Hemodynamic etiology of stroke risk in children with sickle cell anemia

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Introduction: Sickle cell anemia (SCA) is a genetic disorder resulting in microvascular occlusion, hemolytic anemia, and progressive organ damage. Stroke is the most devastating complication of SCA, which occurs in 11% of children before the age of 20 [1]. Stroke in SCA is thought to result from a critical narrowing of the large cerebral arteries that ultimately reduces cerebral blood flow to the point of infarction. However, approximately 32% of post-stroke SCA children have no evidence of stenosis as indicated by magnetic resonance angiography (MRA) [2]. An alternative etiology for stroke risk may be the hemodynamic insufficiency model [3]. SCA children are hematologically anemic as a result of chronic hemolysis, however, the severity of anemia is variable and hematocrit (Hct) levels range from 0.15-0.30 [4]. To maintain a sufficient oxygen supply to the parenchymal tissue in this anemic environment, the body increases perfusion through vasodilation . However, there is a limit to which vessels can distend to, referred to as its vasodilatory capacity. Therefore, critically anemic SCA children may have exhausted vasodilatory capacity and thereby be susceptible to ischemic damage. Vasodilatory capacity can be quantified, in-vivo, by measuring cerebrovascular reactivity (CVR) in combination with MRI. If the degree of anemia is driving the changes in vasodilatory capacity then we hypothesize that CVR will be positively associated with Hct levels in children with SCA with no history of large vessel stenosis.

Methods: 22 SCA patients (14.0 ± 2.30 SD years) were recruited from the Hospital for Sick Children and imaged on a clinical 3T MRI system (Siemens) using a 32-channel head coil. CVR data were acquired using a blood oxygen level dependent (BOLD) MR sequence (TR/TE = 2000/40ms, FOV = 220mm, matrix size = 64×64, slices = 25, slice thickness = 4.5mm, volumes = 240, time = 8 min) and hypercapnic stimulus administered using a prospective computer-controlled gas sequencer (RespirAct^{TM}) and re-breathing mask. The breathing paradigm consisted of four cycles, alternating between 60s of normocapnia ($P_{ET}CO_2$ = 40mmHg, $P_{ET}O_2$ = 100mmHg) followed by 45s of iso-oxic hypercapnia ($P_{ET}O_2$ = 45mmHg, $P_{ET}O_2$ = 100mmHg). T_1-weighted anatomical images were acquired with TR/TE = 2300/2.96ms, FOV = 256mm, voxel size = 1×1×1mm, FA = 9° for co-registration purposes. 3D Time-of-Flight (TOF) Magnetic Resonance Angiography (MRA) images were obtained with TR/TE = 20/3.59ms, FOV = 200, voxel size = 0.5 X 0.5 X 0.5mm to assess the presence of large-vessel stenosis.

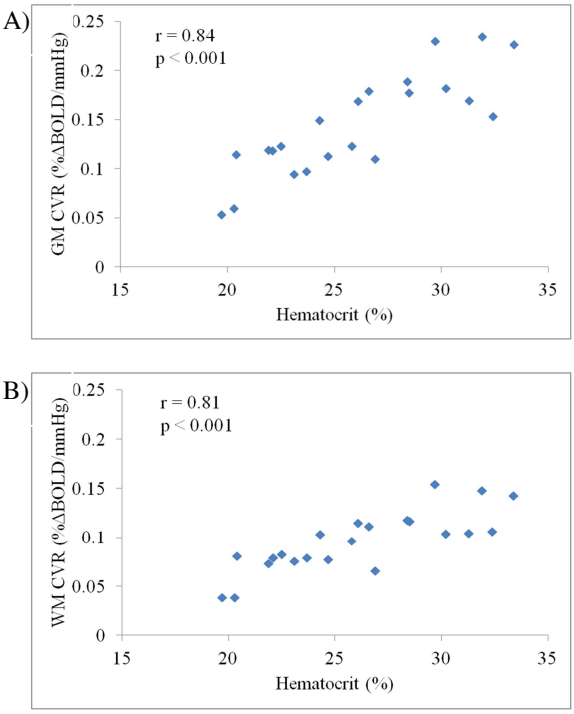

Figure 1. Association between cerebrovascular reactivity and Hematocrit in the gray matter (A) and white matter (B) of children with SCA.

Analysis: CVR maps were generated using FSL v4.1; following motion correction, the voxel-wise BOLD signal changes were correlated to the end-tidal $P_{ET}CO_2$ waveform using a general linear model. CVR maps were then co-registered to the anatomical space. Grey matter (GM) and white matter (WM) masks were segmented from T1-weighted anatomical images and used for calculation of GM and WM CVR. Hct values were obtained from clinical hematology records within 30 days of the MR protocol. An expert neuroradiologist assessed the MRA images for the presence of stenosis of the arteries in the circle of Willis. A correlation analysis (SPSS v.22) was performed to test for associations between CVR and Hct.

Results: GM CVR ranged from 0.053 to 0.2345 %ΔBOLD/mmHg (0.145±0.051 %ΔBOLD/mmHg, mean ± SD). WM CVR ranged from 0.038 to 0.154 %ΔBOLD/mmHg (0.096±0.031 %ΔBOLD/mmHg, mean ± SD). Hct ranged from 0.197 to 0.334 (0.26±0.04, mean ± SD). GM CVR was significantly associated with Hct ($r=0.84$, $p<0.001$) as shown in Figure 1A. WM CVR was significantly associated with Hct ($r=0.81$, $p<0.001$) as shown in Figure 1B.

Discussion: Our results show that the severity of anemia in children with sickle cell anemia, with no history of stenosis, significantly accounts for the variation in CVR reduction. This finding favours the hemodynamic insufficiency model of stroke risk in children with sickle cell anemia.

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