



Brain venular pattern by 7T MRI correlates with memory and haemoglobin in sickle cell anaemia



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ABSTRACT

Sickle cell anaemia (SCA) is a hereditary hemoglobinopathy characterised by extensive vascular dysfunction that stems from inflammation, thrombosis and occlusion of post-capillary venules. Cognitive impairment is a neurological complication of SCA whose pathogenesis is unknown. We hypothesised that cerebral venular abnormalities are linked to cognitive impairment in SCA. Thus, we employed 7T magnetic resonance imaging (MRI) to examine the association between venular density and cognitive function in homozygous SCA. We quantified the density of total, long, and short venules in pre-defined regions of interest between the frontal and occipital cornu on each hemisphere. Cognitive function was assessed using the Hopkins Verbal Learning Test – Revised (HVLT-R) test of learning and memory. Patients ($n=11$) were compared with race, age and gender-equated controls ($n=7$). Compared to controls, patients had an overall venular rarefaction, with significantly lower density of long venules and greater density of short venules which was inversely related to HVLT-R performance and haemoglobin. To our knowledge, this is the first 7T MRI study in SCA and first report of associations between cerebral venular patterns and cognitive performance and haemoglobin. Future studies should examine whether these novel neuroimaging markers predict cognitive impairment longitudinally and are mechanistically linked to severity of anaemia.

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1. Introduction

Sickle cell anaemia (SCA) is a hereditary hemoglobinopathy characterised by endothelial dysfunction, vaso-occlusion and thrombosis of post-capillary venules (Kaul et al., 1989). Neurological complications of SCA include overt and silent cerebrovascular infarction and cognitive impairment (CI) (DeBaun et al., 2012). While CI is associated with cerebrovascular infarction, it also occurs independently from it in SCA (Vichinsky et al., 2010), and is responsible for functional limitations in schooling, occupation and compliance with therapy (Feliu et al., 2011). Our current understanding of the risk factors and pathophysiology of CI in SCA is limited, but based on the

pathophysiology of SCA and the evidence in other diseases with CI and dementia (Brown and Thore, 2011; Hunter et al., 2012; Moody et al., 1997; Sinnecker et al., 2013), it is likely that CI stems from small vessel disease. Post-mortem studies have found evidence of small vessel abnormalities in SCA patients, including congested and thrombosed venules (reviewed by Merkel et al., 1978), but did not assess the patients' cognitive function. Hence, while large vessel stenoses are responsible for overt infarcts in SCA (Switzer et al., 2006), it is not known whether venular abnormalities are associated with CI. Magnetic Resonance Imaging (MRI) is increasingly useful in identifying microvascular abnormalities associated with CI (Rincon and Wright, 2014). Prior MRI studies in adult SCA patients have, however, been limited by the use of lower field 1.5Tesla MRI systems (Alkan et al., 2010; Kugler et al., 1993; Vichinsky et al., 2010), which only provide lower sensitivity markers of small vessel disease, hence hampering detection of microvascular abnormalities. Pre-clinical *in vivo* and *in vitro* evidence has shown that the inciting pathogenic

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event in SCA occurs in post-capillary venules (Kaul et al., 1989; Kaul et al., 1993), including cerebral post-capillary venules of transgenic sickle mice (Wood et al., 2004), and is characterised by increased cellular adhesion, inflammation and endotheliopathy. Thus, we hypothesised that the predominant microvascular abnormality of SCA patients with CI would manifest with markers of venular fragmentation and lower venular density. We applied ultrahigh field, state-of-the-art 7T MRI technology to test this hypothesis by quantifying venular structure in patients with homozygous HbSS SCA. Subjects without SCA underwent the same neuroimaging protocol for comparison. We then explored correlations of venular structure with cognitive function as measured by the Hopkins Verbal Learning Test – Revised (HVLT-R) and with total haemoglobin in the patients.

2. Methods

2.1. Subjects

All participants provided informed consent (University of Pittsburgh IRB PRO12040139). We recruited a convenience sample of consecutive patients from the UPMC Adult Sickle Cell Disease Program outpatient clinic. The only inclusion criteria were HbSS disease (homozygous SCA) diagnosed by high-performance liquid chromatography and haemoglobin electrophoresis, and being in steady-state according to published criteria (Ballas, 2012). Exclusion criteria included the following: blood transfusion within the prior 90 days, pregnancy, any contraindication to MRI and a history of traumatic brain injury or diseases known to cause cognitive dysfunction, including diabetes, systemic lupus erythematosus and other causes of cerebral vasculitis. The blood draw was performed during the patients' routine clinic visit and the HVLT-R and MRI were completed at a separate visit occurring within 2 weeks from the blood draw and in the absence of any intercurrent transfusion or vaso-occlusive episode. Control African American subjects ($n=7$) with no family history of SCA were recruited from the community through IRB-approved flyers and SCA patient referral. They were equated to the patients for age and gender, and subjected to the same exclusion criteria.

2.2. MRI and cognitive assessment

The MRI scans were performed at the University of Pittsburgh using a 7T human MRI system (Magnetom, Siemens Medical Systems, Erlangen, Germany) and utilising an in-house 2-ch transmit and 14-ch receive radiofrequency coil (Ibrahim et al., 2010). Structural image acquisition included a high-resolution Magnetization Prepared Rapid Gradient Echo T1 (MPRAGE-T1WI) image with 3D orientation, $0.6 \text{ mm} \times 0.58 \text{ mm} \times 0.58 \text{ mm}$ resolution, TR/TE/TI=3430/3.69/1200 ms, a T2* Susceptibility Weighted Image (SWI) with axial orientation (64 slices), $0.25 \text{ mm} \times 0.25 \text{ mm} \times 1.5 \text{ mm}$ resolution, TR/TE/TI=2000/15/NA and a T2* SWI with coronal orientation (50 slices), $0.25 \text{ mm} \times 0.25 \text{ mm} \times 1.5 \text{ mm}$ resolution, TR/TE/TI=2000/15/NA. Scans were routinely inspected for stroke and unanticipated findings that warrant a report from the on call neuroradiologist. Small intraparenchymal veins (venules) were quantified from the SWI image within predefined ROIs (width 1 cm, length 4 cm) between the frontal and occipital cornu on each cerebral hemisphere, using a previously published protocol (Sinnecker et al., 2013) with the following modification: short venules were defined as being 3–5 mm in length (dashed arrow), long venules were defined as being 9–10 mm in length (solid arrow) and intermediate venules were defined as being between 6–8 mm in length. The proportion of short or long venules to the total number of venules was also computed for each participant (Fig. 1A).

Patients were administered the HVLT-R based on its brief testing time and sensitivity to the key domains of learning and memory in brain-disordered populations (Lacritz et al., 2001; Shapiro et al., 1999).

3. Results

3.1. Patients

Patient characteristics and laboratory values are shown in Table 1. Eight of eleven patients were receiving hydroxyurea at the time of our study and had relatively high levels of foetal (HbF) and total haemoglobin. In spite of these findings, they had a history of multiple SCA-related complications as outlined in Table 1. Haemoglobin A1 was not detected in any of the patients.

3.2. SCA patients have an abnormal venular pattern by 7T MRI

We employed SWI contrast, which is particularly sensitive to the microvasculature at the 7T field strength, to directly probe the integrity of small vessels in patients and controls (Ding et al., 2008). Total venular density was lower in patients compared with control subjects (33.1 ± 12.0 vs. 42.3 ± 8.6 venules/ 8 cm^2 , $p=0.103$) with the density of long venules being significantly lower (4.4 ± 3.7 vs. 8.8 ± 4.4 venules/ 8 cm^2 , $p=0.028$, Fig. 1A). As a result of preferential loss of long venules, patients had a higher proportion of short venules compared to controls (Fig. 1B).

3.3. Venular pattern by 7T MRI correlates with cognitive function and anaemia in SCA patients

There was a non significant positive correlation between total venular count and HVLT-R retention score, a measure of episodic memory (ρ symbol = 0.486, $p = 0.154$, Fig. 1C). Higher proportion of short venules was inversely correlated with HVLT-R retention score ($\rho = -0.634$, $p=0.049$, Fig. 1C) and with haemoglobin ($\rho = -0.671$, $p=0.027$, Fig. 1D). Higher proportion of long venules was directly correlated with haemoglobin ($\rho=0.586$, $p=0.070$, data not shown) and with HVLT-R retention score ($\rho=0.498$, $p=0.143$ Fig. 1D), although associations were more modest. The HVLT-R score was also correlated with haemoglobin ($\rho=0.632$, $p=0.027$, data not shown).

4. Discussion

To our knowledge, this is the first 7T MRI study in SCA and first report of a cerebral venular pattern associated with worse cognitive performance in SCA. Similar to the results of a published landmark study (Vichinsky et al., 2010), we have also found that lower haemoglobin is positively correlated with worse cognitive function.

Cerebral small vessel disease may arise from venular damage (Rincon and Wright, 2014). For instance, stenosis and occlusion of deep cerebral venules has been associated with leukoaraiosis (Moody et al., 1995). Our finding of venular rarefaction is particularly intriguing, as SCA preferentially targets post-capillary venules (Kaul et al., 1989). Small vessel density also decreases with age in normal subjects and has been observed in Alzheimer's disease (Brown and Thore, 2011). Our vascular findings parallel those observed in patients with Alzheimer's disease, ischaemic brain damage and age-dependent leukoaraiosis, where small vessel degeneration leads to the formation of characteristic "string" vessels resulting from the destruction of longer vascular structures, and associated with poorer cognitive function (Brown, 2010; Hunter et al., 2012). Patients with Alzheimer's disease were also found to have structural changes in retinal venular networks, including narrower and tortuous venules as compared with healthy controls (Cheung et al., 2014), suggesting that alterations in venular anatomy may be linked to decreased cognitive function across a spectrum of neurodegenerative diseases. This novel finding in SCA may, therefore, represent a candidate quantifiable radiological marker of cognitive decline. In keeping with a recent report by Mackin et al. (2014), we did not detect microhemorrhages, another recognised MRI marker of small vessel disease in other conditions (Gouw et al., 2011). This discrepancy between SCA and other vascular diseases may reflect the peculiar nature of SCA neuropathology. While in SCA relative hypertension is associated with stroke (Pegelow et al., 1997), elevated systolic blood pressure (Pegelow et al., 1997) and classical atherosclerosis rarely occur (Mansi and Rosner, 2002).

Decreased venular conspicuity in SCA may stem from multiple mechanisms, complicating the interpretation of this finding. The visibility of venules depends on the effect of deoxygenated

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