Effect of obstructive sleep apnea on cerebrovascular health in children with sickle cell disease

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Introduction: Sickle cell disease (SCD) is a genetic disorder resulting in a sickled erythrocytic phenotype that accounts for the clinical presentation of hemolytic anemia and occlusive vasculopathy.[1] Previous work has demonstrated that cerebrovascular reactivity (CVR) was globally reduced compared to healthy controls in the pediatric SCD population.[2] CVR can be utilized to gauge vascular health and it reflects the capacity of blood vessels to regulate blood flow in the presence of a vasoactive stimulus. In addition, a high percentage of individuals with SCD suffer from obstructive sleep apnea (OSA)[3] characterized by the obstruction of the upper airway during sleep. This can lead to repeated episodes of nocturnal hypoxia, hypercapnia and sleep disruption. It is currently unknown if the presence of OSA in the pediatric SCD population will further impair cerebrovascular health. Therefore, by comparing the MRI derived CVR values in the OSA versus the non-OSA cases in the pediatric SCD population, we will gain valuable insight into their combined effect on cerebrovascular health. We hypothesize that CVR will be further reduced in pediatric SCD OSA patients compared to pediatric SCD patients without OSA.

Methods: 17 SCD patients, 7 with OSA (8-18 years) and 10 without OSA were imaged on a clinical 3T MRI scanner using a 32-channel head coil. CVR data was acquired using a blood-oxygen level dependent (BOLD) sequence during a computer-controlled administration of a vasoactive stimulus delivered in programmed cycles of low and increased levels of CO_2 through a rebreathing mask. The BOLD images were acquired with TR/TE = 2000/40ms, FOV = 220mm, matrix size = 64×64, slices = 25, slice thickness = 4.5mm, volumes = 240, time = 8 min. High resolution CVR maps were computed using FSL v4.1 by correlating the voxel-wise BOLD signal changes to the sampled end-tidal CO_2 waveform, followed by coregistration to the anatomical space. The CVR maps were then converted into surface maps using the Constrained Laplacian Anatomical Segmentation using Proximities (CLASP) method.[4] Next, the surface maps were coregistered into the MNI pediatric MRI Atlas, which was manually segmented into the corresponding Brodmann regions. The MATLAB based program SurfStat was used to perform Student's t-tests on CVR between the groups in order to identify significantly different Brodmann regions.[5] For every Brodmann area, the mean and standard deviations were calculated in the OSA and the non-OSA group using MATLAB.

Results: From the CVR group comparison analysis, we observed that global CVR levels in grey matter was significantly lower in SCD patients with OSA compared to the non-OSA group. Closer investigations of specific regions of interest revealed several Brodmann areas that showed significantly reduced CVR levels in the OSA SCD group (see Figure 1). The left BA 1-3, 4, 5, 7, 8, 17, 18 and 24 and the right BA 1-3, 4, 5, 17 and 23 were the areas found to be significantly different ($p < 0.05$) in the Student's t-test analysis of the regions through SurfStat.

Discussion: In this study, we have demonstrated significantly reduced CVR values in SCD patients with OSA compared to SCD patients without OSA in different parts of the brain. Reduced CVR may expose individuals who suffer from SCD and OSA to a higher risk for serious vasculopathies such as stroke and they should, therefore, be considered for treatments such as adenotonsilectomy or CPAP therapy to reduce stroke risk.

References: 1. Stuart MJ, et al, *Lancet* 2004. 2. Kassner A, et al., Proc from ISMRM 20th Annual Meeting 2011; Montreal, 5649. 3. Kaleyias J, et al, *Journal of pediatric hematology/oncology* 2008. 4. Kim JS et al, *Neuroimage*, 2005 5. Worsley KJ, et al, Paper presented at the Human Brain Mapping 2009, San Francisco.

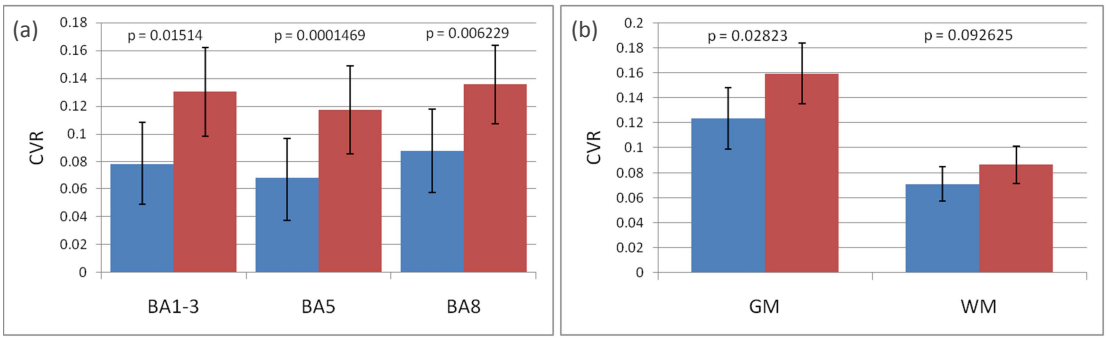

Figure. 1 Bar graphs showing the difference in CVR between the OSA (red) and without OSA (blue) SCD group in
(a) Brodmann areas 1-3, 5 and 8
(b) global GM and WM
The CVR measurements are in units of % ΔBOLD signal / Δvasoactive stimulus.