Hemoglobin Level and Platelet Size Predicts Grey and White Matter Volume Loss Measured By Tensor Based Morphology in Sickle Cell Disease

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

Sickle cell disease (SCD) is a life-threatening genetic disease whose patients suffer from chronic anemia, hemolysis, vascular damage, and impaired cerebral blood flow that lead to early and cumulative neurological insults.[1,2] Patients with SCD have increased cerebral blood flow to compensate for their anemia but nevertheless exhibit regional cerebral hypoperfusion and neurocognitive decline.[1,3,4] Silent strokes and white matter atrophy are common in patients with sickle cell anemia, but the mechanism is unknown. We have previously shown that resting blood flow is increased in these patients such that oxygen delivery is preserved under unstressed conditions.[5] However, resting hyperemia results in blunted vasodilatory reserve, potentially leaving patients at risk for cerebral ischemia in response to desaturation events, acute anemia, or increased metabolic demands.

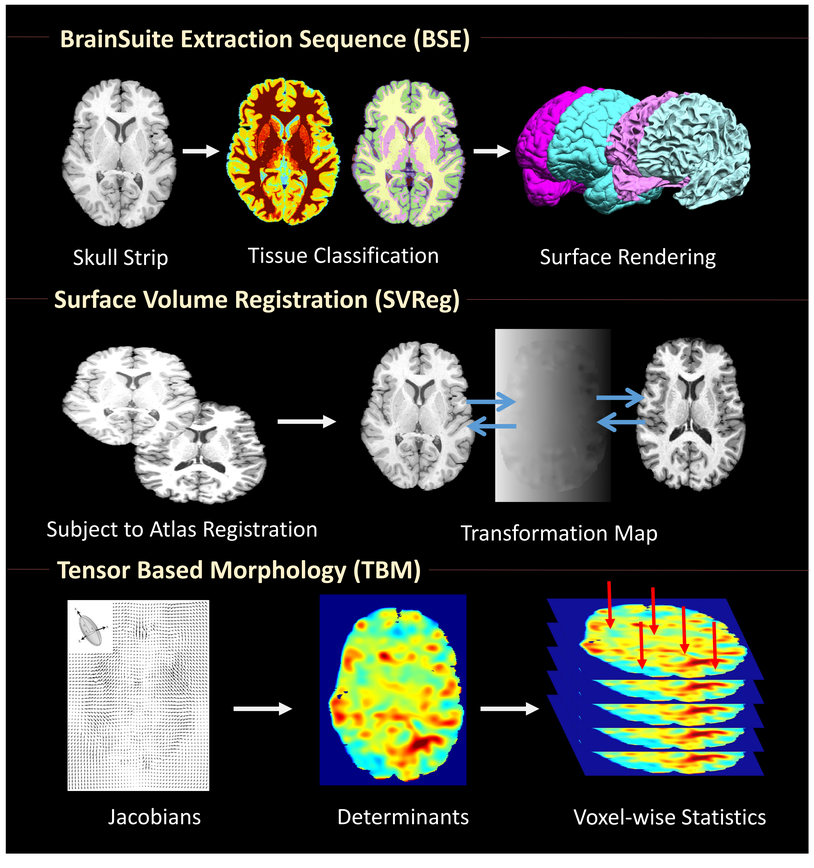
Subjects

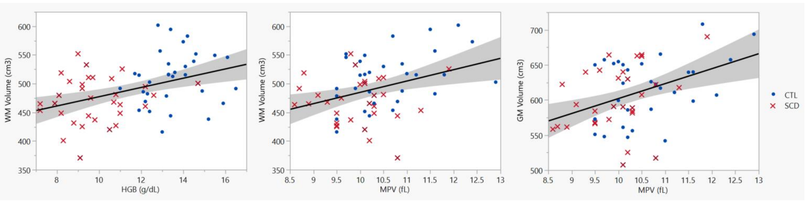
3D T1-weighted MR images (TE =3.8ms TR =8.3ms; resolution = 1mm^3) were acquired on a 3T Philips Achieva (v.3.2.1) using an 8-channel head coil on 33 clinically asymptomatic SCD patients (age=21.3 ± 7.8; F=18, M=15) and 32 ethnically matched control subjects (age=24.4 ± 7.5; F=22, M=10) were recruited as part of a study on Sickle Cell Disease. All patients 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.

	SCD	Control	p-value
N	33	32	
Age	21.3 ± 7.8	24.4 ± 7.5	NS
Male:Female	15:18	10:22	NS
WM Volume (cm^3)	470.8 ± 40.0	510.1 ± 46.1	0.0005
GM Volume (cm^3)	600.6 ± 47.7	615.0 ± 44.5	NS
Hemoglobin	9.7 ± 1.6	13.5 ± 1.4	<.0001
Mean Platelet Volume	10.0 ± 0.7	10.6 ± 0.9	0.0029

Methods

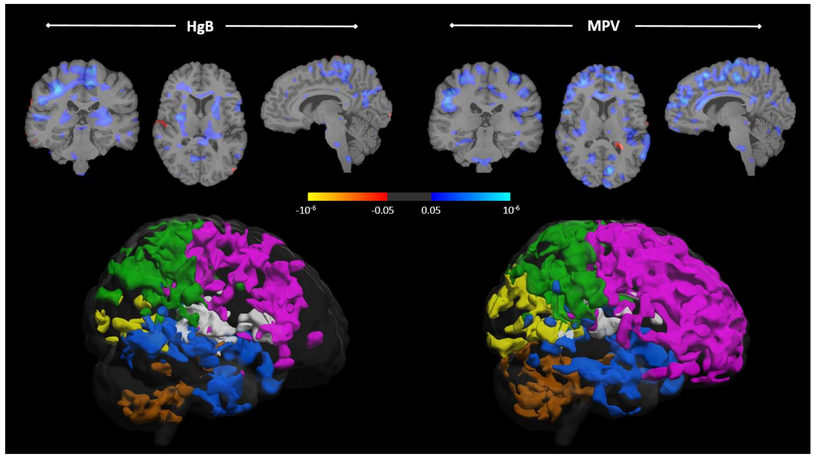
T1 images were processed using BrainSuite (brainsuite.org) in a semi-automated fashion. Stepwise multivariate regression analysis was run on whole brain GM and WM volume against laboratory data and vital signs to find predictors of total brain volume. Laboratory data probed including complete blood counts and indices, quantitative hemoglobin electrophoresis, and markers of hemolysis (LDH, reticulocyte count, cell free hemoglobin). After correcting for age and sex, the remaining predictors of grey and white matter volume were used to probe for voxel-wise changes in brain volume through tensor based morphometry (Brain Suite Statistics Toolbox).





Results: Hematological Predictors of Brain Volume

White matter, but not grey matter, was diffusely smaller in SCD patients. Sex, age (log transformed) and mean platelet volume (MPV) were the parameters retained in the multivariate model to predict GMV (r^2=0.65; F ratio=28.9) where MPV had a positive correlation to GMV. (right panel) Hemoglobin, sex, and MPV were found as predictors of WMV (r^2=0.43; F ratio = 11.8) where both hemoglobin and MPV had a positive correlation to WMV. (left and middle panel)



Results: Voxel-wise Correlations

Using tensor based morphometry (TBM), both hemoglobin (left panel) and MPV (right panel) were positively associated with brain volume changes diffusely in the frontal, parietal, and temporal cortices. Hemoglobin had a strong localized effect on the subcortex (white matter and basal ganglia) suggesting that anemia was associated with volume loss in these areas. MPV overall was found to have a strong effect on cortical morphology diffusely.

Discussion

Hemoglobin's relationship to brain volume and morphology suggests global white matter shrinkage due to anemia. The association is strongest in the phylogenetically younger portions of the brain and co-localizes with brain regions impacted by silent stroke. MPV was an unexpectedly strong predictor of cortical volumes in both SCD and control subjects. MPV is an indicator of platelet activation and is associated with ischemic stroke, hypertension, obstructive sleep apnea, and coronary artery syndromes in the general population, similar to C-reactive protein. However, the broad association of MPV and grey matter volumes in both SCD patients and controls, independently, suggests a developmental interplay between brain maturation and inflammatory signaling that requires further study.

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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.