White matter abnormalities in children with sickle cell anaemia: Potential link with oxygen desaturation

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Target Audience. Neurologists, Haematologists.

Purpose. Sickle cell anaemia (SCA) is a genetic disorder affecting the oxygen-carrying capacity of haemoglobin. Subsequent neurological complications are common; approximately 10% of children will suffer an overt stroke1 and up to 35% will experience covert or ‘silent’ infarction (SCI)2. In patients with no evidence of infarction on T2-weighted MRI, there is evidence of cortical thinning3, decreased white and grey matter density4 and subcortical volumetric deficits5, as well as marked deficits in intelligence and executive functions6. Previous diffusion tensor imaging (DTI) studies found anisotropy reductions and increases in diffusivity in the corpus callosum (CC) and centrum semiovale7, as well as reduced fibre count (i.e. streamlines) and noticeable atrophy of the CC8. Mechanisms for white matter damage in SCA are unclear and possibly related to effects of chronic anaemia and oxygen desaturation9; however the link with structural brain abnormalities in children with SCA and no apparent SCI are unknown.

Methods. Our data included 27 children with SCA (HbSS; age range 8-18 years, mean 13.3 years, 16 M) with no evidence of SCI on T2-weighted MRI, as determined by two independent neuroradiologists (SB, TC), and 21 healthy controls, including 11 sibling controls (age range 9-18 years, mean 13.2 years, 12 M). All children were imaged on a 1.5T Siemens Magnetom Avanto scanner with a 32-channel receive headcoil; the DTI protocol had 60 unique gradient directions (b=1000s/mm², TR=7300ms, TE=81ms, voxel size=2.5mm³). We performed tract-based spatial statistics (TBSS)10, part of FSL11, for a whole-brain voxel-wise white matter (WM) analysis. TBSS co-registers all diffusion data and generates an average WM skeleton on which statistical comparisons are made.

Results. After correcting for the effects of age and gender, we found significantly lower fractional anisotropy (FA), higher mean diffusivity (MD) and higher radial diffusivity (RD) in SCA patients compared to control subjects. FA was significantly lower in the left parietal WM, splenium of the CC, and bilateral internal capsule, thalamus and cerebellar WM. MD and RD were significantly higher in patients widespread across the brain. (Figure 1)

To test the hypothesis that there might be an interaction between daytime oxygen saturation (SpO₂) and the DTI measurements, in 26 patients with SCA (mean SpO₂: 96.2%), we found a trend correlation between lower SpO₂ and higher RD in the entire CC and surrounding frontal and parietal WM. (Figure 2)

Further, in a region-of-interest analysis with the voxels of the CC of the midline sagittal slice, in the same 26 patients, we found that higher SpO₂ correlated with higher FA (r=0.473, p<0.05), lower MD (r=-0.492, p<0.05) and lower RD (r=-0.521, p<0.05).

Discussion. We showed significantly lower FA in mainly subcortical WM and widespread diffusivity increases in cortical and subcortical WM. This is the first study to link markers of disease severity, such as SpO₂, with diffusion data to propose a relationship between chronic mild oxygen desaturation and structural brain abnormality.

Conclusion. We showed significant structural WM abnormalities in SCA patients without evidence of SCI, adding compelling evidence that brain injury in children with SCA is diffuse9,12.