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ORIGINAL PAPER

Brain volume in Tanzanian children with sickle cell anaemia: A neuroimaging study

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Summary

Brain injury is a common complication of sickle cell anaemia (SCA). White matter (WM) and cortical and subcortical grey matter (GM), structures may have reduced volume in patients with SCA. This study focuses on whether silent cerebral infarction (SCI), vasculopathy or anaemia affects WM and regional GM volumes in children living in Africa. Children with SCA (n = 144; aged 5–20 years; 74 male) and sibling controls (n = 53; aged 5–17 years; 29 male) underwent magnetic resonance imaging. Effects of SCI (n = 37), vasculopathy (n = 15), and haemoglobin were assessed. Compared with controls, after adjusting for age, sex and intracranial volume, patients with SCA had smaller volumes for WM and cortical, subcortical and total GM, as well as bilateral cerebellar cortex, globus pallidus, amygdala and right thalamus. Left globus pallidus volume was further reduced in patients with vasculopathy. Putamen and hippocampus volumes were larger in patients with SCA without SCI or vasculopathy than in controls. Significant positive effects of haemoglobin on regional GM volumes were confined to the controls. Patients with SCA generally have reduced GM volumes compared with controls, although some subcortical regions may be spared. SCI and vasculopathy may affect the trajectory of change in subcortical GM and WM volume. Brain volume in non-SCA children may be vulnerable to contemporaneous anaemia.

KEYWORDS
brain volume, magnetic resonance imaging, sickle cell anaemia, silent cerebral infarction, vasculopathy

Hanne Stotesbury and Fenella J. Kirkham are joint senior authors.

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INTRODUCTION

Africa has the highest burden of sickle cell anaemia (SCA), accounting for 75% of the total 300 000 global births per year.[1] The prevalence of overt stroke in people with SCA living in African countries is 3%–17%, with children most commonly affected.[2,3] Transcranial Doppler screening and hydroxycarbamide (hydroxyurea) reduces overt stroke risk in African children.[4] However, little is known about the effect of silent cerebral infarction (SCI), which is also common in patients with SCA,[5] and may be the result of chronic, repetitive injury due to hypoxic or ischaemic exposure. Similar mechanisms may underlie structural brain changes, including volumetric deficits.

Quantitative magnetic resonance imaging (MRI) studies[6–11] have found reduced grey matter (GM) volumes in patients with SCA compared with controls.[9] Only one previous study in a small number of children with SCA reported regional subcortical GM volumes, which were reduced compared with controls ($n = 20$); although the mean volume was slightly less in those with ($n = 13$) and without ($n = 13$) SCI, this was not statistically significant.[11]

Intracranial arterial vasculopathy in patients with SCA on magnetic resonance angiography (MRA) has been associated with both stroke and SCI.[12–14] Vasculopathy of any grade has been identified as an independent predictor of total GM and white matter (WM) atrophy in SCA,[15] but effects on regional GM volumes have yet to be investigated. Lower haemoglobin level has also been associated with decreases in WM volume, specifically in the deep border zone regions, not only in patients with SCA,[16,17] but also in those with non-SCA anaemia.[17] However, as for vasculopathy, effects of anaemia on regional GM volumes are unclear.

In this study we hypothesised that:

1. Reductions in regional GM volumes would increase with presence of SCI on MRI in patients with SCA.
2. Reductions in regional GM volumes would increase with presence of vasculopathy on MRA in patients with SCA.
3. Lower haemoglobin concentration would predict reduced regional GM volumes in patients with SCA and controls.

PATIENTS AND METHODS

A cross-sectional hospital-based brain imaging study was conducted at Muhimbili National Hospital in Dar Es Salaam over 22 months (2016–2018). Ethical approval was obtained from the Muhimbili University of Health and Allied Sciences Institutional Review Board (MUHAS-IRB Ref.2014-11-03/EC/Vol.IX/32). Individual written consent was obtained from parents/guardians of minors and participants aged >18 years, while children were asked whether they assented to participation. Participants with prior stroke and history of seizures were excluded. No patient was on hydroxycarbamide or a chronic blood transfusion regime. Non-SCA siblings of patients with SCA with brain volume data were enrolled as controls.

Image acquisition and classification

The MR images from all participants were acquired at Muhimbili National Hospital on a 1.5-T Phillips scanner (Achieva; Phillips, Best, the Netherlands) using a 16-channel phased-array head coil. The study protocol included a three-dimensional (3D) sagittal T1-weighted (T1-W) volume sequence (repetition time [TR]/echo time [TE], 6.9/3.2 ms) with an isotropic spatial resolution of 1 mm^3. Images from a standard clinical diagnostic protocol were also acquired, including: an axial turbo spin-echo (TSE) T2-weighted (T2W) sequence (TR/TE of 3000/120 ms; slice thickness, 5 mm), a coronal TSE T2-weighted sequence (3000/120 ms; slice thickness, 5 mm), an axial fluid-attenuated inversion recovery (FLAIR) sequence (TR/TE, 6000/120 ms; inversion time, 2000 ms; slice thickness, 5 mm) and a time-of-flight MRA sequence with source and maximum intensity projection.

Clinical images were evaluated by two neuroradiologists (M.J. and D.S. with 8 and 20 years of experience respectively) for diagnosis and verification of MRI abnormalities. The SCI definition developed for the Silent Infarct Transfusion (SIT) trial was used: a lesion measuring at least 3 mm in greatest linear dimension, visible in at least two planes on T2W images.[18] Patients with SCA without and with SCI were grouped as SCI– and SCI+ respectively. Rather than wall structure abnormalities, e.g., stenosis or occlusion, as seen on conventional arteriography, velocity of flow changes are imaged as variations in signal on MRA. As for our previous work,[19,20] examinations were therefore reviewed for turbulence or signal loss in four segments of each intracranial internal cerebral artery (ICA), in one segment of each proximal anterior cerebral artery (ACA; A1), in two segments of each middle cerebral artery (MCA; M1 and M2), and in two segments of each posterior cerebral artery (PCA; P1 and P2). The severity of signal loss was graded as 0 (none–normal); 1 (minor signal attenuation–mild vasculopathy); 2 (obvious signal attenuation, but presence of distal flow–moderate vasculopathy); 3 (signal loss and no distal flow–severe vasculopathy), 4, occlusion with (moyamoya) or without collaterals. The worst vasculopathy in any vessel was recorded. Patients without and with vasculopathy on MRA were grouped as VASC– (Grade

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0) and VASC+ (Grade 1, 2, 3 or 4) respectively. The final diagnosis of SCI and vasculopathy was reached by consensus.

MRI volumetric analysis

Automatic cortical and subcortical volumetric segmentations were performed using Freesurfer version 5.1 for Mac OSX (https://surfer.nmr.mgh.harvard.edu) as described in detail previously.[21–23] Briefly, whole-head high-resolution T1-W 3D images went through the full recon-all pipeline, including motion correction, automated Talairach transformation,[22,23] and intensity segmentation.[24] Specific steps for the segmentation stage include: linear registration to the Gaussian Classifier Atlas, canonical segmentation, and subcortical segmentation of individual structures.[21] Segmentation quality of WM, GM and subcortical structures (caudate, putamen, pallidum, thalamus, hippocampus, amygdala and accumbens) was further assessed by quantitative neuroimaging expert R.M. and J.M.K. with 5 and 7 years of experience respectively in using neuroimaging analysis techniques.

Statistical analysis

All analyses were performed using R (www.r-project.org) or Statistical Package for the Social Sciences (SPSS®) version 28 (IBM Corp., Armonk, NY, USA). Linear models were fit to each variable (i.e., regional GM volume) with age, sex and intracranial volume included as covariates; as cranium size determines the size of brain structures, intracranial volume was included but we did not normalise by creating a new variable. Subjects were excluded on a test-by-test basis. For each test, the sample was tested for deviations from a normal distribution using the Shapiro–Wilk test. Extreme outliers were excluded to ensure a normal distribution before proceeding with the groupwise comparisons.

Analyses of covariance (ANCOVAs) were used to determine differences in regional cortical and specific subcortical volumes as a function of SCI (i.e., controls vs. SCI– vs. SCI+), and intracranial vasculopathy (i.e., controls vs. VASC– vs. VASC+). Age, sex, and total intracranial volume were added as covariates, between group post hoc comparisons were conducted using the Tukey–Kramer method.

A linear model was fit to the data with contemporaneous haemoglobin concentration as a predictor, and age, sex, and total intracranial volume as covariates; these were performed in all study subjects as well as in patients with SCA only. The p values were corrected for multiple comparisons using the false discovery rate (FDR; with adjusted p [q value] <0.05 considered significant).[25] The FDR q value threshold was 0.05.

To assess the effect of age and presence of silent infarction and vasculopathy, trajectories, plotting volume against age, were compared using the method of Thomas et al.[26] (2009; see supplement).

RESULTS

A total of 224 neurologically asymptomatic children and adolescents with SCA underwent brain MRI/MRA; 184 had high-resolution T1-W volume datasets, of which 40 were excluded due to either poor quality of T1-W volume or segmentation data. SCIs were detected in 37/144 (26%) and vasculopathy in 15/144 (10%): right two Grade 0, six Grade 1, seven Grade 2; left four Grade 0, six Grade 1, two Grade 2, three Grade 3. Three patients had bilateral vasculopathy, but none had vasculopathy Grade 4. A total of 57 non-SCA sibling controls had brain volume datasets, four were excluded due to evidence of SCI (two) or poor-quality of T1-W volume or segmentation data (two). The final sample comprised 144 patients (aged 5–20 years; 74 male; all HbSS) and 53 controls (aged 5–17 years; 29 male; 42 with HbAA and the remainder HbAS) (Table 1, Figure 1). The non-SCA siblings were younger than the SCI–, SCI+ and the VASC– groups (Table 1), but there were no between-group differences in sex (Table 1).

Comparison of brain volumes according to SCI and vasculopathy status

Raw data for regional GM volumes in controls, and patients with SCA with and without SCI are presented in Figure 2. Raw data for total GM and for WM volumes are shown in Figures S1 and S2, while trajectories (plotting volumes against age) for cortical and subcortical GM volume and total WM volume are presented in Figures S3–S8 and Tables S1 and S2. For certain volumes, outlier values from two controls, two SCI– patients and two SCI+ patients were excluded from analyses (Table 2). After controlling for age, sex and intracranial volume, significant differences in GM volume between controls, SCI– and SCI+ patients were found for the cerebellar cortex, globus pallidus, and amygdalae bilaterally, the left hippocampus, left putamen, and right thalamus, as well as for total cortical GM, total subcortical GM and total GM (Table 2, Figure 2). Post hoc tests showed that controls had greater mean volumes than both the SCI– and SCI+ patients for the left cerebellar cortex, bilateral globus pallidus, bilateral amygdala, and right thalamus, as well as for total cortical GM, total subcortical GM, and total GM (Table 2). No differences in brain volumes were observed between children with SCA who did and did not have SCI (SCI– vs. SCI+). In controls, total WM volumes were positively correlated with subcortical GM ($r = 0.665$, $p < 0.0005$) and total GM ($r = 0.360$, $p < 0.0005$) volumes with a trend for a correlation with cortical GM volume ($r = 0.256$, $p = 0.067$). In patients with SCA, cortical WM volumes were weakly positively correlated with subcortical GM volumes ($r = 0.205$, $p = 0.013$) with no evidence of a relationship with total GM volume ($r = 0.81$, $p = 0.3$) or cortical GM volume ($r = 0.103$, $p = 0.2$).

Patients with no vasculopathy (VASC–) had significantly greater mean volume than the control group in the left

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TABLE 1 Demographics

	Control ($n = 53$)	SCI– ($n = 107$)	SCI+ ($n = 37$)		p	Post hoc
Age, years, mean (SD, range)	11.2 (3.3, 5–17)	13.3 (3.6, 5–19)		ANOVA $F = 6.694$	0.002	Control < SCI– ** Control < SCI+ **
Sex, n	29M, 24F	53M, 54F	20M, 17F	$\chi^2 = 0.14$	0.707	
Haemoglobin, g/l, mean (SD, range)	119 (11, 89–138)	75 (11, 44–101)	75 (11, 55–100)	ANOVA $F = 188.19$	<0.005	Control > SCI– ** Control > SCI+ **
Genotype	11 AS, 42 AA	All SS	All SS			
	Control ($n = 53$)	**VASC– ($n = 129$)**	**VASC+ ($n = 15$)**			
Age, years, mean (SD)	11.2 (3.35)	13.3 (3.7)	13.1 (3.6)	ANOVA $F = 6.703$	0.002	Control < VASC–** Control < VASC+ *
Sex, n	29M, 24F	67M, 62F	7M, 8F	$\chi^2 = 0.15$	0.699	

Abbreviations: ANOVA, analysis of variance; F, female; M, male; SCI, silent cerebral infarction; VASC, vasculopathy.

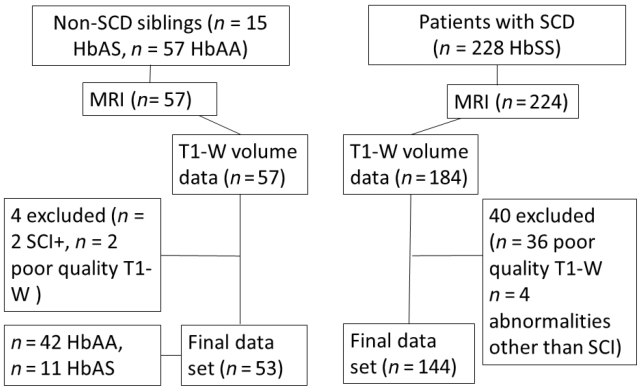


FIGURE 1 Study flow diagram showing total number of recruited patients with SCD and healthy siblings with no history of stroke and those who underwent MRI investigation. Hb, haemoglobin; MRI, magnetic resonance imaging; SCD, sickle cell disease; SCI, silent cerebral infarction; T1-W, T1-weighted MRI

putamen and left hippocampus. In the left globus pallidus, the VASC– group had significantly greater volume than the VASC+ group (Table 3) but the grade of vasculopathy did not significantly affect globus pallidus volume (one-way analysis of variance [ANOVA] $F = 0.814$, $p = 0.5$).

Figures S3–S5 and Table S1 shows the differences in developmental trajectories between the controls and the patients with SCA with and without SCI. Age significantly predicted cortical GM ($p < 0.001$) and WM ($p = 0.016$) volumes, and total subcortical GM volume at trend level ($p = 0.061$) in both patient groups (SCI+ and SCI–) and controls. Only cortical GM volume was significantly delayed in patients at onset ($p = 0.002$). Although rate of development was not significantly different between patients and controls for GM and WM volumes, the rate of development for patients remained below controls (Table S1). There were trend level differences in the rate of development for total subcortical GM volumes between patients and controls ($p = 0.057$). The rate of change in subcortical GM volume was different in SCI+ patients compared with SCI– patients and controls (Figure S4).

Developmental trajectories were also calculated for WM, cortical GM, and total subcortical GM volume by vasculopathy status (Figures S6–S8 and Table S2). Age significantly predicted only cortical GM volume, which was significantly delayed at onset between patients (VASC– and VASC+) and controls. WM volume differed at onset between patients and controls at a trend level ($p = 0.074$), while subcortical volumes did not differ at onset between patients and controls. Rate of development did not significantly differ between patients and controls. However, the rate of development for patients was below controls, while patients with VASC+ showed decreased WM and subcortical GM volumes over time as compared to VASC– patients and controls (Figures S7 and S8).

Association with haemoglobin

In all subjects, after correcting for the effects of age, sex and intracranial volume, there were significant positive effects of haemoglobin level on cerebellar cortex, bilateral globus pallidus, bilateral amygdalae, right thalamus, and total cortical and total GM volumes (Table 4). An identical analysis was performed in a subset comprised of patients only ($n = 135$); no significant effects were observed (Table 4, Figure 3).

DISCUSSION

This is the first study to explore regional GM and WM volumes in children with sickle cell disease (SCD) living in Africa. After accounting for the effects of age, sex, and intracranial volume, patients with SCA with and without SCI and/or vasculopathy had smaller volumes than controls in the cerebral and cerebellar cortex, and several subcortical structures (i.e., globus pallidus and amygdalae bilaterally and the right thalamus), while the volume of other deep GM structures, including the hippocampus, putamen, caudate and accumbens, appeared to be greater on at least one side in those with SCA. In normal children, GM volume peaks at 5.9 years of age and then declines in a near-linear fashion, while WM peaks in young adulthood, at 28.7 years of age.[27] The observed differences in regional GM volumes

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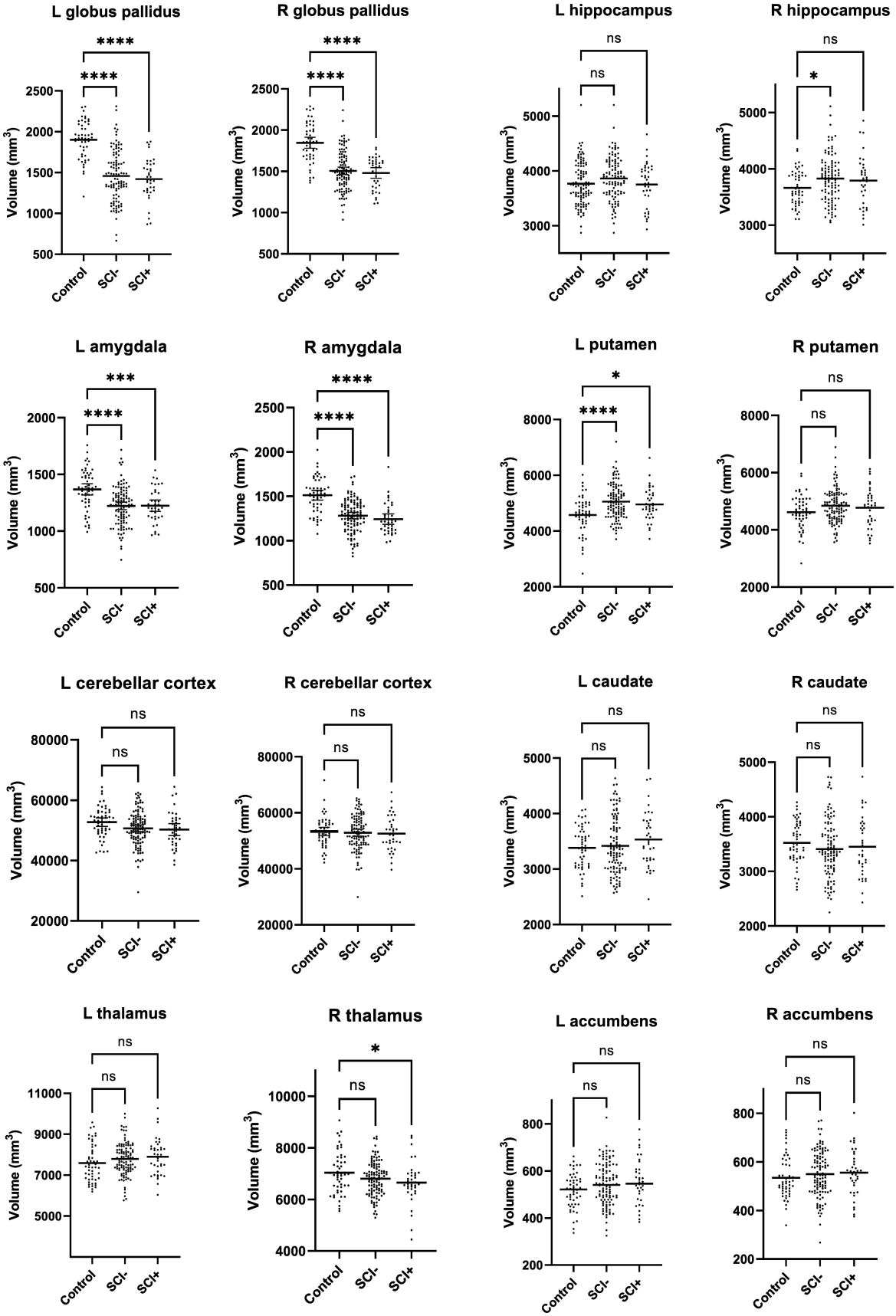


FIGURE 2 Grey matter structure volumes across controls and patients with sickle cell anaemia (SCA) without (SCI–) and with (SCI+) silent cerebral infarction. The eight graphs on the left show data for structures where volumes were higher in controls on at least one side, while the eight graphs on the right show data for the structures where volumes were higher in patients with SCA on at least one side. L, left; R, right

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TABLE 2 Volumetric differences in controls and silent cerebral infarction groups

Volume, mm^3, mean (SD)	Control ($n = 53$)	SCI− ($n = 107$)	SCI+ ($n = 37$)	ANCOVA F	p	Post hoc
Left cerebellar cortex	52 908.1 (5164.7)	50 566.8 (5777.4)	50 103.6 (5950.0)	10.551	<0.001***	Control > SCI− *** Control > SCI+ ***
Left thalamus	7589.2 (905.2)	7790.2 (813.3)	7897.8 (903.2)[a]	0.240	0.787	
Left caudate	3379.9 (376.7)	3416.3 (509.7)	3495.2 (532.4)	0.221	0.802	
Left putamen	4642.7 (578.7)[b]	5057.5 (623.6)	4952.9 (577.3)[a]	7.432	<0.001**	Control < SCI− ***
Left globus pallidus	1904.2 (225.7)	1451.1 (310.6)	1400.2 (278.0)	48.163	<0.001***	Control > SCI− *** Control > SCI+ ***
Left hippocampus	3601.7 (291.4)	3850.5 (427.9)[c]	3750.5 (403.7)	6.517	0.002*	Control < SCI− **
Left amygdala	1365.3 (179.3)	1222.5 (175.7)	1222.9 (148.5)	29.300	<0.001***	Control > SCI− *** Control > SCI+ ***
Left accumbens	513.8 (74.7)	544.92 (89.2)	549.2 (101.0)	2.274	0.106	
Right cerebellar cortex	53 426.9 (5325.9)	52801.1 (6251.2)	52 362.9 (6308.0)	3.112	0.046	Control > SCI+ *
Right thalamus	7042.9 (808.5)	6794.6 (657.2)	6709.8 (727.2)[a]	8.871	<0.001***	Control > SCI− ** Control > SCI+ ***
Right caudate	3527.7 (394.8)	3406.6 (532.3)	3470.9 (541.4)	1.693	0.187	
Right putamen	4618.5(580.2)	4843.6(589.4)	4768.1(670.1)	2.886	0.058	
Right globus pallidus	1848.0 (234.5)	1501.9 (234.9)	1479.1 (193.8)	51.338	<0.001***	Control > SCI− *** Control > SCI+ ***
Right hippocampus	3672.1 (295.1)[d]	3816.3 (396.1)[c]	3770.9 (445.5)[a]	1.525	0.220	
Right amygdala	1514.9 (196.5)	1279.7 (180.8)	1248.1 (177.4)	62.790	<0.001***	Control > SCI− *** Control > SCI+ ***
Right accumbens	533.7 (83.7)	550.5 (96.1)	551.9 (96.7)	0.970	0.380	
Total cortical GM	524 211.1 (43 858.0)	48 3815.9 (50 131.0)	481 036.3 (50 756.9)	32.187	<0.001***	Control > SCI− *** Control > SCI+ ***
Total subcortical GM	54 631.4 (4759.6)[d]	54 200.2 (4089.2)[e]	54 066.1 (4582.1)[a]	4.958	0.008*	Control > SCI− * Control > SCI+ **
Total GM	686 133.7 (51 908.0)	641 177.3 (61 066.9)	636 927.4 (60 906.2)	36.255	<0.001***	Control > SCI− *** Control > SCI+ ***
Total intracranial volume	1 335 946.3 (135 662.1)	1 368 633.3 (121 654.0)	1 389 817.7 (128 239.8)	1.394	0.251	

Abbreviations: ANCOVA, analysis of covariance; GM, grey matter; SCI, silent cerebral infarction.

[a]$n = 37$ SCI+; [b]$n = 51$ controls; [c]$n = 105$ SCI−; [d]$n = 106$ SCI−; [e]$n = 52$ controls; *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ after false discovery rate (FDR) correction for multiple comparisons.

in patients with SCA as compared to controls could be due to differences in developmental trajectories or normal trajectories followed by atrophy in the patients. Interestingly, we have recently reported differences between children with SCA and controls in cognitive trajectories for some domains.[28] As almost all of our patients and controls were aged >5.9 years and all were aged <28.7 years, we plotted trajectories for total GM and cortical WM volume data (see supplement); these suggest that there may be differences in intercept and/or gradient between patients with SCA and controls, consistent with the notion that there is a difference in brain development in youth with SCA. As in the general population, atrophy may supervene subsequently.[27] Analysis of the trajectories of available cross-sectional brain volume data over the paediatric and adult age range would be an appropriate next step. A longitudinal study, ideally including young children, would ultimately be required to determine whether the differences in volume in patients with SCA are developmental or degenerative, or whether both are involved. Although the scanner in Dar es Salaam has been decommissioned for clinical use, the feasibility of undertaking such a study for this cohort is under consideration.

Our data are generally consistent with prior studies.[6,7,11] Steen et al.[9] similarly found that GM volume was reduced in patients with SCA compared to healthy controls, with greater reductions in central than cortical GM. A more recent study found a significant age-related decrease in GM volume in 28 children with SCA not observed in 28 controls,[7] while data from the Silent Infarct Transfusion Trial (SIT) have shown that children with SCA are at risk of global progressive reduction in brain volumes.[6,8]

Despite their potential importance in cognitive function, there are relatively few data on the volumes of regional subcortical structures in patients with SCA compared with controls. One study in adults with SCA found

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TABLE 3 Volumetric differences in controls and vasculopathy groups

Volume, mm^3, mean (SD)	Control ($n = 53$)	VASC− ($n = 129$)	VASC+ ($n = 15$)	ANCOVA F	p	Post hoc
Left cerebellar cortex	52 908.1 (5164.7)	50 585.6 (5845.1)	49 315.3 (5525.8)	10.694	<0.001***	Control > VASC− *** Control > VASC+ **
Left thalamus	7589.2 (905.2)	7778.9 (817.9)	8152.6 (937.0)[a]	2.342	0.098	
Left caudate	3379.9 (376.7)	3444.9 (500.2)	3372.6 (637.9)	0.287	0.751	
Left putamen	4642.7 (578.7)[b]	5042.5 (597.4)	4928.3 (739.5)[a]	6.650	0.002**	Control < VASC− **
Left globus pallidus	1904.2 (225.7)	1458.9 (290.8)	1267.4 (347.7)	52.545	<0.001***	Control > VASC− *** Control > VASC+ *** VASC− > VASC+ *
Left hippocampus	3601.7 (291.4)	3827.8 (408.5)[c]	3792.5 (535.6)	4.414	0.014*	Control < VASC− **
Left amygdala	1365.3 (179.3)	1221.6 (166.6)	1230.4(188.7)	29.083	<0.001***	Control > VASC− *** Control > VASC+ ***
Left accumbens	513.8 (74.7)	549.0 (89.1)	522.3 (114.4)	3.041	0.050	
Right cerebellar cortex	53 426.9 (5325.9)	52 758.5 (6284.7)	52 104.0 (6099.9)	2.771	0.065	
Right thalamus	7042.9 (808.5)	6754.01 (631.7)[d]	6922.8 (963.7)	8.388	<0.001***	Control > VASC− ***
Right caudate	3527.7 (394.8)	3437.6 (527.7)	3309.7 (584.1)	2.248	0.108	
Right putamen	4618.5 (580.2)	4834.0 (591.4)	4742.5 (762.3)	2.415	0.092	
Right globus pallidus	1847.983 (234.5)	1505.9 (222.3)	1415.5 (232.6)	53.013	<0.001***	Control > VASC− *** Control > VASC+ ***
Right hippocampus	3672.1 (295.1)[e]	3811.0 (394.6)[f]	3693.8 (475.4)[a]	1.451	0.237	
Right amygdala	1514.9 (196.5)	1267.9 (178.6)	1300.2(193.4)	60.776	<0.001***	Control > VASC− *** Control > VASC+ ***
Right accumbens	533.7 (83.7)	551.0 (95.9)	550.1 (99.3)	0.969	0.381	
Total cortical GM	524 211.1 (43 858.0)	482 952.7 (50 421.1)	484 173.6 (49 325.8)	31.281	<0.001***	Control > VASC− *** Control > VASC+ ***
Total subcortical GM	54 631.4 (4759.6)[e]	54 243.4 (4221.0)	53 448.1 (4147.1)[g]	4.562	0.012*	Control > VASC− *
Total GM	686 133.7 (51 908.0)	640 184.1 (61 119.1)	63 9091.7 (60 489.5)	34.871	<0.001***	Control > VASC− *** Control > VASC+ ***
Total intracranial volume	1 335 948.3 (133 665.1)	1 372 933.7 (125 235.3)	1 381 815.7 (105 566.7)	1.134	0.324	

Abbreviations: ANCOVA, analysis of covariance; GM, grey matter; VASC, vasculopathy.

[a]$n = 15$ VASC+; [b]$n = 51$ controls; [c]$n = 127$ VASC−; [d]$n = 126$ VASC−; [e]$n = 52$ controls; [f]$n = 128$ VASC−; [g]$n = 14$ VASC+, *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ after FDR correction for multiple comparisons.

reduced volumes in the basal ganglia and thalamus, as well as thinner frontal lobe cortex.[28] Our study found smaller volumes in the cerebellum, amygdala and pallidum in patients with SCA compared to controls, which is consistent with other studies.[11] However, volumes of the putamen and hippocampus were greater in those with SCA without SCI or vasculopathy than in controls, statistically significantly on the left. This observation was unexpected; although we controlled for age, the trajectory of brain growth may be different in SCD and the difference in age may account for this finding. Another possible explanation is that hypoxic anaemia alters the trajectory of brain development in children, provided that cerebrovascular and brain damage do not supervene.

We hypothesised that cortical and subcortical GM volumes would be smaller in patients with SCA with SCI in comparison to those without SCI, but found little evidence for this in our relatively large study, consistent with a study in adults,[29] although smaller studies in children have found an association.[11,30] It is possible that the GM volume decrease precedes the development of SCI, which mainly occur in the WM. Studies with smaller sample sizes have shown a relationship between SCI and brain atrophy, which was not detected in our cross-sectional study, although the trajectory analysis suggests effects. The differences could be due to the smaller proportion of patients with SCA with SCI, 26% (37/144) in our study as compared to 44% (16/36) and 50% (13/26) in the studies of Baldeweg et al.[30] and Kawadler et al.[11]

The novel findings of no significant differences in regional GM volumes between VASC− versus VASC+, could be partly due to a relatively small number of patients with SCA with vasculopathy on MRA (15/144; 10%); again the trajectory analysis suggests an effect. MRA defined intracranial vasculopathy is associated with increased risk of SCI and is an independent predictor of atrophy or reduced total brain volume in patients with SCA.[15] In this study, the volume of the left globus pallidus was smaller in patients with

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TABLE 4 Multiple regression with haemoglobin and brain volumes in all subjects

	Haemoglobin count (n = 168)			
	Left		Right	
Volume	t	p	t	p
Cerebellar cortex	3.581	<0.001**	1.461	0.146
Thalamus	−0.746	0.457	3.654	<0.001***
Caudate	0.266	0.791	1.710	0.089
Putamen	−2.174	0.031	−1.049	0.296
Globus pallidus	7.241	<0.001***	8.319	<0.001***
Hippocampus	−1.736	0.085	−0.930	0.354
Amygdala	5.07	<0.001***	7.545	<0.001***
Accumbens	−0.839	0.403	−2.225	0.027
Total cortex	5.514	<0.001***		
Subcortical GM	2.078	0.039279		
Total GM	5.863	<0.001***		

Abbreviation: GM, grey matter.

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ after false discovery rate (FDR) correction for multiple comparisons.

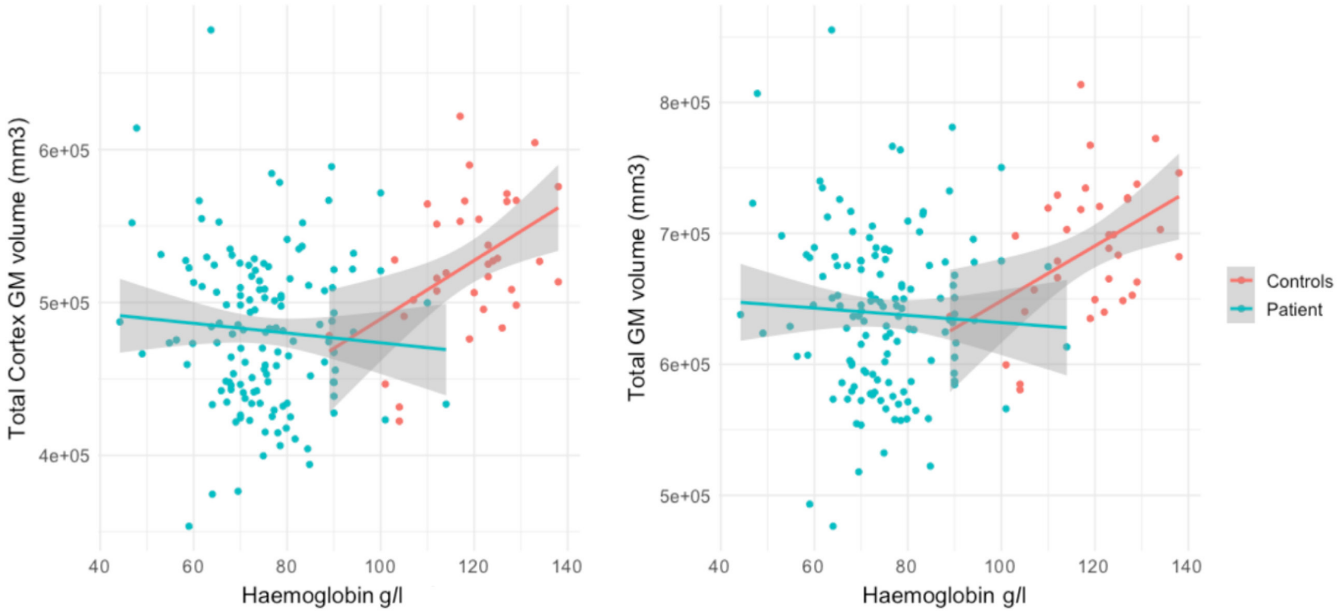


FIGURE 3 Association between haemoglobin and GM volumes. Data for controls are in red, while data for patients with SCA are in green. The grey areas represent the 95% confidence intervals. GM, grey matter; SCA, sickle cell anaemia

SCA with vasculopathy compared to those with no vasculopathy. There are asymmetries in typically developing children with the left globus pallidus larger than the right.[31] The vascular supply to the globus pallidus is somewhat variable between subjects but is usually supplied by perforators from the ACA and MCA, which are involved in patients with intracranial vasculopathy in the context of SCD. It is possible that there is a combination of developmental and hypoxic-ischaemic factors at play in the asymmetry between volumes of the globus pallidus in children with SCA. For other structures, however, any differences between SCA groups were not statistically significant; again there may an interplay between differences in growth trajectory, which for subcortical GM plateaus in typically developing children at 14.4 years of age,[26] and atrophy related to the disease process. A longitudinal study with a large sample size is needed to explore the relationship between vasculopathy and brain volume.

There were significant effects of haemoglobin on total cortical GM and total GM volume in controls but not in patients with SCA. Children with SCA have chronic anaemia, they also experience acute on chronic anaemia. We did not have enough longitudinal haemoglobin data to assess the effect of chronic anaemia

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on the brain volume, but it is possible that early anaemia, relatively severe compared with any iron deficiency anaemia in the controls, and perhaps accompanied by hypoxia, altered the trajectory of brain growth in the children with SCA. The GM and WM volume data in infants with a wide range of haemoglobins and oxygen saturations will be required to explore this possibility. In the context of severe chronic anaemia from infancy, contemporaneous anaemia might not independently affect brain growth detectable on neuroimaging in patients with SCA. Other studies have shown that lower haemoglobin is associated with decreases in WM volume in both controls and patients with SCA,[16,17] as well as in those with non-SCA anaemia.[17] Chronic exposure to low haemoglobin in patients with SCA could have been associated with brain injury early in life, with the normal brain of healthy controls susceptible to effects of low haemoglobin levels over a longer period of time.

Study limitations

This was a cross-sectional study, so causal association cannot be established; longitudinal studies looking at individual trajectories will be important.[32] Although, as well as patients, we recruited a relatively large number of controls, they were significantly younger by an average of 2 years; this effect was mitigated by controlling for age in all analyses. However, the correction might be incomplete and further studies over a wide age range with a larger number of age-matched controls will be important in understanding the factors determining growth and atrophy of the brain in SCD. This study was underpowered to fully explore the effect of vasculopathy or SCI on brain volume due to small numbers of patients who had those abnormalities. Although the present study explored brain volume deficits in neurologically asymptomatic individuals with SCA, they might have less severe vascular abnormalities obscuring our ability to show an effect.

CONCLUSION

This cross-sectional study exploring regional GM volumes in children with SCA living in Africa showed that asymptomatic patients with SCA generally have reduced GM volumes compared with controls, although some subcortical regions may be spared. SCI on MRI or mild and moderate vasculopathy on MRA do not appear to have direct effects on brain volumes. However, the trajectory analyses suggest an effect and a larger cohort studied at higher magnet field strength to increase the detectability of SCI and vasculopathy,[33] and including patients with Grade 4 vasculopathy, would be required to exclude an effect. Brain volume in non-SCA children may be vulnerable to contemporaneous anaemia. A longitudinal study is required to explore changes in brain volumes over time in patients with SCA and to determine any impact of chronic anaemia from infancy, and/or of the development of SCI and vasculopathy, which are pathologies typically not detected at the time they occur.

AUTHOR CONTRIBUTIONS

Mboka Jacob, Jamie M. Kawadler, Russell Murdoch, Karin Shmueli, Dawn E. Saunders, Chris A. Clark, Julie Makani, Hanne Stotesbury and Fenella J. Kirkham designed the study. Mboka Jacob, Magda Ahmed, Hilda Tutuba, Upendo Masamu, Julie Makani acquired data. Mboka Jacob, Jamie M. Kawadler, Russell Murdoch, Karin Shmueli, Dawn E. Saunders, Shifa Hamdule, Hanne Stotesbury and Fenella J. Kirkham analysed data. Mboka Jacob, Jamie M. Kawadler, Russell Murdoch, Karin Shmueli, Magda Ahmed, Hilda Tutuba, Upendo Masamu, Dawn E. Saunders, Chris A. Clark, Jinna Kim, Julie Makani, Shifa Hamdule, Hanne Stotesbury and Fenella J. Kirkham wrote and revised the paper critically. All authors approved the submitted and the final versions.

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CONFLICTS OF INTEREST

Dr Kirkham reports grants from Action Medical Research during the conduct of the study; personal fees from Global Blood Therapeutics (GBT) outside the submitted work. Mboka Jacob, Jamie Kawadler, Russell Murdoch, Magda Ahmed, Hilda Tutuba, Upendo Masamu, Karin Shmuel, Dawn E. Saunders, Chris A. Clark, Jinna Kim, Shifa Hamdule, Julie Makani, Hanne and Stotesbury declare that they have no financial or personal relationship(s) that may have inappropriately influenced them in writing this article.

DATA AVAILABILITY STATEMENT

Data will be available for sharing upon request.

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