Demyelination and remyelination in new multiple sclerosis lesions: Insights from serial myelin water imaging

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INTRODUCTION

Histological studies show evidence of demyelination and remyelination occurring in multiple sclerosis (MS) lesions, but the timescales are unknown since pathological studies provide only snapshots of the state of a lesion. While conventional MR imaging is very effective in detecting areas of damage and demonstrating lesions over time, it is not pathologically specific. MR measures of myelin water fraction (MWF, quantitatively related to myelin content[1]), water content (WC) and geometric mean T_2 (GMT_2), as measured by multi-echo T_2 relaxation, provide specific pathological information about a lesion, and following these measures over time can provide insight into lesion evolution. Employing a single slice T_2 measurement at 1.5T a previous study examined 3 lesions at 2 and 6 month intervals and found evidence of demyelination and remyelination occurring over a 1 year period [2]. Recent technological improvements have led to the development of a 3D multi-echo T_2 relaxation sequence at 3T, which provides a 5-fold increase in brain coverage and improved signal to noise ratio[3]. **We sought to utilize the more extensive coverage of the 3D T_2 sequence to follow MWF, WC, GMT_2 and T_1 on a monthly basis to elucidate the time course of pathological changes in new MS lesions.**

METHODS

Subjects & MR Experiments: 20 subjects with relapsing-remitting MS (15F/5M; median EDSS = 2.5; mean age = 40yrs; mean disease duration = 8.5yrs) were scanned monthly for 6 months on a Philips Achieva 3.0T system. The MR examination was centered on a transverse slab superior to the ventricles, and included the following scans (all with slice thickness=5mm) (1) **3D T_2 relaxation** (7 slices, 32 echoes, 10ms echo spacing)[3]; (2) **T_1 inversion recovery** (5 TIs (150 - 3000ms), 13 slices)[4]; (3) **B_1** (double angle method[5]); (4) **FLAIR** (for lesion detection); (5) **Post-Gad T_1** (5 minutes after the injection of gadolinium-DTPA (0.2 mL/kg)).

Analysis: At the time of new lesion appearance, regions of interest (ROIs) were drawn around gadolinium enhancing lesions on the post-gad T_1 and around contralateral normal appearing white matter (NAWM) on FLAIR and mapped onto registered images from all months. T_2 distributions were calculated for every voxel in the T_2 relaxation data set using a regularized non-negative least squares (NNLS) algorithm[6]. MWF was the area under the T_2 distribution from 0-40ms divided by the total area. GMT_2 were calculated as the mean on a logarithmic scale from 40ms<T_2<200ms. WC was determined from the total area under the T_2 distribution corrected for B_1 inhomogeneity, T_1 relaxation and normalised to external water standards. T_1 was calculated using a mono-exponential fit.

RESULTS

Eighty-four new gadolinium enhancing lesions were identified in 11 MS subjects. Figure 1 shows the changes in gadolinium enhancement, lesion size and MWF over 2 months of a new gadolinium enhancing lesion. Figure 2 shows the average lesion MWF, WC, GMT_2 and T_1 normalized to NAWM for all lesions over time (time zero is when the lesion first appeared). Only time points with greater than 30 lesions contributing were included to minimize variations due to noise. Figure 3 shows the MWF, GMT_2 and T_1 behavior of 4 lesions from one subject and 3 lesions from a second subject over time. Lesion behaviour is different for different subjects.

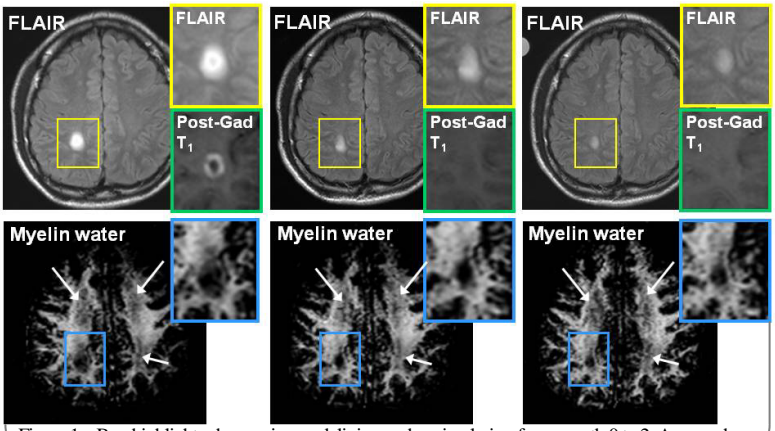

Figure 1 – Box highlights changes in a gadolinium-enhancing lesion from month 0 to 2. Arrows show diffusely abnormal white matter with reduced myelin water, not visible on conventional MRI.

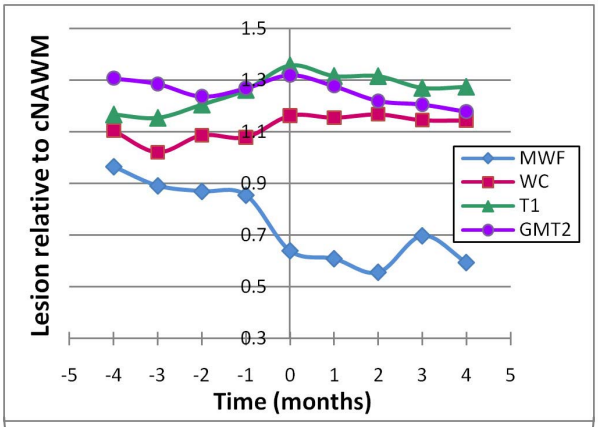

Figure 2 – Lesion MWF, WC, GMT_2 and T_1 normalized to NAWM for all lesions over time (time 0 is when the lesion first appeared).

DISCUSSION/CONCLUSIONS

This work demonstrates that MWF and WC can be used to monitor the evolution of newly active gadolinium enhancing MS lesions. Most lesions showed MWF decreases when first identified and many showed variable MWF increases during the subsequent six months. By measuring WC as well as MWF, it is possible to distinguish MWF decreases that are due to dilution effects (e.g. edema) from actual losses and gains of myelin water (demyelination and remyelination).[7]

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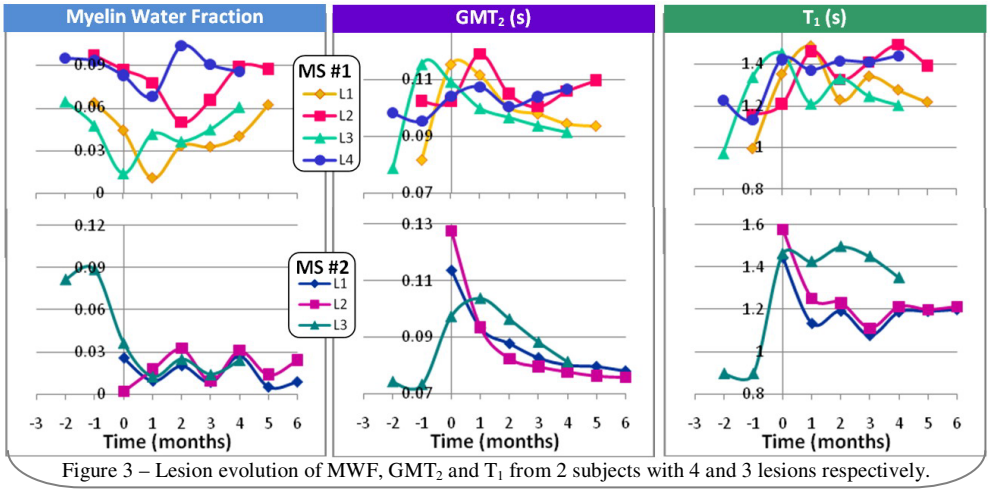

Figure 3 – Lesion evolution of MWF, GMT_2 and T_1 from 2 subjects with 4 and 3 lesions respectively.

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