Abnormal Iron Levels in the Brain of Pediatric Sickle Cell Disease Patients: a Study using Quantitative Susceptibility Mapping (QSM)

Deqiang Qiu[1], R Clark Brown[2,3], Binjian Sun[4], Susan Palasis[4], Thomas G Burns[5], and Richard A Jones[1,4]

[1]Radiology, Emory University, Atlanta, GA, United States, [2]Haematology, Children's Healthcare of Atlanta, Atlanta, GA, United States, [3]Haematology, Emory University, Atlanta, GA, United States, [4]Radiology, Children's Healthcare of Atlanta, Atlanta, GA, United States, [5]Neuropsychology, Children's Healthcare of Atlanta, Atlanta, GA, United States

Target Audience: Radiologists and Clinical Scientists

Introduction: Pediatric sickle cell disease patients with high cerebral blood flow receive chronic blood transfusion to reduce the risk of stroke. As a result they suffer from systematic iron overload that affects multiple organs[1]. While iron overload of the liver and heart has attracted much interest, the effects of blood iron overload on brain iron level of these patients have received less attention. Quantitative Susceptibility Mapping[2] is a recently developed MR method that measures tissue magnetic susceptibility from phase images and is sensitive to iron content in the brain. In the current study, we used QSM to quantify iron storage in the brain of patients with sickle cell disease and compare the findings with age matched normal subjects.

Method: Twenty-five sickle cell patients and 23 age matched healthy normal volunteers were recruited for the study. The mean/SD of age was 13.3/2.8 and 14.0/3.3 years for the patient and the control groups respectively. MRI scan was performed using a Siemens 3T scanner, and included a 3D multi-echo gradient-echo sequence for QSM (FOV=256x192mm, Matrix=256x192, Slice thickness = 2mm, 72 slices, TR = 50 ms, first TE = 3.7ms, 12 echoes, echo spacing = 3.8ms) and a T1 weighted (T1w) structural imaging sequence using MPRAGE for anatomical identification and image normalization. Only the even echoes were used for following QSM processing since the even echoes are flow-compensated in the readout direction. The processing was performed using a software package developed in-house. The phase image from each echo was first unwrapped using a Laplacian method followed by spherical mean filtering to remove the background field to generate the filtered field map. The filtered field maps from each echo were then averaged to increase the signal-to-noise ratio. An L1-norm optimization based method[3] was used to reconstruct susceptibility map from the mean field map.

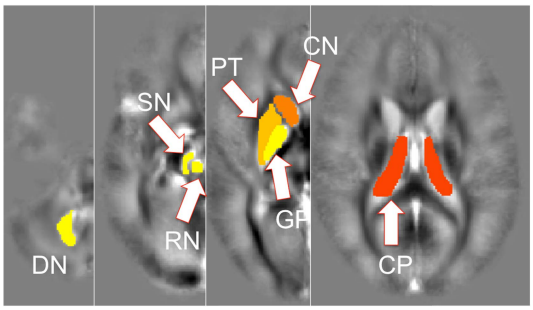

Fig. 1 shows placement of ROIs in the choroid plexus (CP), caudate nucleus (CN), putamen (PT), globus pallidus (GP), red nucleus (RN), substantia nigra (SN), dentate nucleus (DN)

All QSM images were normalized to a standard brain template in SPM using the T1W image as a medium, and the mean susceptibility image was created. Region-Of-Interests (ROI) were drawn on the mean susceptibility map and included bilateral caudate nucleus (CN), putamen (PT), globus pallidus (GP), red nucleus (RN), substantia nigra (SN), dentate nucleus (DN) and choroid plexus (CP) (Fig 1). The mean susceptibility value (SV) was calculated as the mean value of all voxels with positive susceptibility values within a ROI as defined above; the restriction to positive voxels was imposed to improve the sensitivity and avoid the inclusion of neighboring white matter. General linear model analysis was performed to compare differences in the susceptibility value of the ROIs between the patient and control groups using age as a covariate.

Results: Qualitatively, QSM nicely depicts regions known with high iron concentration, including the globus pallidus, substantia nigra and dentate nucleus. Fig. 2 shows a case where high susceptibility value was observed in the choroid plexus of a sickle cell patient and a similar slice from a control is shown for comparison. Table 1 shows the mean and standard deviation of the susceptibility values of different ROIs between the patient and control groups. After controlling for the effect of age, significantly higher susceptibility values were found in the patient group in choroid plexus, red nucleus and dentate nucleus, suggesting high iron loading in these regions. The analysis also showed significantly increasing susceptibility values with age in many of the regions including caudate nucleus, putamen, globus pallidus, substantia nigra, red nucleus and dentate nucleus. Figure 3 illustrates the relationship of susceptibility value of the globus pallidus with respect to age.

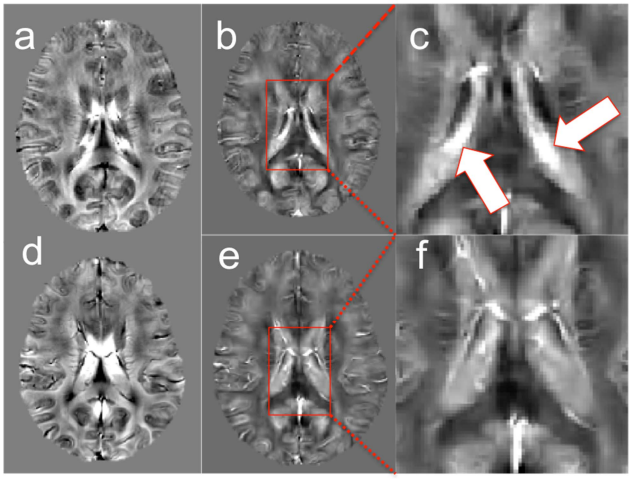

Fig 2. Shows (a, d) processed field map, (b, e) susceptibility image, (c, f) zoom-in of susceptibility map in choroid plexus region for a patient on the top panel and for a control subject on the bottom panel. High susceptibility value can be observed in the choroid plexus of the sickle cell disease patient (arrows) indicating high iron concentration in these regions.

Discussion: QSM is sensitive to iron deposition in the brain, and can nicely visualize areas with high concentrations of iron. We found significantly increasing susceptibility values in multiple ROIs examined, which is consistent with the literature. After controlling for the effect of age, significantly higher iron concentration was found in sickle cell disease patients in the choroid plexus, red nucleus and dentate nucleus. The former has recently been proposed as having an important role in brain iron transport[4], while the latter two are known sites of iron deposition A possible contributing factor to the increased iron content in these regions is the high systemic iron level of these patients due to their blood transfusion therapy. The ability to image brain iron level with QSM provides valuable information that may permit customized treatment strategy for individual patients. In conclusion, QSM is sensitive for measuring iron concentration in the brain of sickle cell patients and provides a valuable tool for iron assessment for both clinical trials and individual evaluations.

References: ***1.*** Harmatz P, et al. Blood.2000; 96:76-79. ***2.*** Shmueli K, et al. *MRM* 2009;62:1510-1522; 17:1141-1148. ***3.*** Qiu D et al. ISMRM. 2011;19:4470. 4 Rouault et al. Metab Brain Dis. 2009 24(4): 673–684

	CP	CN	PT	GP	SN	RN	DN
Patient Mean (SD) 10^{-2}ppm	3.66 (1.74)	2.45 (0.42)	1.61 (0.44)	6.79 (1.13)	4.53 (1.28)	3.92 (1.38)	3.11 (1.36)
Control Mean (SD) 10^{-2}ppm	2.34 (0.37)	2.47 (0.42)	1.80 (0.42)	7.06 (1.14)	4.43 (0.97)	3.14 (0.93)	2.47 (1.09)
P value (Group difference)	<0.001*	0.909	0.230	0.745	0.610	0.006*	0.004*
P value (age)	0.087	0.016*	<0.001*	<0.001*	0.076	0.002*	<0.001*

Table 1 shows mean and standard deviation of susceptibility values of both patient and control groups in different ROIs. P values for age effect and group difference between patients and controls are also shown.

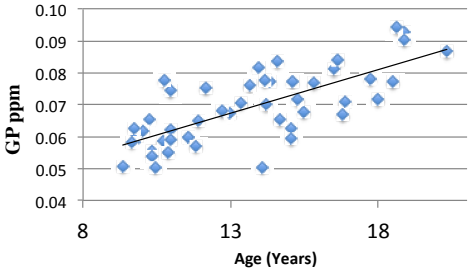

Fig 3. Scatter plot of susceptibility value of globus pallidus (GP) with age