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Research paper

Reduced cerebrovascular reserve is regionally associated with cortical thickness reductions in children with sickle cell disease

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ABSTRACT

Sickle cell disease (SCD) is a genetic disorder which adversely affects cerebrovascular health. Previous studies have demonstrated regional cortical thinning in SCD. However, the reason behind regional reductions in cortical thickness remains unclear. Therefore, we aimed to explore the possible link between the state of cerebrovascular health and cortical thickness. In this study, we obtained magnetic resonance (MR) based measures of cerebrovascular reactivity (CVR), a measure of vascular health, and cortical thickness in SCD patients ($N=60$) and controls of similar age and similar gender ratio ($N=27$). The group comparison analysis revealed significant regionally specific reductions in CVR and cortical thickness in the SCD group compared to the controls. In addition, a regional association analysis was performed between CVR and cortical thickness in the SCD group which revealed a significant regional association in several brain regions with the highest strength of association observed in the left cuneus, right post central gyrus and the right temporal pole. The regional association analysis revealed that significant associations were found in brain regions with high metabolic activity (anterior cingulate, posterior cingulate, occipital gyrus, precuneus) thus demonstrating that these regions could be most vulnerable to structural damage under hypoxic conditions.

1. Introduction

Sickle cell disease (SCD) is a genetic disorder of the red blood cells (RBC) affecting 2.7 per 1000 births around the world. The RBCs become rigid and sickle shaped in its de-oxygenated state which leads to increased adhesion, decreased lifespan and reduced oxygen carrying capacity compared to healthy RBCs (Hare, 2004). As the adhesive property of the RBCs increases, they begin to occlude blood circulation, thereby triggering the onset of inflammation and oxidative damage to the endothelium which leads to endothelial dysfunction (Hebbel et al., 2004; Conran et al., 2009; Akinsheye and Klings, 2010; Hatzipantelis et al., 2013). Furthermore, hyperemia attributable to anemia results in constant vasodilation (Kim et al., 2009; Rees et al., 2010). The combined effect of endothelial dysfunction and chronic vasodilation reduces vascular reserve in SCD, thus compromising the vasculature's ability to adapt to hypoxic conditions.

In the brain, reduced vascular reserve in patients with SCD is associated with increased risk of cerebral injury such as silent infarcts or overt stroke (Nur et al., 2009; Prohovnik et al., 2009). Furthermore, the occurrence of cerebral injury has been associated with complications such as neurocognitive deficits in SCD (Steen et al., 1998; Pegelow et al., 2001; Hogan et al., 2006; Dowling et al., 2010). However, SCD patients also exhibited cognitive deficit even without visible lesions on anatomical MRI scans (Steen et al., 2005). Hence, more advanced imaging and processing techniques are necessary in order to detect possible group differences in brain structure. A study by Kirk et al. (2009) investigated cortical thickness as a potential neuroimaging marker and was able to identify regions of cortical thinning in SCD. Moreover, cortical thinning was most severe in regions of high metabolic activity. While the cause of cortical thinning is not clear, there could be a possible link between cortical thinning and reduced vascular reserve. This is due to the fact that the regions with the most severe thinning coincided with regions of high metabolic activity therefore when there is reduced vascular reserve in these regions, the body may not be able to sufficiently meet the metabolic demands of the regions under hypoxic conditions.

Cerebrovascular reserve can be quantified using advanced MR

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imaging with a measure known as cerebrovascular reactivity (CVR), which measures the change in cerebral blood flow in response to a vasoreactive stimulus to assess the vascular reserve of cerebral blood vessel. Previous studies have demonstrated a global reduction of CVR in SCD patients compared to controls as a result of endothelial dysfunction and hyperemia (Nur et al., 2009; Prohovnik et al., 2009). However, it is not known how CVR reductions vary between regions and whether the reductions are related to cortical thinning. Different brain regions have different metabolic demands (Karbowski, 2007) and as such it is likely that CVR reductions will vary regionally in SCD. Therefore, the effect of hyperemic anemia on vascular reserve may differ in severity for each brain region and the measured reduction in CVR attributable to chronic dilation should vary depending on the blood supply required to sufficiently meet the metabolic demands of the region. Regional variations in CVR reduction could help to explain the regional differences in the degree of cortical thinning. By associating regional values of CVR and cortical thickness, we aim to explore the link between regionally reduced vascular reserve and cortical thinning in SCD. Thus, we hypothesized that CVR and cortical thickness could be reduced in SCD and the regional reduction in CVR could be associated with regional cortical thinning. The regions of highest strength of association will be regions of high metabolic activity.

2. Results

2.1. Subject recruitment

Imaging data were acquired from 60 SCD patients and 27 controls between 12 and 18 years of age. Three sets of SCD data were discarded due to motion artefacts. Patient demographics are reported on Table 1.

2.2. Cortical thickness in the SCD group compared to controls

Mean cortical thickness in the SCD group (3.3 ± 0.34 mm) was significantly reduced compared to controls (3.5 ± 0.3 mm, $p < 0.0001$) (Fig. 1A). In the regional analysis, cortical thickness was reduced in 37 out of the 78 automated anatomical labeling (AAL) areas ($p < 0.05$ for all regions) (Fig. 1B). Analysis of covariance (ANCOVA) revealed no interactions between sex, age and cortical thickness differences between the groups.

2.3. Surface area in the SCD group compared to controls

Mean surface area in the SCD group (2.30 ± 0.57 cm^2) was significantly reduced compared to controls (2.39 ± 0.6 cm^2, $p < 0.0001$). In the regional analysis, there was significantly reduced surface area in the SCD group in 20 out of the 78 AAL areas we investigated ($p < 0.05$ for all regions).

2.4. CVR in the SCD group compared to controls

CVR in the SCD group was significantly reduced compared to the control group within the left GM (0.14 ± 0.05 SCD; 0.27 ± 0.04 control, $p < 0.0001$), right grey matter (GM) (0.136 ± 0.0550 SCD; 0.28 ± 0.04 control, $p < 0.0001$), left white matter (WM) (0.08 ± 0.04 SCD; 0.16 ± 0.03 control, $p < 0.0001$) and right WM (0.09 ± 0.03 SCD; 0.16 ± 0.03 control, $p < 0.0001$) (Fig. 2A). In the regional analysis, there was significantly reduced CVR in the SCD group in 71 out of the 78 AAL areas we investigated ($p < 0.05$ for all regions) (Fig. 2B). ANCOVA revealed no interactions between sex, age and CVR difference between the groups.

Table 1
Demographics of participants in the study.

	SCD	Controls
Total number (males)	60(29)	30(13)
Age	14.5 ± 2.56	15.2 ± 3.16
Hematocrit	0.281 ± 0.09	0.350–0.5
Number of HU	16	N/A
Number with lesions	11	N/A

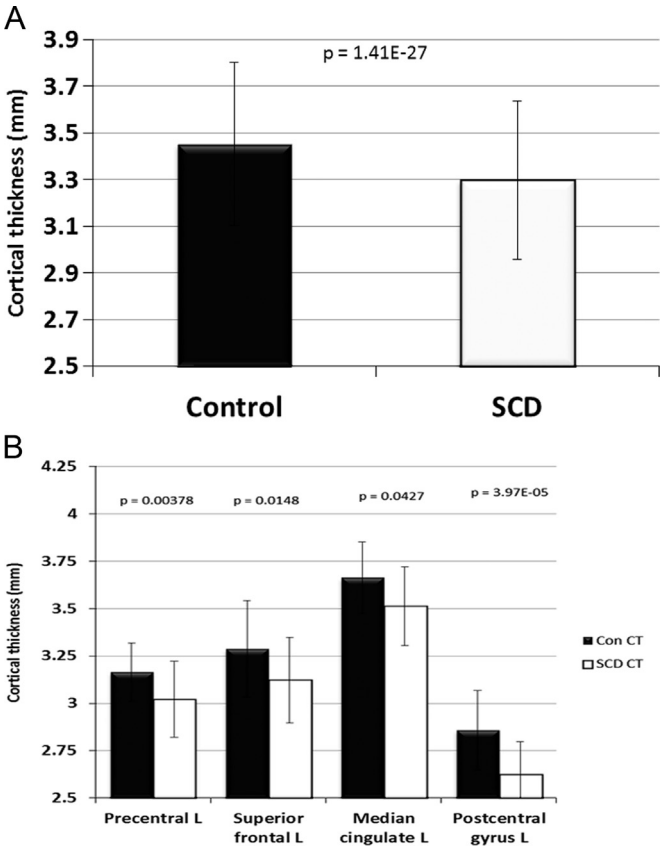

Fig. 1. Group comparisons between controls (black) and SCD (white) for (A) global and (B) regional cortical thickness (left precentral gyrus, left superior frontal gyrus, left median cingulate, left post central gyrus).

2.5. Association of CVR and cortical thickness in the SCD group compared to controls

In the regional association analysis, CVR was significantly associated with cortical thickness in 41 AAL regions of the brain ($r > 0.48$; $p < 0.05$ for all regions). Furthermore the relationship between CVR and cortical thickness was modeled by a second degree polynomial in 13 AAL regions while the other 28 AAL regions were modeled by a first degree polynomial. There were strong correlations in the AAL45 (left cuneus, $r = 0.603$), AAL58 (right post central gyrus, $r = 0.633$), AAL67 (left precuneus, $r = 0.604$), AAL84 (right temporal pole, $r = 0.626$) while AAL areas responding to the cingulate cortex (AAL32–36) was seen to have moderately strong correlation ($r > 0.53$) (Fig. 3). When the same association analysis was applied to control subjects, there was no association between CVR and cortical thickness in any of the AAL regions.