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Longitudinal Change in Magnetic Susceptibility of New Enhanced Multiple Sclerosis (MS) Lesions Measured on Serial Quantitative Susceptibility Mapping (QSM)

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Abstract

Purpose—To measure the longitudinal change in multiple sclerosis (MS) lesion susceptibility using quantitative susceptibility mapping (QSM).

Materials and Methods—The study was approved by our Institutional Review Board. Longitudinal changes in quantitative susceptibility values of new enhanced-with-Gd MS lesions were measured at baseline MRI and on a follow up MRI in 29 patients within two years using a 3D multiple echo gradient echo sequence on a 3T scanner. Paired t-test and the generalized estimating equations (GEE) model was used to analyze the longitudinal change.

Results—Lesion susceptibility values relative to normal appearing white matter (NAWM) changed from 3.61 ± 6.11 ppb when enhanced-with-Gd at the baseline MRI to 20.42 ± 10.23 ppb when not-enhanced-with-Gd at the follow up MRI ($P < 0.001$).

Conclusion—MS lesion susceptibility value increases significantly as the lesion evolves from enhanced-with-Gd to not-enhanced-with-Gd, serving as a disease biomarker.

Keywords

Multiple sclerosis; quantitative susceptibility mapping (QSM); longitudinal change; magnetic resonance imaging; gadolinium enhancement

INTRODUCTION

Multiple sclerosis (MS) lesion dissemination in time and space includes myelin breaking down by inflammatory reaction, myelin debris degradation and removal by M2 microglia/macrophages, and inflammation aggravation by M1 microglia/macrophages laden with iron (1,2). Because both demyelination and iron deposition in multiple sclerosis (MS) lesions can change tissue magnetic susceptibility, gradient echo (GRE) sequence sensitive to the susceptibility induced field has been actively explored in recent years to gain new insights into multiple sclerosis (MS) lesion inflammation activity (3-13). A recent study of quantitative susceptibility mapping (QSM) in MS demonstrated that during lesion development, the magnetic susceptibility of an MS lesion increases rapidly as the lesion changes from enhanced-with-Gd to not-enhanced-with-Gd (9). However, this observation was based on cross sectional measurements of lesions at different ages, not on longitudinal follow up measurements of the same lesions. Better understanding the longitudinal pathophysiological changes underlying MS lesion development may provide new opportunities to monitor disease progression and open avenues for therapeutic intervention.

The purpose of our study was to evaluate the longitudinal change in susceptibility of MS lesions as they transition from enhanced-with-Gd to not-enhanced-with-Gd in a cohort of patients with known MS.

MATERIALS AND METHODS

Subjects

This was a retrospective study of MS patients who received care in our MS center and participated in a prospective, ongoing clinical MS MRI database. This study without informed patient consent was approved by our Institutional Review Board. We examined MR images of MS patients from August 2011 to April 2015 with at least two successive MRI sessions (baseline and follow up) that included T2-weighted (T2w), Gd-enhanced T1-weighted (T1w + Gd) and gradient echo (GRE) imaging. From this population of 445 MS patients, we applied to following inclusion criteria: 1) baseline MRI showing the appearance of a new, enhanced-with-Gd, T2w hyperintense lesion not present on brain MRI performed in the prior 1 year; and 2) documented transition to not-enhanced-with-Gd on follow up MRI. A total of 29 unique patients with a total of 52 lesions were included. The time interval between the two MRI sessions ranged from 0.1 to 2.0 years (0.91 ± 0.61 years).

Imaging Protocol and Reconstruction

All MRI scans were performed on a 3.0-T MR scanner (Signa HDxt; GE Healthcare, Milwaukee, WI), with an eight-channel head coil. The sequences for each patient were: a) T2w fast spin echo (TR/TE = 5250/86 msec, flip angle = 90° , 3-mm-thick section at 0 intervals, 416×256 matrix, 24-cm FOV), b) pre- and c) post-gadolinium three-dimensional inversion recovery-prepared T1w fast spoiled gradient echo (TR/TE = 8.8/3.4 msec, flip angle = 15° , 256×256 matrix, 24-cm FOV, $0.45 \times 0.45 \times 1.2$ mm³ resolution), d) three-dimensional T2*w spoiled multi-echo GRE sequence. Imaging parameters for multi-echo GRE sequence were as follows: repetition time, 57 msec; number of echoes, 11; echo time:

4.3, 9.1, 13.9, 18.7, 23.5, 28.3, 33.1, 37.9, 42.7, 47.5, 52.3 msec; flip angle, 20°; bandwidth, 244 kHz; field of view, 24 cm; matrix, 416×320; section thickness, 2mm. The GRE sequence was performed before Gd injection. The total data acquisition time for the four sequences in this MRI protocol was 16 minutes 30 seconds. QSM was automatically constructed from GRE data and inserted into the scanner image database within 15 min on a desktop computer connected to the scanner using the morphology-enabled dipole inversion (MEDI) (14). The images obtained by the other modalities were registered to QSM and images from the follow up MRI were registered to the baseline MRI using FSL software with the default Correlation Ratio between-modality cost function (FLIRT Linear Registration Tool, FMRIM Software Library, Oxford, England) (15).

Lesion Analysis and Measurement

After localizing all new T1w enhanced-with-Gd lesions on baseline MRI by comparing to their previous MRIs, three neuroradiologists (J.C., A.G. and G.C, with 18, 9 and 8 years of experience, respectively) independently classified all these lesions on QSM as hyperintense and isointense relative to adjacent normal appearing white matter (NAWM). All differences in lesion classification were resolved by majority.

One neuroradiologist (Y.Z., 4 years of experience), drew the areas of each localized lesion on the T2w images. As a reference region for QSM, a region-of-interest (ROI) was chosen in the NAWM at the contralateral mirror site of an identified lesion with a similar shape and size on T2w images to minimize NAWM susceptibility variation with fiber orientation and density (16); in the case of lesion or artifacts occupying the contralateral mirror site, the adjacent NAWM is used. The ROIs of lesions and NAWM references were drew on the follow-up T2w images and then were overlaid on the baseline and follow up QSM images using semi-automated software to assess values of lesion susceptibility. Veins or artifacts inside the ROIs were excluded by inspection. Lesions volume changes were measured on both baseline and follow-up T2w images.

Statistical Analysis

Continuous demographic data are presented as mean $\pm$ standard deviation. To assess a difference in unadjusted MS lesion magnetic susceptibility from baseline to follow up a paired t-test was used. Differences in lesion magnetic susceptibility between the baseline and follow up MRIs were assessed using a generalized estimating equations (GEE) model after controlling for individual lesion size and disease duration. All p-values are two-sided and evaluated at the 0.05 alpha level. All analyses were performed in SAS 9.3 (SAS Institute, Cary, NC).

RESULTS

In the 29 patients who had enhanced-with-Gd lesions on baseline MRI, a total of 512 T2w hyperintense MS lesions were found, including 58 enhanced-with-Gd lesions and 454 not-enhanced-with-Gd lesions. Of the 58 enhanced-with-Gd lesions, 6 were re-enhanced and 52 were new enhanced lesions.

In the 52 new enhanced lesions, 38 (73.1%) were isointense and 14 (26.9%) were slightly hyperintense on QSM with 100% agreement among the three neuroradiologists. 50 of them transitioned to a not-enhanced-with-Gd lesion and the remaining 2 disappeared (in all sequences) on the follow up MRI. All these 50 lesions were decided as hyperintense on QSM (although one lesion was determined as isointense by one neuroradiologist, the differences were resolved by majority). The mean interval between baseline and follow up scans was 0.91 ± 0.61 year.

There was a significant increase in lesion magnetic susceptibility as lesions transitioned from enhanced-with-Gd on baseline to not-enhanced-with-Gd on follow up (mean $\pm$ std-dev 3.61 ± 6.11 ppb in range $[-6.80, 17.05]$ ppb versus 20.42 ± 10.23 in $[5.56, 53.35]$ ppb, $P < .0001$). The susceptibility increase was consistently observed in all lesions, susceptibility difference between follow-up and baseline being 16.81 ± 9.54 in $[3.47, 54.10]$ ppb. These results are displayed in Table 1 and Figure 1. After controlling for size and disease duration in a GEE model, there was still a significant difference in susceptibility compared to NAWM between enhanced-with-Gd and not-enhanced-with-Gd lesions ($P < .0001$). Example images are shown in Figure 2, depicting changes of lesions susceptibilities from enhanced-with-Gd (QSM isointense) to not-enhanced-with-Gd (QSM hyperintense). Images in figure 3-5 include the baseline and follow up QSM of one lesion per patient in 28 patients. All lesions show isointense or slightly hyperintense on baseline QSM and hyperintense on follow up QSM.

DISCUSSION

Our study demonstrates a significant increase in the magnetic susceptibility values of MS lesions as they change from enhanced-with-Gd to not-enhanced-with-Gd. Our finding builds up a prior cross-sectional observation that suggested this lesion susceptibility increase but without statistically significant data support (9). This current longitudinal study may confirm that MS lesion susceptibility increases significantly as a lesion evolves from enhanced-with-Gd to not-enhanced-with-Gd, establishing QSM as an imaging biomarker for monitoring disease activities in MS lesions.

On routine clinical MRI scans monitoring MS patients (imaging interval ~ 6 -12 months), new T2w lesions that enhance on T1w+Gd reflect blood brain barrier (BBB) breakdown. The BBB opens in the initial inflammatory reaction, allowing for the influx of immune cells for about 3 weeks (17). The microglia/macrophages (m/M) during this period take up and degrade myelin fragments (18), which is reflected in the initial no change in the susceptibility of active lesions on QSM. Imaging outside this time window of BBB leakage would find new T2w lesions that are not-enhanced on T1w+Gd. However, after the BBB seals, immune cells remain active in brain tissue (1,19). For example, m/M remove diamagnetic myelin fragments (20), and at the same time or afterwards, m/M cells with paramagnetic iron gather both at the periphery and centrally within a lesion to further aggravate inflammation (2,21,22). Both myelin debris removal and iron accumulation likely contribute to the increase in lesion magnetic susceptibility measured on QSM. This susceptibility increase was suggested from observations in 2 patients in a prior study (9), and has been consistently observed in all 29 MS patients in this study. This susceptibility

increase during MS lesion evolution from enhanced-with-Gd to not-enhanced-with Gd provides a well-defined dynamic pattern for studying MS lesion susceptibility that otherwise appears randomly heterogeneous at a given time snap (23).

Our finding suggests that QSM is an imaging biomarker for monitoring MS lesion activities causing susceptibility changes. Currently, Gd enhancement is the clinical standard for detecting inflammatory activity in MS patients, but its sensitivity is limited to the time window of BBB breakdown (24). QSM may allow MS lesions inflammation to be monitored beyond the relatively short window during which T1w+Gd changes are detectable. In routine MRI monitoring of MS patients, new T2w lesions that are isointense on QSM may correspond to enhanced-with-Gd lesions. On the other hand, new T2w lesions that are hyperintense on QSM may instead represent relatively new but not-enhanced-with-Gd lesions with ongoing microglia/macrophage activities. These implications warrant further investigations.

One strength of our study is the use of QSM as an imaging biomarker in MS, unlike the GRE T2* weighted (T2*w) magnitude or phase imaging which have been the focus of a large body of literature (3-13) but are limited because they are not direct measurements of tissue susceptibility: GRE T2*w hypointensity and phase contrast at a given voxel depend not only on the tissue susceptibility in that voxel but also on that of the nearby voxels in a complex fashion which also is influenced by imaging parameters including field strength, echo time and object orientation. These problems are addressed in quantitative susceptibility mapping (QSM) by deconvolving GRE phase data with the dipole kernel that connects tissue susceptibility with the magnetic field estimated from MRI phase (25,26) in this study.

There are a few limitations in our study. First, in the follow up MRI, the time interval between two scans was not constant across patients. Future prospective longitudinal investigations would benefit from a uniform time interval between scans. Second, the ROI analysis was performed only by one neuroradiologist. The tedious workload of manual ROI made it impossible in busy practice to require additional neuroradiologists for repeating ROI. This problem may be addressed with automated ROI tools. Third, we did not have pathology data to measure directly the contents of myelin and iron and the activities of m/M. Future studies on the relationship between pathology and lesion MR changes may be performed on MS brain samples. Finally, further work is needed to evaluate therapeutic response and potential lesion recovery on QSM to increase the clinical value of this imaging technique to the care of MS patients.

In conclusion, our longitudinal data confirm that the magnetic susceptibility of an MS lesion increases significantly as it evolves from enhanced-with-Gd to not-enhanced-with-Gd, establishing QSM as an imaging biomarker for monitoring MS disease activities.

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Figure 1.
Longitudinal measurements of MS lesion magnetic susceptibility relative to normal appearing white matter.

Figure 2.

MR images of enhanced-with-Gd lesions in a 40-year-old man with relapsing-remitting MS.

a) T2w, b) T1w+Gd and c) QSM at baseline MRI scan. d) T2w, e) T1w+Gd and f) QSM at follow up scan four months later. One enhanced-with-Gd lesions (b, arrows) were found in the first T1w+Gd and appeared QSM isointense (c, box). Four months later, it changed to not-enhanced-with-Gd in T1w+Gd (e, arrows) and appeared hyperintense in QSM (f, box).

Figure 3. 28 pairs of lesion on baseline and follow-up QSM images. (a, baseline, white arrows and b, follow up, black arrows).

Figure 4. 28 pairs of lesion on baseline and follow-up QSM images. (a, baseline, white arrows and b, follow up, black arrows).

Figure 5. 28 pairs of lesion on baseline and follow-up QSM images. (a, baseline, white arrows and b, follow up, black arrows).

Table 1

Relative Quantitative Susceptibility and Volume Change of Enhanced-with-Gd Lesions in Two Successive MRIs

	Baseline MRI	Follow up MRI
No. of patients	29	29
Age of patients (y)	36.5 ± 6.97	37.2 ± 7.1
Follow-up time interval (y)	0	0.91 ± 0.61
No. of lesions	52	50 [*]
Volume of lesions on T2w (mm ³)	383 ± 410	148 ± 129
Susceptibility relative to NAWM (ppb)	3.61 ± 6.11	20.42 ± 10.23

^{*} Of 52 enhanced-with-Gd lesions appeared at the baseline QSM, 50 lesions were found at the follow up MR imaging and 2 lesions disappeared on all sequences. Therefore, they were not available to measure lesions volume and susceptibility in the follow up MR imaging.