eNeurologicalSci 3 (2016) 64–68

Contents lists available at ScienceDirect

eNeurologicalSci

journal homepage: http://ees.elsevier.com/ensci/

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

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ARTICLE INFO

Article history:
Received 1 November 2015
Received in revised form 24 February 2016
Accepted 25 February 2016
Available online 3 March 2016

Keywords:
Stroke outcome
Sickle cell trait
Stroke mortality

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 had1 a worse 30-day mortality and outcome in patients with sickle cell trait (HbAS) than in patients with normal adult haemoglobin (HbAA).

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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http://dx.doi.org/10.1016/j.ensci.2016.02.009

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 Mannhein 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 out[36]. 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 reasons[25]. For those that died, the next of kin whose phone number was