



Short term stroke outcome is worse among individuals with sickle cell trait



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ABSTRACT

Background: Most (86%) of the global stroke mortality are from low- and middle-income countries (LMIC) including African countries which have the highest prevalence of the sickle cell trait (Hb AS). The effects of this trait on stroke occurrence and outcome are poorly understood. We aimed to investigate the effects of the sickle cell trait on the 30-day stroke mortality in Nigerian-Africans.

Method: This was a prospective study of 35 stroke patients with sickle cell trait (Haemoglobin AS) and 35 age and sex-matched controls without haemoglobinopathy (Haemoglobin AA). Haemoglobin electrophoresis was performed for all before recruitment and they all had neuroimaging done. Patients with haemoglobin AS were used as cases and those with haemoglobin AA as controls. The National Institute of Health Stroke Scale (NIHSS) was used to assess the severity of stroke at presentation and the Modified Rankin Scale for 30-day stroke outcome.

Result: There was no significant difference in the baseline stroke severity between the two groups ($p = 0.21$). Univariate analysis of the factors predicting the 30-day stroke outcome revealed that NIHSS score > 20 ($p < 0.001$), haemorrhagic stroke ($p = 0.01$) and the presence of Hb AS ($p < 0.001$) were significantly associated with 30-day mortality. Haemorrhagic stroke type was strongly associated with HbAS (OR = 2.9, 95% CI = 1.10–7.99, p -value = 0.02). With multiple logistic regression model, the presence of Hb AS ($p = 0.01$) and NIHSS score > 20 ($p = 0.05$) emerged as independent risk factors for 30-day mortality. The cases had worse stroke outcome at 30 days.

Conclusion: Stroke had a worse 30-day mortality and outcome in patients with sickle cell trait (HbAS) than in patients with normal adult haemoglobin (HbAA).

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1. Background

In a retrospective study by Owolabi et al. on the racial disparity in stroke risk factors, the Berlin–Ibadan experience, it was observed that stroke patients in Ibadan were younger than those in Berlin. Hypertension was more common in Ibadan while cigarette smoking, dyslipidaemia, atherosclerosis and cardiac risk factors were more frequent in Berlin [1]. Caughey et al. [2], in a prospective epidemiological study observed an increased risk of ischaemic stroke in blacks with sickle cell trait. Given its high frequency among blacks, sickle cell trait should be evaluated whether it contributes to the peculiarities of stroke in people of black ancestry.

Sickle cell trait is not a risk factor for the development of hypertension in Nigerians. However, its presence was found by Ahmed et al. to be associated with poor blood pressure control which would lead to high risk of end organ damage and poor prognosis [3]. Personalized medicine may have to be used for sickle cell trait patients in terms of stroke prevention and treatment.

In Africa, the highest prevalence of HbAS occurs between latitudes 15° North and 20°S.

This ranges between 10% and 40% in some areas. The geographical distribution is very similar to that of malaria against which it has a protective effect [4,5].

Approximately three hundred million individuals have sickle cell trait worldwide [6], with a prevalence ranging from 24 to 25% [7,8,9] in Nigeria. Considering this high prevalence and the fact that sickle cell trait, from clinical and epidemiological studies, has been associated with some health conditions such as venous thromboembolic events, exercise-related sudden death, splenic infarction and renal papillary

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necrosis [10,11], a look at its relationship with stroke in terms of outcome is essential.

A 10-fold increase in the risk of haemorrhagic stroke has been observed in individuals with Hb AS [12]. It has also been found that there is a higher prevalence of haemoglobinopathies in patients with stroke than in the general population and that the existence of sickle cell trait in the population studied may reduce the age at onset of cerebral haemorrhage [13]. It has even been suggested that the presence of sickle cell trait should be considered as a cause of stroke [14] and this will influence decision making on the primary and secondary prevention of stroke. Homozygous sickle cell disease (sickle cell anaemia) is a well-documented risk factor for both ischaemic and haemorrhagic stroke. In the case of sickle cell trait, there are conflicting reports as to whether it is a risk factor for stroke or not [5]. There is insufficient data in the literature regarding the relationship between the sickle cell trait and stroke outcome. This study was therefore designed to investigate whether sickle cell trait is associated with worse short-term outcome.

2. Methodology

2.1. Study design

This was a case–control prospective study on first ever acute stroke patients attending the Emergency Department of the University College Hospital Ibadan.

2.2. Study location

This was at the Accident and Emergency department and the medical wards of the University College Hospital, Ibadan.

2.3. Study subjects

Cases were stroke patients (both haemorrhagic and ischaemic) with sickle cell trait having first episode of stroke seen at the Emergency Department of the University College Hospital Ibadan. The age- and sex-matched stroke patients with Haemoglobin AA were recruited at the same time from the same hospital as controls. All were Nigerians. All the subjects had their haemoglobin electrophoresis done before recruitment. Stroke was confirmed in all subjects by neuroimaging; either a brain CT or a brain MRI.

Stroke patients who were unable to communicate because of severe stroke, aphasia or dementia but with valid surrogate respondents (spouse or first degree relatives who had lived with the patients in the last one year) were also eligible. They all had either brain CT or brain MRI done.

2.4. Ethical approval

This was obtained from the University of Ibadan/University College Hospital Health Research Joint Institutional Review Board.

2.5. Procedure

Informed consent was obtained from the subjects and controls. Also, the surrogate respondents gave informed consent before commencing the study. Demographic data and clinical characteristics of all subjects and control were collected. The following information was obtained: age, occupation, level of education, history of hypertension and diabetes mellitus, family history of hypertension, diabetes mellitus sudden cardiovascular death and stroke. Their waist and hip circumferences were also measured.

All subjects had their blood samples collected from the right or left cubital vein after the overlying skin must have been cleaned with 70% methylated spirit. Five millilitres (mls) of blood was collected in lithium

heparin bottles for lipid profile analysis. The Borhringer Mannheim Hitachi 704E autoanalyser in the Chemical Pathology Laboratory of the University College Hospital, Ibadan was used for the lipid profile. The level of blood sugar was determined using the capillary blood by glucometer.

Haemoglobin phenotype and haemoglobin S quantification were determined using 2 ml of venous blood collected in EDTA bottles with high performance liquid chromatography at the Genetic Laboratory of the Institute for Advanced Medical Research and Training of the College of Medicine, University of Ibadan.

In the laboratory, all blood samples from the stroke patients were initially screened by the use of the Haemoglobin Electrophoretic Tank to determine those who were having sickle cell trait and normal adult haemoglobin. This machine separates the haemoglobin constituents of the red cells based on their migration on cellulose acetate paper in an alkaline medium using the principle of gel electrophoresis. Those with sickle cell anaemia (HbSS), sickle cell disease and other traits such as haemoglobins AC, SC were excluded. The remaining blood samples of those with sickle cell trait were later subjected to further analysis using the HPLC machine (VARIANT II Haemoglobin Testing System). This is a powerful tool in analytical chemistry. It has the ability to separate, identify and quantitate the compounds that are present in any sample of that can be dissolved in a liquid. The percentage component of each haemoglobin constituents was analysed by eluting process in the fractionating column of the chromatographic station of the machine. The results were displayed on the computer monitor component with the percentage haemoglobin concentration represented by the area under the curve. The level of stroke severity was assessed within 24 h of admission and on the seventh day post stroke for those that survived the acute phase of stroke using the National Institute of Health Stroke Scale. Diagnosis of stroke was confirmed with brain CT or brain MRI and also, stroke mimics were ruled out³⁶. The National Institute of Health Stroke Scale (NIHSS) was administered on all the stroke patients that meet the inclusion and the exclusion criteria within 24 h of admission to assess the severity of stroke in them. While on admission, the same assessment was repeated on the 7th day post stroke. The scale takes approximately 8 min to administer [15]. Those with a score of 0 were classified as having no stroke while those with a score of 1–4 were classified as having minor stroke. Those with a score of 5–15, 15–20 and 21–42 were classified as having moderate, moderate to severe and severe stroke respectively. These were done on consecutive hospitalization until the desired number of patients for the study was got.

2.5.1. Management protocol

All patients (cases and controls) received the same standard management in accordance with the management guidelines of the neurology unit of the hospital which was adopted from various international management guidelines. The patients had isotonic fluid infusion and regular physiotherapy, with early ambulation where possible. All patients with elevated blood pressure did not have antihypertensives within the first 48 h of stroke onset except there were compelling indications like acute left ventricular failure, myocardial ischemia/infarction, rapid decline in renal function, severe hypertension, or dissecting aortic aneurysm. Unconscious patients were turned in bed to prevent pressure sores while those with dense hemiplegia had prophylactic subcutaneous heparin to prevent deep venous thrombosis. The patients were followed up daily while on admission to document improvement and development of neurological and non-neurological complications until they were fit for discharge. Regular clinic visits to monitor and control cardiovascular risk factors were continued as well as physiotherapy.

The stroke outcome was assessed on the 30th day post stroke both in the clinic during the follow-up visit or using the telephone for those that did not come for the follow-up visit either by virtue of death or for other reasons²⁵. For those that died, the next of kin whose phone number was

Table 1
Socio-demographic characteristics of respondents.

Demographic characteristics	Cases n = 35 (%)	Controls n = 35 (%)	p-Value
Age (years) mean (SD)	61.0(15.0)	62.1(15.6)	0.433
Sex			0.810
Male	20 (57.1%)	19 (54.3%)	
Female	15 (42.9%)	16 (45.7%)	
Marital status			0.006
Single	3 (8.5%)	0 (0.0%)	
Married	28 (80.0%)	20 (57.1%)	
Divorced	1 (2.9%)	2 (5.7%)	
Widowed	3 (8.6%)	13 (37.1%)	
Religion			0.788
Christian	26 (74.3%)	25 (71.4%)	
Muslim	9 (25.7%)	10 (28.6%)	
Ethnicity			0.148
Yoruba	32 (91.4%)	32 (91.4%)	
Hausa	0 (0.0%)	2 (5.7%)	
Igbo	3 (8.6%)	1 (2.9%)	
Respondents' educational status			0.349
No formal education	2 (5.7%)	6 (17.1%)	
Primary	6 (17.1%)	3 (8.6%)	
Secondary	16 (45.7%)	14 (40.0%)	
Tertiary	11(31.4%)	12 (34.3%)	
Respondents' occupation			0.000
Trading	11 (32.4%)	22 (62.9%)	
Artisan	4 (10.3%)	4 (10.3%)	
Farmer	10 (29.4%)	0 (0.0%)	
Civil servant	7 (20.6%)	6 (17.1%)	
Banker	2 (5.7%)	1 (2.9%)	

earlier collected gave the required information. The assessment tool used is the Modified Rankin Scale. This is a clinician-reported measure of global disability widely applied for evaluating stroke patient outcomes.

Those that died during admission were noted. The Modified Rankin Scale was filled for those that were discharged home and presented in the clinic on the 30th day post stroke. Until after during the time of analysis of the results, none of these patients was known to be having either sickle cell trait or normal adult haemoglobin.

2.6. Statistical analysis

Data analysis was done using the Statistical Package for the Social Sciences (SPSS), version 16 (SPSS Inc., Chicago, IL, U.S.A.) and all generated data were presented as means \pm S.D., median, frequencies and percentages. For variables with normal distribution, comparison between groups was performed using independent t-test. Correlation between continuous variables was tested using Spearman's correlation coefficient. Relationship between categorical variables was done using Chi-square test. A 5% significance level (p -value ≤ 0.05) was considered significant. Univariate and Multivariate logistic regression analyses adjusting for potential confounders (complications and risk factors that influence stroke outcome) were also performed.

3. Results

There was no statistically significant difference in the mean age between the cases and controls. Except for the occupations of the respondents in which the cases were predominantly farmers and controls predominantly traders, there was no statistically significant difference in their sociodemographic factors (Table 1).

Table 2
Showing the mean NIHSS scores of the cases and controls.

	NIHSS score		p-Value
	Mean	SD	
Cases	13.91	10.88	0.10
Controls	10.11	8.91	

Table 3
Haemorrhagic stroke type among cases and controls.

Category	Haemorrhagic stroke		p-Value	OR (CI)
	Yes	No		
Cases	25(71.4%)	10(28.6%)	0.02	2.9(1.10–7.99)
Controls	16(45.7%)	19(54.3%)		

The mean values of NIHSS at presentation were 13.91 and 10.11 for the cases and controls respectively (t-test, $p = 0.100$). The cases had a range of 1–42 while for the controls, their NIHSS ranged between 0.00 and 30.00. There was no statistically significant difference between the mean NIHSS scores of the two groups at presentation (Table 2).

The odds of having haemorrhagic stroke among sickle cell trait was 2.9 (95% CI = 1.10–7.99) while the odds of having ischaemic stroke was 0.27 (95% CI = 0.09–0.72). This suggests protection against ischaemic stroke. There is a statistically significant higher proportion of haemorrhagic stroke among the cases compared to the control group and a higher proportion of ischaemic stroke among the controls in this cohort (Table 3).

Table 4 shows the anatomical locations of stroke in both the cases and controls. It was observed that brainstem stroke occurred in 5.7% of the cases and 14.3% of the controls. Basal ganglia stroke occurred in 71.4% of the cases while it occurred in 5.7% of the controls. Eighty percent of the controls developed lobar stroke while it occurred in 22.9% of the cases.

A univariate analysis was conducted on both the cases and controls to examine the factors that have independent effect on the 30-day stroke mortality. NIHSS score > 20 (OR = 39.0, 95% CI = 56–336.6), haemorrhagic stroke (OR = 1.4, 95% CI = 1.3–3.4) and being an haemoglobin AS patient (OR = 1.3, 95% CI = 1.1–3.5) were found to have independent effect (Table 5).

Multivariable logistic regression analysis was then conducted on these independent factors. It was found that being an haemoglobin AS patient and having an NIHSS score > 20 at presentation had a significant independent effect on 30-day mortality (Table 6).

Table 7 shows the stroke risk factors among the cases and controls. It was found that low HDL-c (p -value = 0.00) and high triglycerides (p -value = 0.02) among the cases were the only statistically significant risk factors.

3.1. Thirty-day fatality between cases and controls

Eighteen (51.4%) of the cases were alive by the 30th day post stroke while 17 (48%) were dead. Among the controls, 30 (85%) were alive while 5 (14%) were dead. Ten (28.6%) of the cases independent while 8 (22.9%) were still dependent. Among the controls, 24 (68.6%) were independent while 6 (17.1%) were still dependent. This was statistically significant ($p = 0.002$). This is shown in Table 8.

4. Discussion

4.1. Determinants of 30-day case fatality

The results of the univariate analysis in this study showed that NIHSS score above 20 and the presence of haemorrhagic stroke among the traditional risk factors, were associated with high mortality among all the patients, both cases and controls. Also, the presence of HbAS

Table 4
Anatomic locations of stroke among the respondents.

Anatomic location	Cases	Controls
Brain stem	5.7%	14.3%
Basal ganglia	71.4%	5.7%
Lobar	22.9%	80.0%

Table 5
Risk factors for 30-day mortality among the cases and the controls using univariate analysis.

Risk factor	F (%)		OR (CI)	p-Value
	Alive	Dead		
NIHSS > 20	1 (9.1%)	10 (90.9%)	39 (26–336.6)	0.00 ^a
Age > 70 years	17 (81.0%)	4 (19.0%)	0.4 (0.1–1.4)	0.40
Blood glucose > 140 mg/dl	8 (61.5%)	5 (38.5%)	1.5 (0.4–5.6)	0.50
Systolic hypertension > 140 mm Hg	9 (75.0%)	3 (25.0%)	1.4 (0.3–5.9)	0.60
Diastolic hypertension > 90 mm Hg	20 (71.4%)	8 (28.6%)	1.2 (0.4–3.5)	0.70
Haemorrhagic stroke (Yes)	9 (39.4%)	23 (60.6%)	1.4 (1.3–3.4)	0.01 ^a
AS (present)	8(31.4%)	27 (68.6%)	1.3 (1.1–3.5)	0.00 ^a

Chi square test.

^a Statistically significant.

was associated with high mortality. This was similar to what Mustapha et al. found in their study conducted at the same study center in between July 2002 and September, 2003. They found out that NIHSS greater than 20 was the only independent predictor of 30 days mortality in their study [16]. Glasgow Coma Scale Score at presentation and presence of complications were closely related to the over-all mortality in their study. With logistic regression analysis, the presence of HbAS and NIHSS score > 20 was significant. The observed wide confidence interval can be explained by the small sample size. In this study, there was only one case of sepsis with focus in the urinary tract among the cases. The absence of significant complications might be due to the improved level of stroke care among others in the center.

4.2. Thirty-day stroke outcome between cases and controls

In this study, there was a statistically significant relationship between having a sickle cell trait (Hb AS) and worse stroke outcome in terms of morbidity and mortality when compared with stroke patients with normal adult haemoglobin (HbAA). No published study was found that looked at the relationship between having a sickle cell trait and stroke outcome to compare this study with. This significant association can be explained by the fact that following stroke, the hypoxia generated in the microvasculature [17], the ensuing inflammatory process, acidosis, fever and dehydration are known risk factors for sickling.

This leads to prolongation of hypoxia which will further increase sickling in the microvasculature. The net effect is further expansion of the area of ischaemic penumbra in ischaemic stroke and expansion of peri-haematomaedema in haemorrhagic stroke. There was no statistically significant difference in stroke severity at presentation between the cases and the controls and when other risk factors for poor 30-day stroke outcome were corrected for, it was found that sickle cell trait patients had worse stroke outcome. At this point, the only difference between the two groups is the presence of S haemoglobin.

Another factor which might have contributed to the worse outcome is the relative higher prevalence of haemorrhagic stroke among the patients with sickle cell trait. It is a well-known fact that 30-day mortality following haemorrhagic stroke is higher than that of ischaemic stroke. In a study conducted by Ajayi et al. [12], there was a 10-fold increase in the risk of haemorrhagic stroke in sickle cell trait. This same value

Table 6
Predictors of 30 days mortality among the cases using a multivariate logistic regression analysis model.

Covariate	OR (95% CI)	p-Value
AS (presence)	136 (8.0–231.6)	0.01 ^a
NIHSS at presentation > 20	19.3 (2.3–159.8)	0.05 ^a
Haemorrhagic stroke	1.3 (0.3–5.7)	0.60

^a Statistically significant.

Table 7
Risk factors among cases and controls.

Risk factor	Cases	Controls	p-Value	95% CI
Age < 70 years	26 (74.3%)	23 (65.7%)	0.40	0.5–4.2
Age ≥ 70 years	9 (25.7%)	12 (34.3%)		
GCS ≤ 8	13 (41.7%)	8 (25.0%)	0.20	0.7–6.3
GCS > 8	18 (58.1%)	24 (75.0%)		
Haemorrhagic stroke	19 (53.3%)	15 (45.7%)	0.50	0.5–3.6
Ischaemic stroke	16 (46.7%)	20 (54.3%)		
Blood glucose < 140 mg/dl	23 (74.2%)	30 (85.7%)	0.30	0.1–1.7
Blood glucose ≥ 140 mg/dl	8 (25.8%)	5 (14.3%)		
Systolic BP ≥ 140 mm Hg	7 (21.2%)	5 (14.3%)	0.40	0.4–5.7
Systolic BP < 140 mm Hg	26 (78.8%)	30 (85.7%)		
Diastolic BP < 90 mm Hg	12 (36.4%)	16 (45.7%)	0.40	0.3–1.8
Diastolic BP ≥ 90 mm Hg	21 (63.6%)	19 (53.3%)		
LDL < 100 mg/dl	8 (33.3%)	5 (14.3%)	0.08	0.8–10.7
LDL ≥ 100 mg/dl	16 (66.7%)	30 (85.7%)		
HDL < 50 mg/dl	21 (87.5%)	7 (20.0%)	0.00	6.5–121.3
HDL ≥ 50 mg/dl	3 (12.5%)	28 (80.0%)		
Triglyceride < 150 mg/dl	19 (79.2%)	34 (97.1%)	0.02	0.01–1.0
Triglyceride ≥ 150 mg/dl	5 (20.8%)	1 (2.9%)		
Total Chol. < 200 mg/dl	13 (54.2%)	12 (34.3%)	0.10	0.8–6.6
Total Chol. ≥ 200 mg/dl	11 (45.8%)	23 (65.7%)		

was also observed by Lannuela et al. in a retrospective study to assess the main risk factors and the role of stroke in sickle cell trait [18]. In this study, the odds of developing haemorrhagic stroke was almost three times higher among the sickle cell trait patients and when compared with previous observational studies of the prevalence of stroke and its types in haemoglobinopathies [18], there was a relative protection against ischaemic stroke [19].

The possible reason for the higher prevalence of haemorrhagic stroke among the patients with sickle cell trait is the possibility of Moyamoya disease which is more common among the sickle cell trait patients than in those with normal adult haemoglobin [24]. In this study, it was found that the only difference in the risk factors for stroke and perhaps its severity between the cases and controls were the significantly lower HDL-c and higher triglycerides among the cases. This can predispose the cases to progressive occlusion of the carotid vessels with eventual development of collaterals with poor endothelial integrity and subsequent rupture in the presence of hypertension.

There is a relative higher risk of having haemorrhagic stroke in sickle cell trait in this study compared with the works of Adesuyi et al. and Lannuela et al. This can be explained from the fact that the controls were highly selected to be age- and sex-matched with the cases. In their studies, their controls were from a large pool which might have included the younger age group among whom ischaemic stroke is more prevalent [20]. In this cohort, all the basal ganglionic strokes in sickle cell trait patients were haemorrhagic.

Overall, 30-day mortality in this study was 31.4%. The 30-day mortality was higher (48%) among the patients with sickle cell trait than the controls (14%). The overall 30-day mortality was lower when compared with other studies by Komolafe et al. [21] (45%), Ojini et al. (41%) [22] and Abubakar (38%) [23]. An explanation for this study was the fact that there was just one patient with complication among the cases. Improvement in stroke care might have also contributed to this.

Table 8
Thirty-day stroke outcome.

Outcome	Cases	Controls	p-Value
<i>Functionality</i>			
Dependent	8 (22.9%)	24 (68.6%)	0.03
Independent	10 (28.6%)	6 (17.1%)	
<i>Mortality</i>			
Dead	17 (48.6%)	5 (14.3%)	0.00
Alive	18 (51.4%)	30 (87%)	

This value is expected to be lower in a few years' time if sickle cell trait patients with stroke are recognized and treated as high risk individuals.

4.3. Strengths, limitations and future directions

The strength of this study lay in the fact that all the patients had neuroimaging done which confirmed the diagnosis of stroke. Stroke mimics were ruled out and there was categorical classification of stroke into ischaemic and haemorrhagic. All the patients also had sickle cell trait were confirmed with the use of the HPLC machine.

This study was limited by a small sample size; though based on the prevalence of stroke in patients with sickle cell trait.

5. Conclusions and implications

This study showed that 30-day stroke outcome and mortality in patients with sickle cell trait was worse than in patients with normal adult haemoglobin.

Therefore, a trait awareness programme involving screening, education and counselling is warranted so that those with the trait can be targeted for primary prevention efforts.

Haemoglobin electrophoresis should be part of the routine investigations in stroke management irrespective of the age of the patients so that specialized care is provided to improve outcome in them.

Conflict of interest

The authors declare that there are no conflicts of interest.

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