***MRI analysis: Lesion-based analysis of CEL MTR recovery:*** The mean MTR was calculated for each CEL and normalized to mean MTR of 6 NAWM regions of interest from the same subject. For analysis of the B1-CEL, the second baseline scan and all follow-up scans were registered to the B1 time point, and the maps of the B1-CEL were then propagated forward to the follow-up time points. For analysis of the B2-CEL, the B1 scan and all follow-up scans were registered to the B2 time point, and the maps of the B2-CEL were then propagated backward to the B1 time point and forward to the follow-up time points. ***Voxel-based analysis of CEL MTR recovery:*** MTR difference maps were calculated for registered image pairs (-2.5→-0.5, 2→4, 4→6, 6→9 mo post-ASCT). We identified the CEL voxels with significant changes in MTR by multiplying the MTR difference maps by the CEL masks and establishing a threshold for significant change of MTR based on twice the robust range (95% of MTR values in 6 NAWM regions) at baseline. Thus, for each pair of scans for each subject, we obtained: 1) the proportion of CEL (% GdLV) that showed decreased MTR between the 2 time points and 2) the %GdLV that showed increased MTR between the 2 time points.

Results: ***Lesion-based analysis of CEL MTR recovery:*** Figure 1 shows the mean normalized lesion MTR in CELs normalized to the mean MTR in NAWM for 4 SPMS patients. Two months prior to CEL appearance, the mean normalized MTR for the *pre-lesional* regions was 0.85±0.08. At the time of contrast enhancement, the mean normalized lesion MTR decreased to 0.70±0.04, consistent with inflammatory demyelination. Two months later, still prior to ASCT, the mean normalized lesion MTR CEL regions had increased to 0.74±0.04, corresponding to the spontaneous resolution of inflammation and remyelination. There was no significant change in mean normalized lesion MTR of CEL regions after 2 mo following enhancement (p=0.65 compared to 14 mo, paired T-test). ***Heterogeneity of CEL MTR recovery between patients:*** The mean normalized MTR hid significant heterogeneity. Some patients showed continuing destruction in the CEL region. For example, subject 1 "o" (Fig 1.) showed a decrease of 7 to 10 % in mean normalized lesion MTR between contrast-enhancement and scans done 12 - 14 months later. ***Heterogeneity of CEL MTR recovery between a patient's lesions:*** A subject may have CELs that improve over time and CELs that worsen over time. For example, in Fig. 1 subject 2 "□" shows a 10 % increase in mean normalized MTR in B2-CELs over 12 mo after enhancement of lesions, and an 8 % decrease in mean normalized lesion MTR in B1-CELs over 14 mo after enhancement.





Subject	B1-CEL	B2-CEL
1	○ N=21	◎ N=23
2	□ N=14	▣ N=8
3	◇ N=21	◈ N=18
4	▽ N=6	▼ N=6
post-ASCT	•	
mean	*, ×, +	

Voxel-based analysis of CEL MTR recovery: Figure 2 (top & bottom) shows the dynamics of the MTR changes Gd+ lesion voxels. At the time of CEL appearance (–2→0 mo), MTR has decreased in a large portion of the GdLV (73±14 %GdLV) consistent with inflammatory demyelination (Fig.2, top). During the interval immediately following CEL appearance (0→2 mo), still prior to ASCT, MTR is increasing in a large proportion of GdLV (34±6 %GdLV), presumably corresponding to resolution of inflammation and remyelination in some lesion regions (Fig.2, bottom). At the same time, MTR is decreasing in a smaller proportion of GdLV (12±7 %GdLV), consistent with ongoing demyelination in some lesion regions (Fig.2, top). Surprisingly, the mean proportion of GdLV with evidence of ongoing demyelination *increases* after this time, reaching 42±12 %GdLV at 12 mo (Fig. 2, top). The mean proportion of remyelinating GdLV peaks at 6 mo (achieving 52±21 %GdLV), and then *decreases.* However, at 12 mo, 28±4 %GdLV still show evidence of active remyelination (Fig. 2, bottom).

Discussion: Using a lesion-based analysis, we found that on average, normalized MTR in CELs decreases at lesion appearance, partially recovers over the next 2 mo, and then stabilizes. However, the evolution of normalized MTR in lesions was heterogeneous, differing between individual patients and lesions. In some patients, normalized lesion MTR 12 mo after enhancement was lower than it was at the time of enhancement, suggesting ongoing demyelination and tissue destruction inside these lesions despite a "closed" blood-brain barrier. In other patients, normalized lesion MTR was higher 12 mo after enhancement than it was 2 mo after enhancement, suggesting ongoing remyelination more than 2 months after the acute phase of lesion development. To explore this heterogeneity in CEL evolution, we developed a voxel-based method to quantify MTR-increasing and MTR-decreasing processes concurrently. Our analysis revealed that demyelination and remyelination are active and occurring concurrently in CEL voxels for at least one year following enhancement. The natural course of the disease is associated with substantial repair immediately following enhancement. In our patients, the repair peaked only at 6 months, possibly reflecting an effect of the treatment. The fact that we measured MTR changes after immunoablative therapy had suppressed inflammation allows us to interpret the changes principally in terms of demyelination and remyelination without the need to consider possible inflammation-related confounds.

Conclusion: Voxel-based analysis of CEL evolution in MS patients reveals that, despite stable normalized lesion MTR, demyelination and remyelination are active for at least 12 mo following contrast-enhancement. This technique offers new possibilities for the efficient evaluation of therapeutic strategies aimed at myelin protection. and repair.

References: [1] Richert et al, Multiple Sclerosis, 2001.