Regional Susceptibility to Chronic Anemia in WM Microstructure Using Diffusion Tensor Imaging

Soyoung Choi[1,2], Adam Bush[3], Matt Borzage[2], Anand Joshi[4], Thomas D Coates[2], Richard M Leahy[4], and John C Wood[2]

[1]Neuroscience Graduate Program, University of Southern California, Los Angeles, CA
[2]Department of Pediatrics and Radiology, Children's Hospital Los Angeles USC, Los Angeles, CA
[3]Department of Biomedical Engineering, University of Southern California, Los Angeles, CA
[4]Signal and Image Processing Institute, University of Southern California, Los Angeles, CA

Introduction

White matter strokes are a major concern for patients with sickle cell disease and other forms of anemia. SCD patients are known to have diffuse white matter volume loss, abnormal WM microstructure, silent strokes, and poor neurocognitive function.[1,2] Similar neurological abnormalities have been described in thalassemia intermedia.[3] Low levels of hemoglobin have been associated with risk of silent cerebral infarctions across patient populations with chronic anemia and severe anemia may increase the risk for cerebral vascular accidents.[4,5,6] In this current study, we use MRI brain mapping techniques to explore the relationship between a wide range of hemoglobin levels and WM neural tissue properties.

Subjects

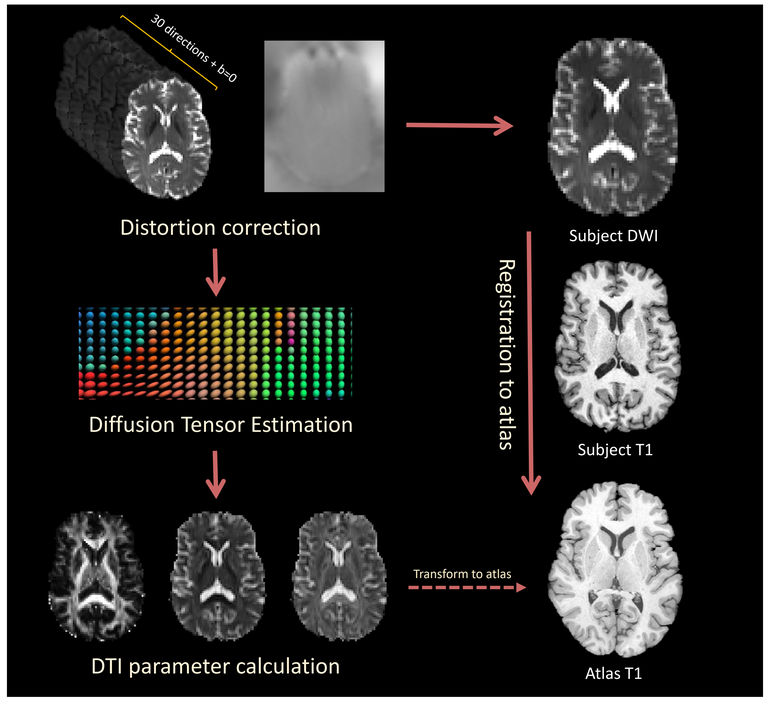
16 SCD patients (age=26.1 ± 10.3; F=9, M=7; hemoglobin=9.4 ± 2.1), 8 patients with non-sickle anemia (age=23.6 ± 7.4; F=4, M=4; hemoglobin=12.2 ± 3.2), and 15 control subjects (age=22.8 ± 7.2; F=10, M=5; hemoglobin=13.2 ± 1.3) were recruited with informed consent or assent; the study was approved by the Institutional Review Board at Children's Hospital Los Angeles (CCI#11-00083). Exclusion criteria included pregnancy, previous overt stroke, acute chest, or pain crisis hospitalization within one month. MRI data were acquired on a 3T Philips Achieva (v.3.2.1) using an 8-channel head coil.

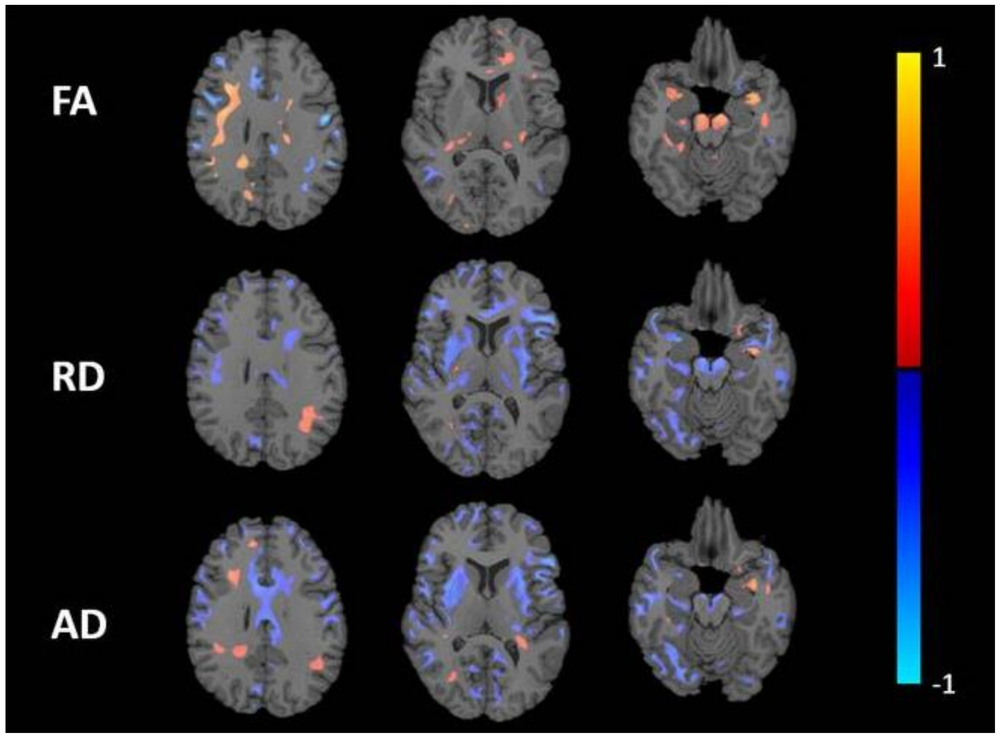
	SCD	ACTL	CTL
N	16	8	15
Age	26.1 ± 10.3	23.6 ± 7.4	22.8 ± 7.2
Male:Female	7:9	4:4	5:10
Hemoglobin	9.4 ± 2.1	12.2 ± 3.2	13.2 ± 1.3

SCD: sickle cell disease; ACTL: non-sickle anemia; CLT: control

Methods

3D T1-weighted images (TE =3.8ms TR =8.3ms; resolution = 1mm^3) were pre-processed using BrainSuite (brainsuite.org) and registered to a common atlas space using Surface Volume Registration (SVReg15a). Diffusion weighted images (TE = 2.5ms; TR = 4.8ms; 2.5mm isotropic voxels) included 30 diffusion-encoding directions at b-value=1000m/s^2 and a reverse-gradient b=0. Fieldmaps were estimated using FSL's topup module. BrainSuite Diffusion Pipeline (BDP15a) performed distortion correction, co-registration to T1-weighted images, and diffusion tensor modeling. Voxel-wise calculations of DTI metrics including fractional anisotropy (FA), axial diffusivity (AD), and radial diffusivity (RD) were transferred to the common atlas space. Pearson correlations were performed using BrainSuite Statistics Toolbox.





Significant correlations of hemoglobin to FA (top row), RD (middle row), and AD (bottom row) labeled on the T1 MR image of the atlas template.
R-values are labeled according to the color bar (on right) where red indicates a positive correlation while blue indicates a negative correlation. Results are thresholded to have a minimum 1cm^3 cluster size.
Three corresponding axial slices are shown from top (left panel) of the brain to the bottom of the brain (right panel)

Results

Hemoglobin was correlated to FA, AD, and, RD in multiple brain regions after controlling for age and sex. The colorbar represents the r-value for the correlations (red positive, blue negative) and only statistically significant values of a 1 cm^3 minimum cluster size are displayed. Anemia was associated with decreased FA (red) and increased RD and AD broadly over the brain (blue), including corpus callosum, subcortical nuclei, and frontal and parietal white matter. These regions represent classic "watershed" areas that are the primary targets of silent strokes in sickle cell disease, hypertension, aging, and obstructive sleep apnea.

Discussion

Our study suggests that the severity of anemia, rather than the type of anemia, is the primary risk factor for white matter damage. Low hemoglobin concentration correlated to decreases in FA and increases in RD and AD, suggestive of decreasing WM microstructural integrity. Interestingly, the regions of abnormal diffusivity parallel the pattern of regional vulnerability to stroke in SCD patients in previous literature (frontal lobe > parietal lobe, subcortical nuclei, > temporal lobe, >> occipital lobe and cerebellum). While silent strokes and abnormal diffusivity co-localize, the volume of infarcted tissue is much smaller, suggesting that changes in RD and AD are detecting preclinical white matter injury in anemic patients. Large clusters of correlating voxels were located along pathways of the superior longitudinal fasciculus (SLF), inferior longitudinal (ILF), cingulum, cortico-spinal tract (CST), and cortico-cerebellar tract which may help us to predict the functional consequences of WM injury due to anemia. We postulate that anemia, by depleting cerebrovascular reserve, leaves patients vulnerable to acute interruptions in supply or increases in metabolic demand. Our observations may have important implications for choosing set points for chronic transfusion therapy in anemic patients.

References

1. Platt OS, Brambilla DJ, Rosse WF, et al. Mortality in sickle cell disease. Life expectancy and risk factors for early death. *N Engl J Med*. 1994;330(23):1639-44. doi:10.1056/NEJM199406093302303.
2. Schatz J, White D a, Moinuddin A, Armstrong M, DeBaun MR. Lesion burden and cognitive morbidity in children with sickle cell disease. *J. Child Neurol.* 2002;17(12):891–5.
3. Borzage MT, Bush AM, Choi S, et al. Predictors of Cerebral Blood Flow in Patients With and Without Anemia. *J. Appl. Physiol.* 2016;jap.00994.2015.
4. DeBaun MR, Sarnaik S a, Rodeghier MJ, et al. Associated risk factors for silent cerebral infarcts in sickle cell anemia: low baseline hemoglobin, sex, and relative high systolic blood pressure. *Blood*. 2012;119(16):3684–90.
5. Bush AM, Borzage MT, Choi S, et al. Determinants of resting cerebral blood flow in sickle cell disease. *Am J Hematol.* 2016;9(91):912-917. doi: 10.1002/ajh.24441
6. Choi S, Bush AM, Borzage MT, et al. Hemoglobin and Mean Platelet Volume Predicts Diffuse T1-MRI White Matter Volume Decrease in Patients with Sickle Cell Disease. *Neurology.* Submitted 2016.

neuroimage.usc.edu/~choisoyo

This work was supported by NHLBI (1U01-HL-117718-01), NCRR (5UL1 TR000130-05), NIH (R01 NS074980), and NIH T32 (MH 111360-1 A1). Philips Healthcare provided support for protocol development and applications engineering on a support-in-kind basis.