**Research Article**

**Sickle Cell Trait Appears to Increase the Risk of Hemorrhagic Stroke in African Adults with Dyslipidaemia: A Pilot Study**

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**Received:** May 28, 2017; **Accepted:** June 19, 2017; **Published:** July 04, 2017

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**Abstract**

**Background:** The association of sickle cell trait (HbAS) with stroke occurrence, type, and outcome is controversial. HbAS has now been regarded as a disease state such that a 10-fold increase in the risk of haemorrhagic stroke has been observed.

**Objective:** To confirm and quantify the effect of sickle cell trait on stroke type among Africans with and without cardiovascular risk factors.

**Methods:** This was pilot, analytical study conducted between 1st February, 2014 and 31st January, 2015 at the University College Hospital, Ibadan, Nigeria. All stroke patients, both ischaemic and haemorrhagic admitted during the study period had haemoglobin electrophoresis done and separated into two groups: HbAS as cases and HbAA as controls. Stroke was confirmed with brain CT scan or MRI. These groups were age- and sex-matched; 35 cases and 35 controls. The severity of stroke within 24 hours of presentation was compared using the NIHSS and GCS within 24 hours of presentation. Also, cardiovascular risk factors were compared.

**Results:** We observed that the prevalence of haemorrhagic stroke was higher among the sickle cell trait patients (71.4%) compared with age-and sex-matched controls with normal adult haemoglobin (45.7%) p=0.02, OR=2.9, 95% CI=1.10-7.99. There was no significant difference in stroke severity at presentation between the two groups p=0.10. The only observable difference in the cardiovascular risk factors between the two groups was a significant higher prevalence of low HDLc among the sickle cell trait individuals (87.5%), p<0.001.

**Conclusion:** We therefore concluded that the presence of sickle cell trait could be a risk factor for haemorrhagic stroke in Africans and may be related to the presence of low HDL-c.

**Keywords:** Sickle cell trait; Dyslipidaemia; Haemorrhagic stroke; Africa

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**Introduction**

Intracerebral haemorrhage is defined as a focal collection of blood within the brain paraenchyma or ventricular system which is not due to trauma. It includes paraenchymal haemorrhage after CNS infarction [1]. In this type of stroke, the primary pathology is an area of bleeding caused directly to the brain tissue. I hospital based studies, It constitutes up to 37.0%-40.9% of all strokes in Nigeria [2,3] with a significantly higher morbidity and mortality compared with ischaemic stroke. A 10-fold increase in the risk of haemorrhagic stroke has been observed in individuals with HbAS [4]. 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 [5]. In the INTERSTROKE STUDY, [6] haemorrhagic stroke accounted for 34% of all stroke cases in the African cohort. Stroke mortality is quite high ranging from 35 - 45% [7-9]. Hence, the consideration of a factor, sickle cell trait, which is peculiar to the black race, that might be a contributor to why stroke is more severe with worse outcome among blacks compared with Caucasians [9].

Sickle cell trait (heterozygotes) describes a condition in which an individual has one abnormal allele of the β haemoglobin gene (haemoglobin S) and a normal allele of the β gene (haemoglobin A). The two alleles are co-dominant. The abnormal gene occurs as a result of glutamic acid-to-valine substitution at the sixth base position in the β globin gene on chromosome 11 [10].

In Africa, the highest prevalence of HbAS occurs between latitudes 15° North and 20°S; ranging between 10% and 40% in some areas and specifically from 24-25% [11-13] in Nigeria. There is insufficient evidence to suggest an independent association between HbAS and stroke. The data relating to the association between HbAS and stroke are sparse in the literature and the available ones are case reports. Feldenzer, et. al. [14] reported three cases of patients with sickle cell trait who developed superior sagittal sinus thrombosis with haemorrhagic infarct. These patients had normal vital signs and no risk factors for cardiovascular disease were identified. It was...
A study was recently conducted observing an increased risk of ischaemic stroke in blacks with sickle cell trait [20]. In this study, the frequency of ischaemic stroke was slightly higher with sickle cell trait (13%) than in participants with normal adult haemoglobin (10%). The difference was not statistically significant. In multivariable analysis that controlled for the traditional risk factors for stroke, sickle cell trait was associated with a 40% higher risk of stroke [20]. Despite this, further investigation of the incidence and pathophysiology of stroke in patients with sickle cell trait is warranted. Since patients with sickle cell traits are usually asymptomatic and cannot be recognised by any facies or body shape unlike in patients with sickle cell anaemia (Hb SS), diagnosis by haemoglobin electrophoresis is required [21]. We set up this study to confirm and quantify the relationship between HbAS and stroke in the presence of other cardiovascular risk factors.

### Materials and Methods

#### Subjects, setting and procedure for data collection

This was a pilot analytical study on first ever acute stroke patients attending the Emergency Department of the University College Hospital, Ibadan between 1st February, 2014 and January 31st 2015. These were stroke patients (both haemorrhagic and ischaemic) with sickle cell trait having first episode of stroke seen at the Emergency Department of the study location above. The age and sex matched stroke patients with Haemoglobin AA were recruited at the same time from the same hospital. All were Nigerians. All the subjects had their haemoglobin electrophoresis done before recruitment. Stroke was confirmed in all subjects by brain CT scan or MRI.

#### Selection criteria

Consecutive consenting Nigerian stroke patients with sickle cell trait having first ever stroke confirmed with brain CT scan or MRI that presented within seven days of stroke onset were included. 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 included. Patients with repeat stroke, sickle cell anaemia or sickle cell disease e.g. Hb SS, Hb SC, Hb AC, lack of consent, and no neuroimaging done were excluded.

#### Control group

These were age and sex matched Nigerians who developed first episode of stroke and presented within seven days of onset during the period of study and who had haemoglobin AA. They had their stroke confirmed with neuroimaging and gave consent to be recruited.

#### 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 mean±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 are performed for potential confounders (cardiovascular risk factors for stroke) were also performed.

#### 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 n (%)                   |               |                  |         |
| Male                        | 20 (57.1%)    | 19 (54.3%)       | 0.810   |
| Female                      | 15 (42.9%)    | 16 (45.7%)       |         |
| Ethnicity n (%)             |               |                  |         |
| Yoruba                      | 32 (91.4%)    | 32 (91.4%)       | 0.148   |
| Hausa                       | 0 (0.0%)      | 2 (5.7%)         |         |
| Igbo                        | 3 (8.6%)      | 1 (2.9%)         |         |
| Educational Status n (%)    |               |                  |         |
| No formal education         | 2 (5.7%)      | 6 (17.1%)        | 0.349   |
| Primary                     | 6 (17.1%)     | 3 (8.6%)         |         |
| Secondary                   | 16 (45.7%)    | 14 (40.0%)       |         |
| Tertiary                    | 11 (31.4%)    | 12 (34.3%)       |         |
| Occupation n (%)            |               |                  |         |
| Trading                     | 11 (32.4%)    | 22 (62.9%)       | 0.000   |
| 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%)         |         |

#### Table 2: Stroke severity at presentation between cases and controls.

| Category | NIHSS | p-value |
|----------|-------|---------|
|          | ≤20   | > 20    |
| Cases    |       |         |
|          | 20 (57.1%) | 15 (42.9%) | 0.21 |
| Controls | 25 (71.4%) | 10 (28.6%) |       |

suggested that haemoglobin electrophoresis should be carried out in young black patients with unexplained neurologic symptoms or sign.

Also reported by Pai, et al. [15] was the case of an Arab teenage boy who presented with a sudden loss of vision in his left eye of one hour duration in which the ocular examination revealed acute central retinal artery occlusion. Blood investigations revealed sickle cell trait and abnormal partial thromboplastin time. No other contributing factors for this were identified.

Twelve cases have been reported in the literature that suggest the association of stroke with sickle cell trait; [16] the age range of the individuals affected being between 12 and 38 years. Wolman, et al. [17] reported a case of a 60-year-old woman who was found to have the sickle cell trait with paraplegia. The patient died from respiratory failure and autopsy showed microinfarcts at various levels in the spinal cord resembling features of spinal cord embolism.

In another study, [18] it was observed that cases of stroke in sickle cell trait occurred by chance. Therefore, stroke was not considered to be associated with sickle cell trait. Also, there has not been any significant difference in the outcomes of stroke for sickle cell patients compared with normal haemoglobin [19]. In order to shed more light on this debatable association, a 24-year prospective epidemiological study was recently conducted observing an increased risk of ischaemic stroke in blacks with sickle cell trait [20]. In this study, the frequency of ischaemic stroke was slightly higher with sickle cell trait (13%) than in participants with normal adult haemoglobin (10%). The difference was not statistically significant. In multivariable analysis that controlled for the traditional risk factors for stroke, sickle cell trait was associated with a 40% higher risk of stroke [20]. Despite this, further investigation of the incidence and pathophysiology of stroke in patients with sickle cell trait is warranted. Since patients with sickle cell traits are usually asymptomatic and cannot be recognised by any facies or body shape unlike in patients with sickle cell anaemia (Hb SS), diagnosis by haemoglobin electrophoresis is required [21]. We set up this study to confirm and quantify the relationship between HbAS and stroke in the presence of other cardiovascular risk factors.

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Ethical approval

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

Procedure

Informed consent was obtained from the subjects and controls. The following information was obtained: age, gender, occupation, level of education, history of hypertension, diabetes mellitus, and stroke.

All subjects had their blood samples collected from the right or left cubital vein after the overlying skin had been cleaned with 70% methylated spirit. Five millilitres (mls) of blood was collected in lithium heparin bottles for plasma lipid profile analysis after an 8-12-hour fast. The lipid profile was determined using the Randox Laboratories Limited UK kits, Total Cholesterol (TC) was determined by the enzymatic endpoint method, [22] triglycerides (TG) by the enzymatic-colorimetric method, and high density lipoprotein cholesterol (HDL) determined by the precipitation method [23]. Low density lipoprotein (LDL) was calculated using the Friedwald’s formula, [24] LDL=TC-HDL- (TG/2.2) in mmol/l or LDL=TC-HDL- (TG/5) in mg/dl, when plasma TG concentration < 4.52 mmol/l (400 mg/dl). Five millilitres of blood was collected in sodium fluoride bottle using the plasma to determine the fasting blood glucose level by the glucose oxidase method, [25] using the Randox Laboratories Limited United Kingdom (UK) Glucose (GLU PAP) kit. Haemoglobin phenotype and haemoglobin S quantification were determined using 2 millilitres of venous blood collected in EDTA bottles with high performance liquid chromatography (HPLC) 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. Those with sickle cell anaemia (HbSS), sickle cell disease and other traits such as haemoglobins AC, SC were excluded. Hemoglobin S quantification was then carried out on the samples of the cases (HbAS subjects) using a high performance liquid chromatography method (VARIANT II Haemoglobin Testing System).

The level of stroke severity was assessed within 24 hours of admission using the National Institute of Health Stroke Scale. The Glasgow Coma Scale Score was also assessed at presentation. Diagnosis of stroke was confirmed with brain CT or brain MRI while stroke mimics were ruled out (Table 1).

Results

Comparison of stroke severity at presentation between HbAS and HbAA groups

Twenty (57%) of the cases had moderate stroke while 15 (42%) had severe stroke. Among the controls, 25 (71.4%) had moderate stroke and 10 (28.6%) had severe stroke. The difference of the two groups failed to reach statistical significance (p=0.21). This is depicted in Table 2 below.

| Category | GCS <8 | GCS >8 | p-value |
|----------|-------|-------|--------|
| Cases    | 13 (41.9%) | 18 (58.1%) | 0.21    |
| Controls | 25 (71.4%) | 10 (28.6%) |          |

Table 3: Comparison of Glasgow Coma Score between cases and controls at presentation.

| Risk factor | Cases | Controls | p-value |
|-------------|-------|----------|---------|
| Age < 70 years | 26 (74.3%) | 23 (65.7%) | 0.40    |
| Age ≥ 70 years | 9 (25.7%) | 12 (34.3%) |          |
| Blood glucose < 140 mg/dl | 23 (74.2%) | 30 (85.7%) | 0.30    |
| Blood glucose ≥ 140 mg/dl | 8 (25.8%) | 5 (14.3%) |          |
| Systolic BP ≥ 140 mmHg | 7 (21.2%) | 5 (14.3%) | 0.40    |
| Systolic BP < 140 mmHg | 26 (78.8%) | 30 (85.7%) |          |
| Diastolic BP < 90 mmHg | 12 (36.4%) | 16 (45.7%) | 0.40    |
| Diastolic BP ≥ 90 mmHg | 21 (63.6%) | 19 (53.3%) |          |
| LDL < 100 mg/dl | 8 (33.3%) | 5 (14.3%) | 0.08    |
| LDL ≥ 100 mg/dl | 16 (66.7%) | 30 (85.7%) |          |
| HDL < 50 mg/dl | 21 (67.5%) | 7 (20.0%) | 0.00    |
| HDL ≥ 50 mg/dl | 3 (12.5%) | 28 (80.0%) |          |
| Triglyceride < 150 mg/dl | 19 (79.2%) | 34 (97.1%) | 0.02    |
| Triglyceride ≥ 150 mg/dl | 5 (20.8%) | 1 (2.9%) |          |
| Total Chol. < 200 mg/dl | 13 (54.2%) | 12 (34.3%) | 0.10    |
| Total Chol. ≥ 200 mg/dl | 11 (45.8%) | 23 (65.7%) |          |

Table 4: Cardiovascular risk factors among cases and controls.

The relationship between sickle cell trait and Glasgow coma score at presentation

Thirteen (41%) cases and 25 (71%) controls had GCS score of 8 and below at presentation while 18 (58.1%) of the cases and 10 (28.6%) of the controls had a GCS score >8 at presentation. This did not show any statistical significance. (p=0.21). This is shown in Table 1.

Discussion

Demographic characteristics

The mean age of 62.1 years in this study for both the cases and controls is similar to findings in other previous studies from the South western part of Nigeria [26]. There was a slight male preponderance in this study similar to many other hospital-based studies [27,28]. Some of the reasons attributed to the male preponderance were the enhanced risk for thrombotic stroke and higher presence of cardiovascular risk factors in them [29].

Relationship between sickle cell trait and stroke severity at presentation

There was no statistically significant difference in stroke severity at presentation between the sickle cell trait individuals and the age-and sex- matched haemoglobin AA patients in this study. In a prospective study by Stark, et al. [30], there was no evidence of excess mortality or differential causes of mortality between HbAS and HbAA individuals. Also, in a study on blood pressure and other cardiovascular disease risk factors in black civil servant adults in Benin...
City, Nigeria by Nwankwo, et al., there was no significant difference in the cardiovascular risk factors between normal subjects and sickle cell trait [31]. Our study was conducted among stroke individuals that were expected to constellations of cardiovascular risk factors which may explain why we were able to detect low HDLc among the cases. Therefore, stroke was expected to be worse at presentation among the cases in this study but the small sample size might be the reason for the lack of statistically significant difference. However, other factors such as the volume and location of intracerebral haemorrhage that are determinants of stroke severity and prognosis were not considered [32].

Types of stroke in patients with sickle cell trait compared with the types in patients with normal adult haemoglobin

Haemorrhagic stroke was more common among the sickle cell trait patients than among the patients with normal adult haemoglobin in this study. Some studies have found haemorrhagic stroke to be commoner in adults with sickle cell disease as a result of the development of moyamoya disease [33,34] which results from the formation of poorly endothelialised vessels following vascular occlusion. In most studies on the pattern of stroke in Nigeria, ischaemic stroke has always been the more common [35-38] except in a few cases in urban centres [39] in one of which Ogun, et al. used the WHO criteria to classify the stroke types. The significant difference between the two groups in this study in terms of the pathologic stroke types is likely to be due to the presence of sickle cell trait in line with the observation of Ajayi, et al. [4] in their study that the risk of haemorrhagic stroke was 10 times that of ischaemic stroke in sickle cell patients. Owolabi, et al. in the Berlin-Ibadan experience, observed that cerebral haemorrhage was less common (20%) in Berlin than in Ibadan (37%) [2]. An observable reason for the higher prevalence of haemorrhagic stroke among the cases is the significant higher proportion of low HDLc in them. A low HDL-c has also been found as a risk factor for haemorrhagic stroke in black Africans [40]. This could cause atherogenesis in the cerebral vessels and development of poorly endothelialized collateral circulation which is susceptible to rupture most especially when hypertension among other cardiovascular risk factors supervenes.

Conclusion

The presence of sickle cell trait appears to be associated with haemorrhagic stroke most especially when dyslipidaemia is present. Particular attention should be paid to the modifiable cardiovascular risk factors in sickle cell trait individuals to forestall haemorrhagic stroke.

Strength

Neuroimaging was done in all the patients to confirm stroke diagnosis and categorically classify stroke into ischaemic and haemorrhagic. Sickle cell trait was confirmed with the use of the HPLC machine.

Limitation

This study was limited by the small sample size; though a Pilot study, larger studies such as the SIREN study are needed to confirm this observation. The volume of the haemorrhage was not calculated in this study to correlate with severity at presentation as there were varying time intervals between stroke onset and presentation. The locations of intracerebral haemorrhage also were not determined.

Acknowledgement

Stroke Investigative Research and Education Network (SIREN) projects.

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