Validations of Quantitative Susceptibility Mapping in Excised Human Cerebral Cavernous Malformation Lesions and in Mice

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Introduction: Quantitative susceptibility mapping (QSM) is a new technique with the potential to estimate brain iron contents (1-2). Limited validations were performed on post mortem brains (3-4). To our best knowledge to date, QSM has not been fully tested in a human disease model with pathophysiological tissue validation. In this study, we performed QSM in cerebral cavernous malformation (CCM) lesion specimens excised during surgery, and correlated to the iron estimation by Inductively Coupled Plasma Mass Spectrometry (ICPMS). In addition, we performed qualitative comparison between susceptibility distributions measured by QSM and histology in a CCM murine model.

Methods: Cerebral cavernous malformation (CCM) is a common hemorrhagic vascular anomaly of the human brain, characterized by high lesional iron deposition from hemoglobin breakdown products. All imaging data was acquired on a Siemens Verio 3T scanner using a 3D, multi-echo, T2*-weighted, spoiled gradient echo sequence. Image reconstruction was performed offline using MEDI (5). A custom 1.5 cm single loop coil (Stark Contrast, Erlangen, Germany) was used for data collection. Both the ex-vivo CCM lesion fragments and the mouse brain were immersed in formalin in a vial, bottom of which was filled with Agar gel prior to imaging. The imaging parameters were: TE [min, max] = [4, 52] ms; TR = 58ms; flip angle = 15°; field of view = 25 x 50 mm; acquisition matrix = 64 x 128; slice thickness = 0.4 mm. The imaging time was 2 minutes and 29 seconds.

Four human CCM lesions were extracted during surgery. The lesion specimens were stored in 10% formalin. Lesions with a volume diameter greater than 10mm were cut into 4 – 6 smaller pieces and each piece was imaged separately. A total of 18 fragments were obtained for imaging. In the animal study, three $Ccm3^{+/-}$ $Trp53^{-/-}$ mouse brains were used for imaging. Serial 1-mm-thick coronal slices of each brain were microsectioned at 5 μm and performed by Perls' staining to visualize iron deposition. Regions of interest identified iron "patches" on histology (Perls' blue staining) and QSM images. Cross comparisons were performed to determine the sensitivity and specificity of QSM.

Results: The mean and total susceptibility values of the human lesion specimens and the ICPMS results were plotted in Figure 1. Chemical analysis of all lesion fragments revealed the total iron content ranged from 0.0033 to 0.2158 mg and concentrations from 0.057 to 2.57 mg/g wet tissue. The susceptibility was correlated to the iron content by mass spectroscopy with a correlation coefficient of 0.999 ($p < 0.01$) for total iron and 0.86 (0.96 excluding the first sample point as an outlier) for iron concentration. In the murine study, local susceptibility distribution by QSM correlated well with the iron deposition in tissue based on qualitative comparison (Figure 2). QSM achieved a sensitivity of 0.79 ($p < 0.01$) and specificity of 0.94 ($p < 0.01$).

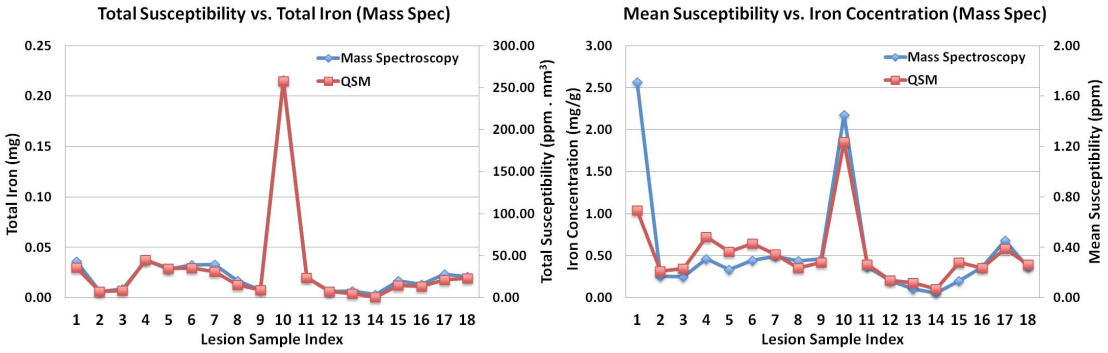

Figure 1. lesion sample validation results. The cause for the high iron concentration in lesion sample 1 is unknown, likely a consequence of instrumentation errors.

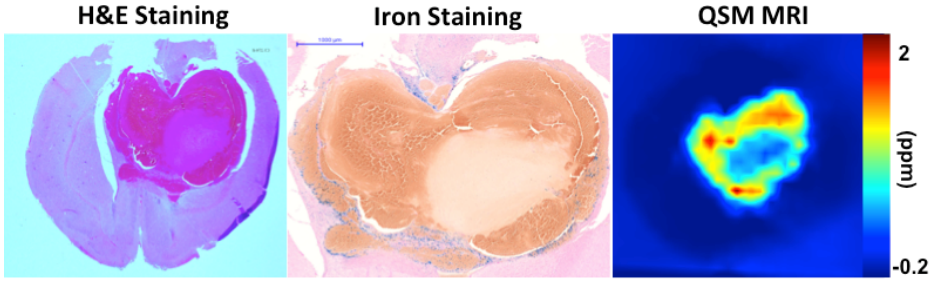

Figure 2. Comparison of H&E staining, Perls' blue string, and QSM images of the CCM mouse brain. A positive correlation in iron deposition patterns within the lesion is identified.

Conclusion: QSM, a non-invasive imaging technique, is feasible and may provide quantitative evaluation of iron burden in human CCM lesions. Our preliminary findings indicates QSM may be applied as a novel imaging biomarker to access iron burden in lesions, for the longitudinal monitoring of disease progression and response to potential therapeutic interventions.

References: 1) Rochefort et. al. MRM. 2010. 2) Schweser et. al. Neuroimage. 2011. 3) Zheng et. al. Neuroimage, 2013. 4) Langkammer et. al. Neuroimage 2012. 5) Liu et al. MRM. 2011.