Chronic Anemia is Associated with Significant White Matter Atrophy

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Introduction

Sickle cell disease (SCD) is a genetic blood disorder associated with anemia, chronic vascular damage, overt stroke, silent cerebral infarctions, and early mortality.[1,2] Patients with SCD have increased cerebral blood flow to compensate for their anemia but nevertheless exhibit regional cerebral hypo-perfusion 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

To remove the confounding influence of sickle hemoglobin, 14 thalassemia major patients (hemoglobin level 10.3 ± 0.9 g/dl, age 24.2 ± 6.8 yrs, 36% male) and 38 African-American subjects without sickle cell disease (hemoglobin level 13.5 ± 1.3 g/dl, age 27.2 ± 10.6 yrs, 26% male) were recruited as part of a study on Sickle Cell Disease. 3D T1-weighted, T2 FLAIR and phase contrast imaging was acquired on a 3T Philips Achieva. 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.

Methods

3D T1-weighted MR images (1 mm3 isotropic resolution) were processed using BrainSuite (brainsuite.org) in a semi-automated fashion to extract, classify tissue types, and calculate brain volumes, with manual correction as needed. 3D T2-FLAIR MR images (1.2 mm x 1.2 mm x 1.2 mm) were collected to quantify number and volume of white matter strokes. Total cerebral blood flow was measured using phase contrast imaging of the carotid and vertebral vessels in a single axial slice placed 5 mm above the carotid bifurcation. Total brain blood flow was normalized to brain volume x an assumed density of 1.05 g/cm3.

Results

Cerebral blood flow was reciprocally related to blood oxygen content (1.34 x Hb x Oxygen Saturation + 0.3) with an r2 of 0.50, p<0.0001, such that resting oxygen delivery was normal in all subjects. (Figure 1)

Age and sex-corrected white matter volume had a reciprocal relationship with resting cerebral flow (r2 = 0.14, p=0.0071) and a linear relationship with hemoglobin (r2 = 0.16, p=0.0042). (Figure 2 and 3)

White matter volume was 470.4 ± 38 cm^3 in anemic subjects and 504.9 ± 49 cm^3 for the control group, p=0.0121. Rare white matter hyperintensities were seen in both groups with no significant differences.

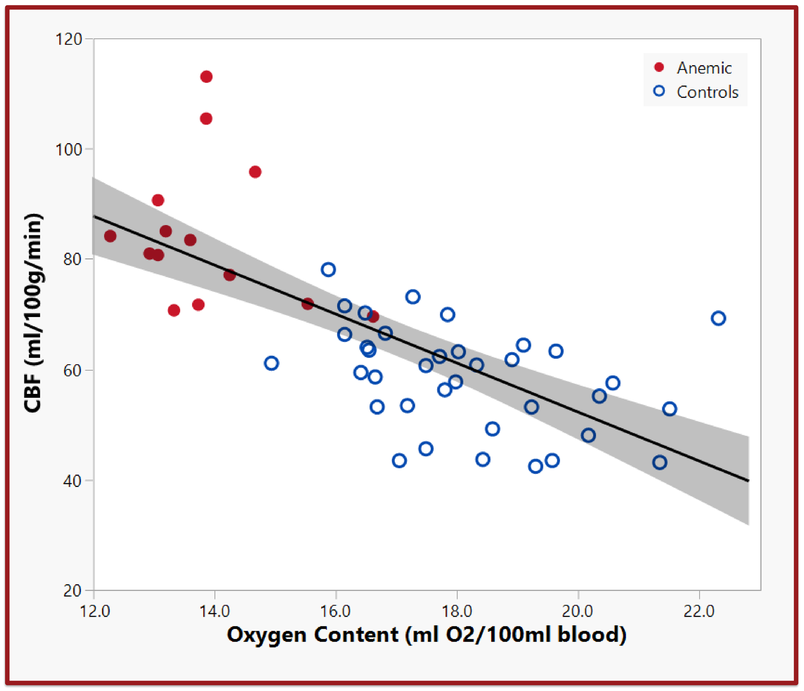

Figure 1: Relationship between resting cerebral blood flow (CBF) and oxygen content in anemic and control subjects.

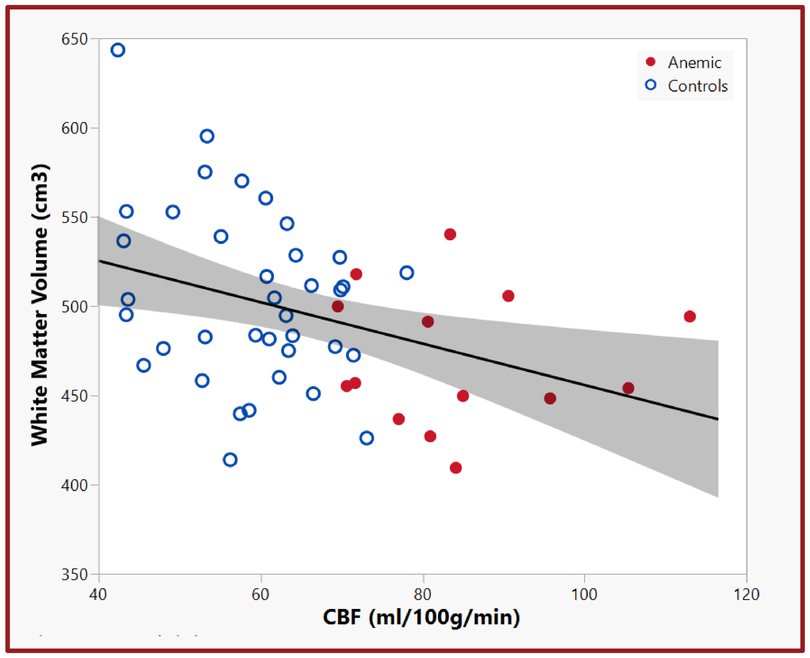

Figure 2: Relationship between white matter volume and resting cerebral blood flow (CBF) in anemic and control subjects.

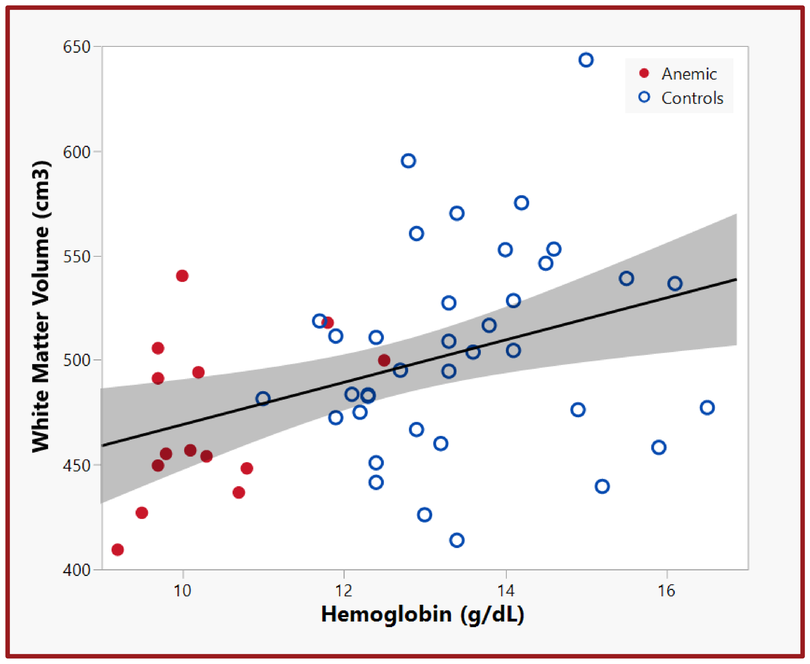

Figure 3: Relationship between white matter volume and hemoglobin in anemic and control subjects.

Conclusions

Taken together, these data indicate the white matter volume is decreased in anemic subjects, proportionally to their hemoglobin levels, independent of silent stroke. We postulate that the increased resting hyperemia observed in these patients limits their vasodilatory reserve, leaving them vulnerable to acute interruptions in oxygen delivery or increased brain metabolic needs.

References

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