Exploring Anemia's Impact on Brain Microstructure, Volume, Functional Connectivity, Iron and Cognitive Performance

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Introduction

We used MR imaging techniques to investigate the neurological consequences of chronic anemia in human patients with sickle cell disease, non-sickle anemic syndromes (called anemic-controls) and non-anemic controls. Previously we found anemia is an independent predictor of white matter (WM) damage and cognitive dysfunction regardless of disease type in a study of clinically asymptomatic adults with hemoglobinopathies[1,2]. Importantly, WM volume was independent of genotype (sickle vs non-sickle), treatment type, HgB S%, fetal HgB level, LDH and presence of silent strokes[1].

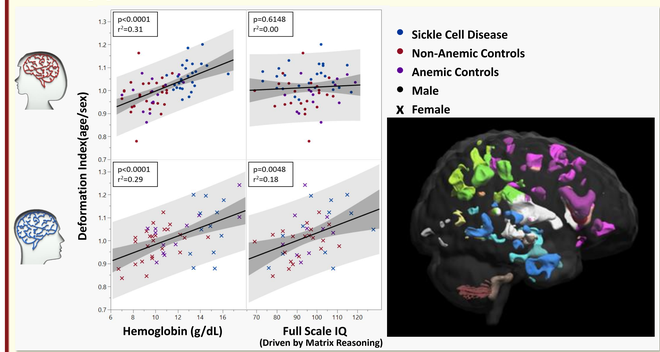

Figure 1. Scatterplots of correlation between hemoglobin level and Deformation Index (age and sex regressed) that reflects lower white matter volume associated with anemia in the brain regions rendered in the right figure. Deformation Index correlates with Full Scale IQ in males but not females[1].

We also demonstrated that low hemoglobin is associated with abnormal brain functional connectivity and iron levels in select brain regions.[3,4]

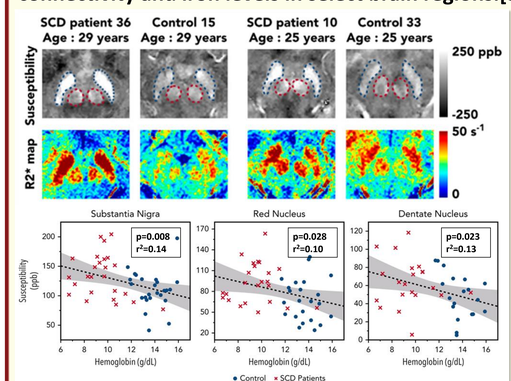

Figure 2. Examples of QSM susceptibility and R2* maps in the regions of substantia nigra and red nucleus. Susceptibility maps (top), R2* maps (middle), and T2*- weighted images at an echo time of 20 ms (bottom) are shown. Blue and pink dashed boxes highlight the regions of substantia nigra and red nucleus, respectively. Hyperintensity in susceptibility and R2* maps may infer higher density of iron levels.
Age corrected susceptibility measurements present significant negative correlation with hemoglobin in substantia nigra, red nucleus and dentate nucleus.
Dotted lines show the linear regression of the data, and shaded areas delimit the 95% confidence interval[3].

In the present study, we examine the effects of anemia on brain integrity using apparent diffusion coefficient (ADC) calculated from diffusion weighted imaging (DWI). ADC measures the magnitude of the motion of water in tissue and can be used to imply tissue damage, making it highly sensitive to neuropathology as altered tissue integrity and loss of cellular structures can change the diffusivity of water. We then explore the associations between ADC, local brain volume, functional connectivity, iron and cognitive performance.

Data Acquisition & Subjects

MRI data, CBC and neuropsychological testing results were obtained from 26 sickle cell disease (age = 20.9 ± 11.3, F:M = 13:13, HgB = 9.7 ± 2.1), 20 anemic-control (age = 25.9 ± 11.3, F:M = 10:10, HgB = 10.9 ± 0.5) and 25 control subjects (age = 23.1 ± 8.4, F:M = 16:9, HgB = 13.2 ± 1.2). (Recruited with informed consent or assent; IRB: CHLA CCI#11-00083).
DWI (TE = 86ms; TR = 6700ms; resolution=2.5mm3; 30 directions; bvalue=1000m/s2; reverse-gradient b=0) were acquired on a 3T Philips Achieva (v.3.2.1) using an 8-channel head coil.

Data Analysis

Images were corrected for motion and distortion then voxel-wise calculations of ADC were computed then transferred to a common atlas space. (brainsuite.org, v18). 3D T1 weighted, quantitative susceptibility mapping, and functional MRI (fMRI) images were collected using our previously published protocols.
After regressing out age and sex, we determined the effect of hemoglobin level at each voxel of the brain on ADC then corrected for multiple comparison (BH FDR α=0.1). Significant regions were retained, (p<0.05), and a mean ADC was computed for each subject from those regions. Pearson's correlations were used to determine the effects of hemoglobin level on the following measures: (1) mean ADC, (2) WMV, (3) Connectivity Dissimilarity Index (CDI), a measure quantifying the dissimilarity of functional connectivity pattern between each subject and a reference fMRI atlas (4) Iron measured in the substantia nigra of the brain's basal ganglia through R2* and susceptibility images and (5) Matrix Reasoning, a nonverbal measure of novel problem solving (fluid reasoning).

Discussion

Increased ADC, correlating with anemia severity, was observed in subcortical structures of an anemic population at risk for white matter shrinkage and cognitive dysfunction. ADC (but not WMV) correlated with brain iron which is known to accumulate in the presence of cerebral hypoxia. ADC and WMV changes were comparable in males and females but only males showed lower fluid reasoning. This data shows that anemia and brain iron are associated with brain tissue disruption and function.

References

[1] Choi, S., Bush, A. M., Borzage, M. T., Joshi, A. A., Mack, W. J., Coates, T. D., … Wood, J. C. (2017). Hemoglobin and mean platelet volume predicts diffuse T1-MRI white matter volume decrease in sickle cell disease patients. NeuroImage: Clinical, 15(January), 239–246.
[2] Choi, S., Bush, A. M., Borzage, M. T., Joshi, A. A., Mack, W. J., Coates, T. D., … Wood, J. C. (2017). Hemoglobin and mean platelet volume predicts diffuse T1-MRI white matter volume decrease in sickle cell disease patients. NeuroImage: Clinical, 15(January), 239–246. https://doi.org/10.1016/j.nicl.2017.04.023
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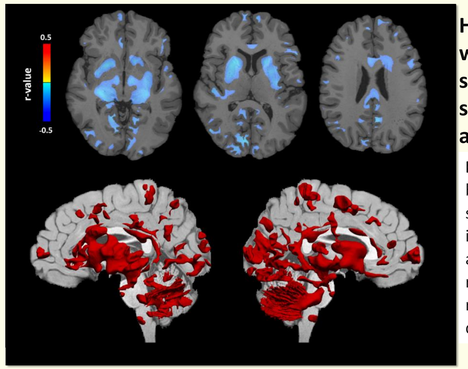
Results:

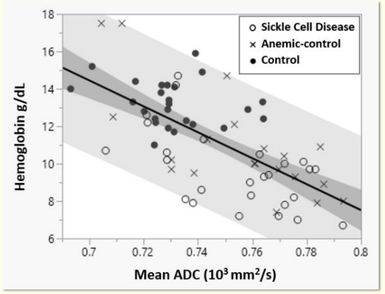


Hemoglobin level significantly correlated with ADC throughout the brain, but most strongly in deep white matter and subcortex, followed by the occipital lobe and cerebellum

Figure 3. (Top row) R-values for the correlation between ADC and hemoglobin are shown superimposed on the brain atlas template. Blue indicates a negative correlation (higher ADC with anemia) as indicated by the colorbar. These are the regions most adversely affected by anemia.(Bottom row) 3D-rendering of left and right hemispheres demonstrating significant voxels colored in red.

The scatterplot between mean ADC and hemoglobin showed no discernable differentiation between anemia subtypes (Figure 4).

Mean ADC and our previously developed markers of disease correlated well with each other showing that the severity of anemia correlates with higher ADC, lower white matter volume (WMV), abnormal functional connectivity (CDI), higher brain iron and lower Matrix Reasoning scores (males only; Table 1).



	HgB	ADC	WMV	CDI	Iron (R2*)	Iron (ppb)
ADC	<0.0001 -0.45					
WMV	<0.0001 +0.31	0.0046 -0.14				
CDI	0.0049 -0.15	0.019 +0.14	0.016 -0.12			
Iron (R2*)	0.047 -0.077	0.033 +0.13	NS	0.0032 +0.28		
Iron (ppb)	0.025 -0.10	0.18 +0.16	NS	0.013 +0.22	<0.0001 +0.57	
MR (males)	0.036 +0.083	0.020 -0.18	0.0010 +0.24	NS	NS	NS
MR (females)	NS	NS	NS	0.042 -0.32	NS	NS

Table 2. Correlation matrix. Each cell (top row) shows p-values and (bottom row) shows r^2. Positive r^2 describes positive correlations and negative r^2 describes negative correlations. NS: non-significant
HgB: hemoglobin
ADC: apparent diffusion coefficient
WMV: white matter volume
CDI: Connectivity Dissimilarity Index quantifies the dissimilarity of functional connectivity. pattern between each subject and a reference fMRI atlas. Higher CDI has greater difference.
Iron (R2*): iron level measured by R2* in the substantia nigra.
Iron (ppb): iron level measured by quantitative susceptibility imaging (QSM) in the substantia nigra.
MR: Matrix Reasoning separated by males and females. A nonverbal measure of novel problem solving (fluid reasoning).

neuroimage.usc.edu/~choisoyo **brainsuite.org**

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