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Original Article

Quantitative Volumetric Analysis of the Brain Using Magnetic Resonance Imaging in Sickle Cell Anaemia

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Abstract

Background: Sickle cell disease (SCD) is a group of inherited hemoglobinopathies caused by a mutation in the β-globin gene, with sickle cell anaemia (SCA) representing the homozygous and most severe form. The disease burden is highest in sub-Saharan Africa, India, and the Mediterranean region. Neurological complications, including overt stroke and silent cerebral infarcts (SCI), contribute significantly to morbidity, with a markedly increased risk observed among affected individuals. The objective of the study is to assess and compare brain gray matter and white matter volumes in patients with sickle cell anaemia with and without silent cerebral infarcts, and in healthy controls.

Methodology: This cross-sectional study included 264 participants divided into three groups: SCA patients with SCI, SCA patients without SCI, and age- and sex-matched healthy controls. All participants underwent brain magnetic resonance imaging using a 1.5 Tesla scanner. Image segmentation and volumetric analysis were performed using the Computational Anatomy Toolbox (CAT12).

Results: White matter volume was significantly reduced in SCA patients, both with and without SCI, compared to controls. Gray matter volume was significantly increased in SCA patients, particularly among those without SCI, relative to controls.

Conclusion: Sickle cell anaemia is associated with significant reductions in white matter volume and alterations in gray matter volume, highlighting the impact of the disease on brain structure even in the absence of overt neurological deficits.

Keywords: Brain Volume Segmentation, Magnetic Resonance Imaging, Sickle Cell Anaemia, Silent Cerebral Infarct, CAT12

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Introduction

Sickle cell disease (SCD) is a major global health burden, particularly in sub-Saharan Africa, India, and the Middle East, where it contributes significantly to morbidity and mortality. Sickle cell anaemia (SCA), the most severe form, results from a mutation in the haemoglobin gene (Glu6Val, βS) leading to homozygous HbSS.1 Under hypoxic conditions, sickle haemoglobin polymerizes, causing erythrocyte deformation, chronic haemolysis, and microvascular occlusion.[1]

Approximately 300,000 infants are born with SCD annually, with the disease accounting for 5–16% of under-five mortality in parts of Africa.[2] In Nigeria, the pooled prevalence of SCA is 2.9%, with higher rates in the northwest region (5.6%).[3]

Silent cerebral infarcts (SCI) are among the most common neurological complications of SCA and are defined as areas of abnormal T2 signal intensity on magnetic resonance imaging (MRI) in the absence of overt neurological deficits.[4] More precisely, SCI are lesions measuring at least 3 mm and visible in at least two planes on T2-weighted images.[5] MRI remains the modality of choice for detection, while magnetic resonance angiography may identify vascular abnormalities associated with increased stroke risk.[6,7]

Neurological complications are highly prevalent in SCA, with many patients developing cerebral infarcts over time.[8,9]The incidence of stroke is approximately 2 per 1000 person-years in children and 9 per 1000 person-years in adults.[10]

Beyond focal infarction, SCA is associated with diffuse structural brain changes, including brain atrophy.[11] Quantitative brain morphometry using MRI enables objective assessment of gray matter (GM), white matter (WM), and cerebrospinal fluid volumes, providing a complementary approach to lesion-based imaging. [12,13] Alterations in these volumes may reflect disease severity and underlying pathological processes.[12,14-18]

Previous studies have demonstrated structural brain changes in SCA, including reduced gray matter volumes, cortical thinning, and white matter abnormalities.[4,19-22] However, there remains a need for further quantitative evaluation of global brain tissue volumes, particularly in relation to silent cerebral infarcts.

Therefore, this study aimed to perform MRI-based brain segmentation and quantitative volumetric analysis of gray and white matter in patients with sickle cell anaemia with and without silent cerebral infarcts, and to compare these findings with healthy controls.

Methodology

This was a cross-sectional case–control study conducted over a one-year period at a tertiary health facility in Northwestern Nigeria. The study included 264 participants, comprising 88 patients with silent cerebral infarcts (SCI), 88 patients without SCI, and 88 age- and sex-matched healthy controls. Ethical approval for this study was obtained from the Health Research Ethics Committee of Bayero University, Kano (NHREC/BUK-HREC/456/10/2311; dated 7th March 2025). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patients with sickle cell anaemia (homozygous HbSS) who had no neurological deficits on examination, no prior history of overt stroke, and transcranial Doppler ultrasound mean velocities ≤170 cm/s on routine screening were included in the study.

Silent cerebral infarcts were defined as focal lesions ≥3 mm in greatest dimension, visible on at least two planes of T2-weighted MRI, in the absence of neurological deficits.[5]

Exclusion criteria included a history of major head injury requiring emergency care, seizure disorders requiring anticonvulsant therapy, chronic transfusion therapy, acute chest syndrome, prenatal or perinatal hypoxic–ischemic brain injury, and HIV infection/AIDS.

The control group consisted of age- and sex-matched individuals without sickle cell anaemia who were referred for brain MRI and had normal imaging findings.

Magnetic resonance imaging of the brain was performed using a 1.5T Siemens Magnetom Essenza. All patients were examined in the supine position with the head immobilized in a dedicated head coil. Images were acquired in axial, coronal, and sagittal planes with a slice thickness of 3 mm. For the purpose of this study, only T1-weighted sequences were utilized for analysis. The protocol included axial and coronal T1-weighted imaging, acquired with typical parameters of repetition time (TR) 400–600 ms and echo time (TE) 15–25 ms, a matrix size of approximately 320 × 320, and a field of view of 210–230 mm. Although additional sequences were obtained as part of the routine clinical protocol, they were not included in the present analysis. Patients were instructed to remove all metallic objects and remain still during the examination, which lasted approximately 23–30 minutes. No contrast agent was administered.

Structural MRI data were processed using the Computational Anatomy Toolbox (CAT12) implemented within the Statistical Parametric Mapping (SPM) software in MATLAB. Following data conversion to NIfTI format, images were imported into CAT12 and subjected to automated segmentation into grey matter, white matter, and cerebrospinal fluid compartments using default parameters, with optional atlas-based parcellations enabled where required. Quality control of the segmented outputs was performed by visual inspection of the generated images to identify preprocessing errors. Total intracranial volume (TIV) was subsequently extracted from the generated XML files for each subject and incorporated as a covariate in downstream statistical analyses to account for inter-individual variability in head size. Regional brain volumes were obtained from atlas-based region-of-interest outputs (catROIs), allowing extraction of quantitative measures for grey matter, white matter, and cerebrospinal fluid across predefined anatomical regions. These volumetric data were then exported for further statistical analysis using appropriate software packages.[23]

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics version 27 (IBM Corp., Chicago, IL, USA). Data were initially entered into Microsoft Excel, cleaned, and subsequently exported to SPSS for analysis.

Descriptive statistics were expressed as mean ± standard deviation (SD) for continuous variables. The normality of data distribution was assessed using the Shapiro–Wilk test.

For comparisons across the three study groups (SCA patients with SCI, SCA patients without SCI, and healthy controls), the Kruskal–Wallis test was used for non-normally distributed variables. Where a statistically significant difference was identified, post hoc pairwise comparisons were performed using the Mann–Whitney U test with Bonferroni adjustment for multiple comparisons.

Comparisons between two independent groups (e.g., gender-based comparisons) were performed using the independent samples t-test for normally distributed variables.

Correlation analysis between continuous variables (e.g., age and brain volume measurements) was performed using Pearson's correlation coefficient for normally distributed data and Spearman's rank correlation coefficient for non-parametric data.

Categorical variables were presented as frequencies and percentages. A p-value of less than 0.05 was considered statistically significant.

Results

This study included 264 participants, comprising equal numbers of patients with sickle cell anaemia (SCA) with silent cerebral infarcts (SCI), those without SCI, and healthy controls. The age range for these groups was 16–37 years, 16–36 years, and 16–37 years, respectively, with mean ± SD of 22.2±4.8, 22.1±4.8, and 22.2±4.9 years. There was a female predominance, with females accounting for 62% of the study population across all groups.

The body mass index (BMI) of the study participants ranged from 10.0–28.0 kg/m² (mean ± SD: 17.6±2.9 kg/m²) among patients with SCI, 13.0–24.0 kg/m² (17.9±2.5 kg/m²) among patients without SCI, and 16.0–34.0 kg/m² (23.8±3.5 kg/m²) among the controls.

Comparing the white matter volumes, mean ± SD values of 389.0±65.8 cm³ and 473.0±193.1 cm³ were observed among SCA patients with SCI and healthy controls, respectively. This difference was statistically significant (p<0.001) (Table 1).

Similarly, white matter volumes of 417.3±81.5 cm³ and 473.0±193.1 cm³ were observed among SCA patients without SCI and healthy controls, respectively, with a statistically significant difference (p=0.014) (Table 1).

Table 1: Quantitative comparison of brain tissue volumes (white matter, gray matter, and cerebrospinal fluid) among sickle cell anaemia patients with silent cerebral infarcts, without silent cerebral infarcts, and healthy controls, including post hoc pairwise analysis

Part of the Brain	SCI	No SCI	Normal	*P*-Value
White Matter Volume (cm^3)	389.0±65.8	417.3±81.5	473.0±193.1	<0.001*
Gray Matter Volume (cm^3)	506.1±58.1	528.5±69.0	461.2±116.4	<0.001*
Cerebrospinal Fluid (cm^3)	312.1±93.5	263.2±78.1	300.4±113.0	0.003*

Part of the Brain	Comparison Groups		Mean Difference (cm^3)	*P*-Value
White Matter Volume	Normal	SCI	84.0	<0.001*
	Normal	No SCI	55.7	0.011*
	No SCI	SCI	28.3	0.302
Gray Matter Volume	Normal	SCI	-44.8	0.002*
	Normal	No SCI	-67.3	<0.001*
	No SCI	SCI	22.5	0.188
Cerebrospinal Fluid	Normal	SCI	-12.2	0.696
	Normal	No SCI	37.1	0.038*
	No SCI	SCI	-49.4	0.003*

SCI=Silent Cerebral Infarcts

For gray matter volumes, mean ± SD values of 506.1±58.1 cm³ and 461.2±116.4 cm³ were observed among SCA patients with SCI and healthy controls, respectively. This difference was statistically significant (p=0.001) (Table 1).

Likewise, gray matter volumes of 528.5±69.0 cm³ and 461.2±116.4 cm³ were observed among SCA patients without SCI and healthy controls, respectively, and this difference was also statistically significant (p<0.001) (Table 1).

Comparing SCA patients with SCI and those without SCI, mean gray matter volumes of 506.1±58.1 cm³ and 528.5±69.0 cm³ were observed, respectively. This difference was statistically significant (p=0.025) (Table 1).

Similarly, white matter volumes of 389.0±65.8 cm³ and 417.3±81.5 cm³ were observed among SCA patients with SCI and those without SCI, respectively, with a statistically significant difference (p=0.017) (Table 1).

Among SCA patients with SCI, mean white matter and gray matter volumes were slightly higher in females than in males, while cerebrospinal fluid (CSF) volume was slightly higher in males than in females. These differences were not statistically significant (Table 2).

In contrast, among SCA patients without SCI, mean white matter and gray matter volumes were slightly higher in males than in females, while CSF volume was slightly higher in females. However, only the difference in gray matter volume was statistically significant (*p*=0.014)

Among the healthy controls, mean white matter volume and CSF were higher in females than in males, whereas mean gray matter volume was higher in males. None of these differences was statistically significant (Table 2).

Table 2: Gender-based comparison of brain tissue volumes (white matter, gray matter, and cerebrospinal fluid) among sickle cell anaemia patients with and without silent cerebral infarcts and healthy controls using an independent samples t-test

Variable(s)	Study Group n=88				
	Males (n=31)	Females (n=57)		*t*	*p*-value
SCI	WMV (cm^3)	386.2±82.3	390.6±55.5	-0.29	0.770
	GMV (cm^3)	499.4±68.4	509.7±51.9	-0.81	0.429
	CSF (cm^3)	316.3±77.1	310.6±101.9	-0.27	0.787

No SCI	WMV (cm^3)	425.0±83.8	413.2±80.7	0.65	0.517
	GMV (cm^3)	552.8±81.2	515.3±58.1	2.51	0.014*
	CSF (cm^3)	257.7±96.8	266.3±66.6	-0.49	0.626
Healthy Controls	WMV (cm^3)	438.5±167.9	491.8±204.5	-1.24	0.218
	GMV (cm^3)	484.0±103.7	448.8±121.9	1.36	0.177
	CSF (cm^3)	298.5±132.1	301.4±118.8	-0.11	0.917

*Statistically significant at ≤0.05 level, **WMV=White Matter Volume, GMV=Gray Matter Volume, and Cerebrospinal Fluid=CSF, Silent Cerebral Infarcts=SCI**

For white matter volume, no significant correlation with age was observed across any of the groups. In the control group, the correlation coefficient was -0.054 (p=0.615). In the SCI group, the correlation was -0.024 (p=0.825), while in participants without SCI, it was 0.128 (p=0.236).

For gray matter volume, no significant correlation with age was observed in the control group (r=-0.018, p=0.866) or in the SCI group (r=-0.011, p=0.921). However, among participants without SCI, a statistically significant inverse correlation was observed (r=-0.223, p=0.037).

For CSF volume, no significant correlation with age was observed in any group. In the control group, the correlation coefficient was 0.048 (p=0.656), in the SCI group it was -0.125 (p=0.247), and in participants without SCI it was 0.033 (p=0.763).

Overall, white matter and CSF volumes did not demonstrate significant age-related changes across the groups studied.

Discussion

Brain volume measurement plays a crucial role in the evaluation of neurological and psychiatric disorders. Changes in gray matter volume (GMV), white matter volume (WMV), and cerebrospinal fluid (CSF) enable objective assessment of underlying physiological processes, disease states, and severity.[5,24]

This study included 264 participants, comprising equal numbers of patients with sickle cell anaemia (SCA) with silent cerebral infarcts (SCI), those without SCI, and healthy controls. The age ranges observed in this study (16–37 years, 16–36 years, and 16–37 years, respectively) differ from those reported by Jamie et al.[24]

in East London (9–24 years, 7–25 years, and 11–21 years) and Grant et al.[6]at St. Jude Hospital (3.9–18 years and 4.3–18 years). These differences are likely attributable to variations in study design and inclusion criteria, as previous studies predominantly focused on paediatric populations, whereas the present study involved adults. Additionally, this study included a larger sample size compared to Jamie et al. [24] and Grant et al. [6], which may enhance the robustness of the findings.

The female predominance observed across all study groups does not reflect the known epidemiology of SCA, which typically shows an approximately equal sex distribution. This imbalance may be explained by differences in health-seeking behavior, survival patterns, and willingness to participate in research. A similar female predominance was reported by Jamie et al.[24], whereas Grant et al.[6] observed a male predominance, possibly reflecting regional differences in healthcare access and utilization.

The lower body mass index (BMI) observed among SCA patients compared to healthy controls is consistent with previous studies.[25-27] This finding likely reflects the effects of chronic inflammation, increased metabolic demand, and ongoing organ damage associated with SCA.

Consistent with the findings of this study, previous MRI-based studies have demonstrated structural brain changes in SCA patients. Reduced white matter density has been reported in SCA patients, particularly among those with SCI.[4,20] In the present study, WMV was significantly reduced in SCA patients, both with and without SCI, compared to healthy controls. However, the difference in WMV between SCA patients with and without SCI was relatively small, although statistically significant.

In contrast, gray matter findings in this study differed from several previous reports. While earlier studies have demonstrated reduced GMV and cortical thinning in SCA patients [4,20], the present study found significantly higher GMV in SCA patients compared to healthy controls, with the highest values observed in patients without SCI. Similar variability in GMV findings has been reported in the literature. Grant et al.[6] observed significant differences in GMV, whereas Jamie et al [24] reported no significant differences between groups.

Niebanck et al.[28] reported reduced total brain volume in SCA patients, with slightly lower GMV and more pronounced reductions in central gray matter structures. In contrast, no significant differences in WMV or ventricular volume were observed in their study. These findings differ partially from the present study, which demonstrated significant reductions in WMV but increased GMV. Such discrepancies may be related to differences in study populations, imaging protocols, and analytical techniques.

Several studies have reported reduced subcortical volumes in both children and adults with SCA, including reductions in the hippocampus, amygdala, basal ganglia, and thalamus. [24-26,29] These reductions have been associated with cognitive impairment, particularly reduced working memory index.[29] Although the present study did not assess regional or subcortical volumes, the observed global reductions in WMV are consistent with these findings. The increased GMV observed in this study, however, contrasts with these reports and may reflect differences in methodology or population characteristics.

A systematic review and meta-analysis by Hamdule et al. [29] demonstrated inconsistent findings regarding WMV in SCA patients, with some studies reporting reductions and others showing no significant differences. The reduction in WMV observed in this study is therefore consistent with a substantial proportion of existing evidence. It has been suggested that WMV reduction may result from chronic hypoxia, microvascular occlusion, and impaired cerebral perfusion, particularly in regions supplied by the middle cerebral artery.

The finding of increased GMV in SCA patients, particularly among those without SCI, is noteworthy and requires cautious interpretation. This observation is counterintuitive and does not necessarily indicate preserved or improved brain integrity. Possible explanations include compensatory neuroplastic responses to

chronic hypoxia, altered cerebral blood flow, gliosis, or delayed cortical pruning. Additionally, methodological factors such as segmentation inaccuracies, partial volume effects, or normalization biases inherent in automated pipelines may contribute to this finding.

Previous studies have demonstrated that reduced hemoglobin levels and decreased arterial oxygen content are associated with reductions in both GMV and WMV.[5] Furthermore, increased cerebral blood flow has been linked to WMV reduction and regional gray matter changes.[5] These findings support the hypothesis that chronic hypoxia and altered hemodynamics play a central role in structural brain changes in SCA.

Overall, the findings of this study demonstrate that SCA is associated with significant alterations in brain structure, characterized by reduced WMV and increased GMV. While WMV reduction is consistent with existing literature, the increase in GMV highlights the complexity of brain adaptation in SCA and underscores the need for further studies incorporating regional volumetric and functional analyses to clarify its clinical significance.

Conclusion

Sickle cell anaemia patients, with or without silent cerebral infarcts, demonstrate significantly reduced white matter volume compared with healthy controls, while gray matter volume is paradoxically increased, particularly among patients without silent cerebral infarcts. Cerebrospinal fluid volume differences were modest and varied between subgroups.

These findings indicate that brain volumetric alterations in sickle cell anaemia are complex and likely reflect a combination of injury-related tissue loss and compensatory structural changes. Further longitudinal studies incorporating regional volumetric analysis and cognitive assessment are required to better elucidate the clinical and functional significance of these alterations.

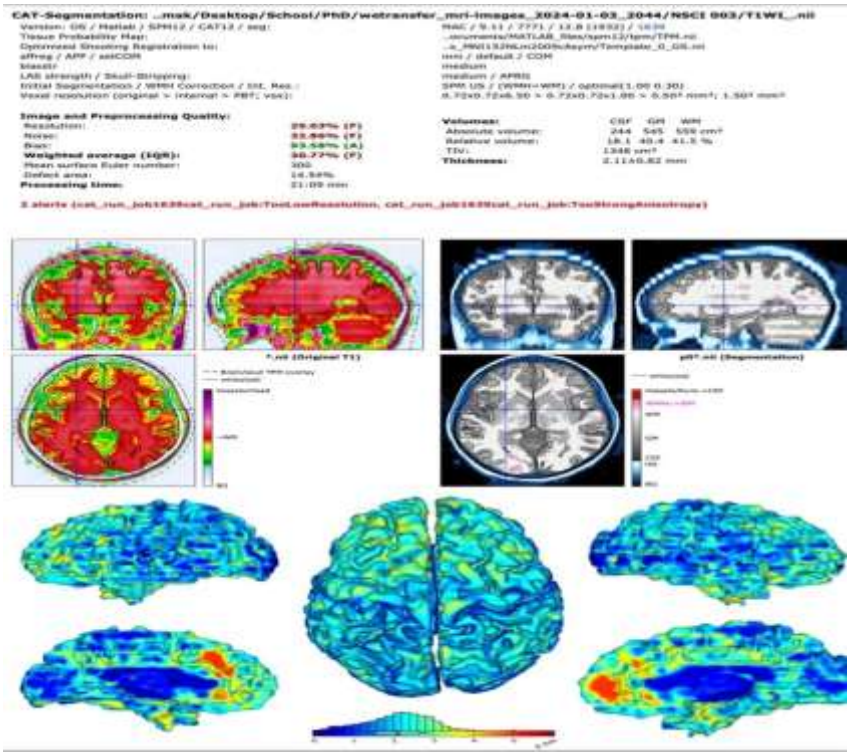

Figure 1: Representative CAT12 segmentation output demonstrating automated classification of brain tissues into gray matter, white matter, and cerebrospinal fluid, as used for volumetric analysis.

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