Iron and Non-iron Related Pathological Features of Multiple Sclerosis Lesions using Multiparametric 7T MRI

Sanjeev Chawla[1], Ilya Kister[2], Jens Wuerfel[3], E Mark Haacke[4], Tim Sinnecker[3], Jean Christophe Brisset[1], Friedemann Paul[3], and Yulin Ge[1]

[1]Radiology, New York University Langone Medical Center, New York, NY, United States, [2]Neurology, New York University Langone Medical Center, New York, NY, United States, [3]Radiology, Universitätsmedizin Göttingen, Berlin, Germany, [4]Radiology, Wayne State University, Detroit, Michigan, United States

Introduction: Multiple sclerosis (MS) is an inflammatory, demyelinating and neurodegenerative disease of CNS. The classic pathological hallmarks of MS lesions include edema due to inflammation demyelination, gliosis and axonal loss. Recent studies have also reported abnormal iron accumulation in MS lesions.[1,2] Several histopathological reports of MS suggested that the iron content can be increased or decreased, and these changes can be subtle and are related to dying oligodendrocytes (iron release), microglia and macrophage activities (increased iron uptake), and upregulation of iron-exporting ferroxidases (iron decrease) in the plaques [3,4]. Owing to better spatial resolution, higher signal-to-noise ratio and increased susceptibility effects, ultrahigh field MRI (e.g. 7T) has shown markedly improved the detection of iron-containing pathology with gradient echo or susceptibility weighted imaging (SWI).[5] Abnormal or excessive iron accumulation is also considered promoting oxidative injury of brain tissues.[6] Recent advances[7] of quantitative susceptibility mapping (QSM) also provides a useful tool in quantification and differentiation of paramagnetic iron content from diamagnetic materials (e.g. myelin, calcification), which are indistinguishable on SWI. The purpose of the present study was to explore the potential of multiparametric 7T MRI including T1, T2, T2*/SWI, and QSM imaging to characterize MS lesions based on iron and non-iron related pathological features.

Methods: Twenty-one clinically confirmed MS patients (mean age=49.2±11.7 years) underwent imaging at 7T (Siemens) MRI using a 24-channel Nova head array coil. The imaging protocol included standard GRE-T2*, 3D T1-weighted MPRAGE, and 3D T2-weighted FLAIR imaging, and high resolution (in plane: 0.23x0.23mm^2) 3D SWI with the following parameters: TR/TE=27/18ms, flip angle=18°, BW=110Hz/px, slice thickness=2mm, FOV=240mm^2, base resolution=1024, acquisition time=7:49min, IPAT factor=2. An in-house developed susceptibility weighting imaging map (SWIM) algorithm was used to reconstruct QSM maps. Patterns of MS lesions were assessed based upon the differential signal intensity on GRE-T2*, SWI and QSM images. Lesions were classified as iron laden pathology (if lesions demonstrated hypointensity on T2* and/or SWI images and hyperintensity on QSM) and non-iron laden pathology (if lesions were hyperintense on T2* images and inconspicuous or hyperintense on QSM). QSM values computed from all lesions which demonstrated hyperintensity on QSM. A two-tailed student t-test was performed to compare the QSM values between pattern B and pattern C lesions.

Results and Discussion: A total of 345 MS lesions were observed. Of 21 patients, 19 MS patients (90.5%) had at least one QSM hyperintense lesion. Based upon the signal intensity on GRE T2*, SWI and QSM, three morphologically distinct lesion patterns were observed (Fig. 1). Majority of the lesions (n=259, 75.0%, Fig. 2) were hyperintense on T2* images and inconspicuous on QSM (**Pattern A**), suggesting variable degree of demyelination, micronecrosis, edema, and gliosis, which T2 FLAIR and T1-weighted imaging provided additional verification. Some lesions (n=33, 9.56%) showed hyperintensity on T2* and hyperintensity on QSM (**Pattern B**), suggesting lesions with non-iron related pathology but likely with extensive demyelination. We found 15.5% (n=53) lesions demonstrating hypointensity on T2* and/or SWI images and hyperintensity on QSM (**Pattern C**) indicating that that these lesions encompass predominant iron content. Iron laden lesions (Pattern C, 34.7 ±17.5ppb) had significantly higher QSM values than non-iron laden lesions (pattern B, 21.7±9.5ppb, p<0.001) (Fig. 3). The iron deposits in pattern C lesions are likely to be caused by iron rich, non-phagocytic and pro-inflammatory microglia. A vast majority of MS lesions were inconspicuous on QSM images and this pattern is often seen in chronic lesions[8] where positive phase shift (paramagnetic) caused by demyelination and negative phase shift (diamagnetic) caused by the destruction of micro-architecture (edema, micronecrosis, and gliosis) counteract each other.

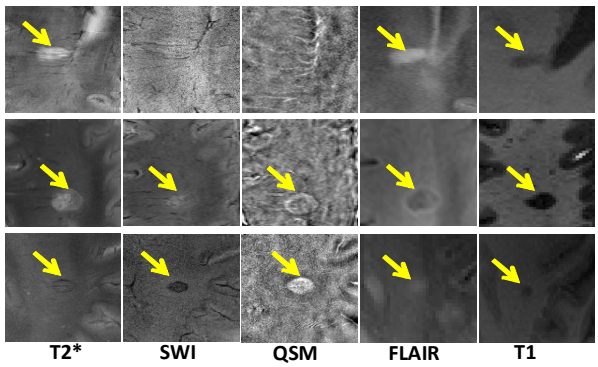

Figure 1. Three different patterns of MS lesions and on GRE T2*/SWI and QSM signals. Pattern A lesions were hyperintense on T2* images but were not visible on QSM. Pattern B lesions were hyperintense on both T2* and QSM. Pattern C lesions showed hypointesnity on T2*/SWI and hyperintensity on QSM.

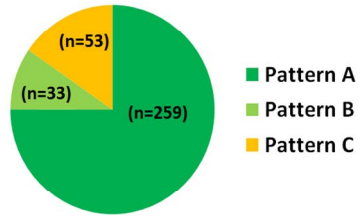

Figure 2. Pie chart shows the distribution of lesions into three morphological patterns in MS. Majority of the lesions (84.6%) were related to non-iron pathology (Patterns A+B). Only 15.4% of the lesions were related to iron pathology (Pattern C).

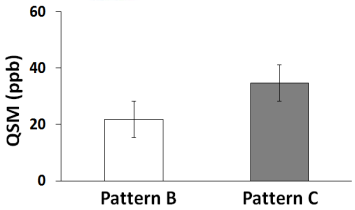

Figure 3. Bar diagram showing variations in mean QSM (ppb) from pattern B and Pattern C lesions. Iron laden lesions (pattern C) had significantly higher QSM than non-iron laden lesions (pattern B). Error bars indicate ± 1SD. * indicates significant difference (p <0.001).

Conclusions: Ultra-high field MRI provides *in vivo* insights into the lesion pathogenesis, activity, and iron-related tissue and cellular degeneration. Our data showed different imaging patterns of MS lesions, which can be used for future longitudinal monitoring of evolution of iron-laden and non-iron laden pathology.

Acknowledgement: This work was partly supported by grant numbers: NS-029029, 3NS-029029-20S1 and 5NS-076588 from National Institute of Health (NIH) and Research Grant (RG4707A1) from National Multiple Sclerosis Society (NMSS). This study was also supported by 'Cure Grant' from Guthy Jackson Charitable Foundation and Research Grant from Nat'l MS Society.

References: **1.** Haacke EM, J Magn Reson Imaging. 2009;29:537-44. **2.** Wisnieff C, Magn Reson Med 2014: Aug 18. **3.** Hametner S, Ann Neurol 2013:74:848-61. **4.** Mehta V PLos One 2013; Mar 14. **5.** Al-Radaideh AM. Mult Scler. 2013;19:896-903. **6.** Stephenson E. Nat Rev Neurol. 2014;10:459-68. **7.** Absinta M. Ann Neurol 2013;74, 669-78. **8.** Pitt D. Arch Neurol. 2010;67:812-8.