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SICKLE CELL ANAEMIA: A MODIFIABLE RISK FACTOR OF STROKE AMONG YOUNG BLACK ADULTS: A REVIEW OF THE CURRENT LITERATURE

¹Ndakotsu M.A., ²Balarabe S.A

¹Department of Haematology and Blood Transfusion, and ²Department of Medicine, Usmanu Danfodiyo University Teaching Hospital Sokoto, Nigeria

Abstract:

Incidence of stroke among young adults between the age brackets of 20 to 54 years of age has increased significantly; suggesting that stroke in the young is on the rise. In a community based retrospective study, the proportion of all strokes that occurred in young adults increased from 13% to 19% over one decade. Additionally, the incidence rate of stroke among blacks increased from 83 per 100,000 to 128 per 100,000, as compared to whites in whom, the incidence rate increased from 26 to 48 per 100,000. Therefore, aggressive risk factor control particularly among blacks is extraordinarily important. Furthermore, almost all the conventional stroke risk factors for incident stroke, proved to also be a risk factor for recurrent stroke, suggesting that equal vigilance for risk-factor prevention and control is appropriate for primary and secondary stroke prevention. This review tends to shed some light on the role of sickle cell anaemia in the pathophysiologic mechanism of stroke hoping that, the review would not only create more awareness on stroke management but would inform policy-makers on the urgency and mechanism required for cheap and affordable treatment of acute stroke among sickle cell anaemia patient, particularly in resource limited countries like Nigeria. It would also be a useful resource material for regional, national and international bodies that are involved in the management of patients with stroke.

Key words: Sickle cell Anaemia, Stroke, Modifiable risk factors, Young black Adults, Cerebrovascular disease

Corresponding Author:

Dr. M.A. Ndakotsu,

Department of Haematology Usmanu
Danfodiyo University Teaching
Hospital Sokoto P.M.B. 2370 Sokoto,
Nigeria.

E-mail: mndakotsu@yahoo.com;
Phone: +2348035073579

INTRODUCTION

Acute stroke is a common and devastating complication of Sickle Cell Anaemia (SCA).¹ Without effective primary stroke prevention, approximately 10% of children with Haemoglobin electrophoresis pattern HbSS, will have clinical evidence of stroke and an additional 20% to 35% will have silent cerebral infarction, which may cause cognitive impairment and predispose the patients to secondary stroke.² Stroke complicating sickle cell disease (SCD) occur as a result of polymerized red blood cells, resulting in small vessel occlusion and sickle-related arterial disease.^{3, 4} About 25% of individuals with SCD experience a stroke by age 45 years with the highest incidence of ischemic stroke occurring at 2-5 years.⁵ At early adulthood, the risk of haemorrhagic stroke becomes higher, while ischemic stroke take the centre stage during the third decade of life. Risk of a recurrent stroke is as high as 90% among untreated patients with sickle cell associated first stroke.⁶ Lacuna or multiple silent infarcts

presenting with cognitive dysfunction may be more common than overt clinical infarcts.^{7,8}

Sickle Cell Disease among blacks

Sickle cell disease affects 0.3 to 7.3% of the black population worldwide. Approximately 17% of affected patients develop cerebrovascular symptoms; 75% of those patients have cerebral infarction, 20% have either cerebral or subarachnoid haemorrhage, while a small percentage may have other lesions such as cerebral sinovenous thrombosis.⁹ However, contrary to findings from previous studies^{10, 11}, recent studies^{12,13} have found that in-hospital and all-cause mortality rates for up to one year are lower among black stroke patients than white patients. The study¹³ also showed that black patients are more likely to receive critical care interventions, have longer hospital stays, and are less likely to be discharged. The lower mortality rates among black patients may result not so much from varying stroke severity but from differences in life-sustaining interventions.

Aetiopathogenesis

There are various forms of crises in patients with sickle cell anaemia (SCA) that include painful crisis, conditions that are reminiscent of other acute illnesses, (such as acute chest syndrome and priapism,) to crises involving the central nervous system such as seizures, coma or stroke. Among patients with SCA, ischemic stroke tends to occur in patients who have more frequent crises particularly at the time of crisis. Infarction also tends to occur in patients with concurrent systemic infections. Generally, stroke in sickle cell anaemic patients may either be ischemic or haemorrhagic, depending on the patient's age.¹⁴ Ischemic stroke peaks in the first decade of life and at 25 years of age. Haemorrhagic stroke on the other hand peaks in the second and third decades of life¹⁴.

Several studies have reported intravascular coagulopathy in patients with sickle cell anaemia.¹⁴⁻

²¹Some of the mechanisms of intravascular coagulation abnormalities in sickle cell anaemia include, defective release of endogenous t-PA19 and an increase in the plasminogen activator inhibitor 1 level²⁰ as well as imbalance between the profibrinolytic and antifibrinolytic systems, such as decreased levels of prothrombin complex, proteins C and S, and coagulation factors II, V, VII, and X and an increased level of factor VIII:C. In view of these abnormalities, some authorities suggest that fluid therapy to correct hydration and exchange blood transfusion should form part of the treatment protocol in sickle cell anaemia associated stroke.^{22,}

²³

Another important vascular derangement among sickle cell anaemia patients is intracranial vasculopathy, which usually affects the terminal end of internal carotid artery within the cranium that forms an area of vascular occlusions surrounded by small collateral vessels, which are at risk of haemorrhage or aneurysm formation. Furthermore, vasculopathy affecting external carotid artery may lead to carotid occlusion, dissection, or intracranial aneurysm formation²³.

Cerebral Aneurysms

Cases of cerebral aneurysms in patients with sickle cell anaemia including many cases involving multiple aneurysms (an average of three per patient), small aneurysms (3 to 7 mm in diameter) have been reported in the literature.¹¹⁻²⁵⁻³³

Additionally, aneurysmal rupture leading to intracranial haemorrhages tend to occur earlier in patients with sickle cell anaemia

Differential Diagnosis

Differential diagnosis of stroke in the young may be due to: (1) Disorders of brain tissue (e.g., MELAS [mitochondrial encephalomyopathy, lactic acidosis, and stroke like episodes]). (2) Disorders of cervicocranial vasculature (e.g., systemic inflammatory disorders). (3) Disorders of the heart (4) Disorders of the blood and coagulation. Generally, the most common causes of stroke in young patients are cardioembolism, dissection, migraine, angiopathies of various types, and other causes, including coagulopathies associated with the use of oral contraceptives or with the presence of antiphospholipid antibodies.

Treatment

Thrombolytic Therapy: Although the use of intravenous t-PA has been shown to improved long-term outcomes among patients with non-sickle cell associated stroke,³³⁻³⁶ use of t-PA has not been studied in patients with sickle cell associated stroke. Current guidelines suggest the use of t-PA in adults who have acute stroke due to sickle cell anaemia providing that the criteria for its use (i.e., a NIHSS score of >4 and administration <3 hr after stroke onset) are met.³⁷ However, it should be noted that there are concerns about using t-PA in patients with cerebral aneurysms.³⁸

Blood Transfusion: The rational of blood transfusion in acute ischemic stroke patients with Sickle cell anaemia is to correct low blood level due to anaemia in order to improve cerebral perfusion and thereby circumvent the degree and extent of ischemic cerebral injury.³⁹ Blood transfusion may either be a simple transfusion, or exchange

transfusion. Although both methods can be used to correct anaemia, exchange transfusion is preferable to simple transfusion because it has the added advantage of clearing sickled red cells, reducing the plasma viscosity and subsequently minimizing vaso-occlusion.^{40, 41} Exchange blood transfusion also limits iron overload.⁴²

Clinical evidence supports the use of long term blood transfusion for both primary and secondary preventions of ischemic strokes in children with sickle cell anaemia⁴³⁻⁴⁷ It has been reported that, the risk of recurrent stroke was lower among children with sickle cell anaemia who received an exchange transfusion than among those who received a simple transfusion. However, this conclusion may be limited in view of the retrospective nature of this study and by variability in the administration of subsequent transfusions (exchange vs. simple) after treatment for acute stroke.⁴⁸ Despite these drawbacks, it should be noted that, exchange transfusion remains a recommended intervention for the treatment of acute stroke among SCA patients, largely on the basis of expert opinion.^{49, 50} Phenotypic matching of blood before transfusion, reduces the risk of alloimmunization to red-cell antigens and subsequent delayed haemolytic transfusion reactions,⁵¹⁻⁵⁵ The usual target haemoglobin S concentration in sickle anaemia patients with acute stroke is a haemoglobin S concentration of less than 30% and a haematocrit of approximately 30% after transfusion.⁵⁶ It is important to know that patients with sickle cell anaemia and stroke have an estimated lifetime risk of a second stroke of 50%, and most second strokes occur within 3 years after the first.^{25, 47} Prophylactic transfusion programme is recommended for the prevention of recurrent strokes.^{50, 57} Treatment with hydroxyurea may be used to increase foetal haemoglobin levels if transfusion programme is not feasible.⁵⁰

Hydroxyurea Therapy: Long-term daily oral hydroxyurea treatment has been shown to prevent many acute complications of SCA. In the 1980s, hydroxyurea was recognized as an important agent

in reducing and preventing crises and complications of SCA by increasing foetal haemoglobin levels.⁵⁸ Moreover, hydroxyurea lowers the number of circulating leukocytes and reticulocytes and decreases their expression of adhesion molecules, thus reducing vascular occlusion.⁵⁹ Hydroxyurea also increases red blood cell size (higher mean corpuscular volume) and improves cellular deformability, which increases blood flow and reduces vasoocclusion. In addition, nitric oxide released directly from hydroxyurea metabolism may contribute to local vasodilation.⁶⁰ Hydroxyurea therapy substantially reduces the frequency of painful episodes and ACS events and the need for erythrocyte transfusions and hospitalizations.⁶¹ Long-term hydroxyurea administration results in a reduction in mortality.^{62, 63}

Conclusions

Stroke complicating sickle cell anaemia (SCA) occur as a result of polymerized red blood cells, resulting in small vessel occlusion and sickle-related arterial disease.⁴ About 25% of individuals with SCA experience a stroke by age 45 years with the highest incidence of ischemic stroke occurring at 2-5 years.⁵ At early adulthood, the risk of haemorrhagic stroke becomes higher, while ischemic stroke take the centre stage during the third decade of life. Stroke in those with SCA often has similar mode of clinical presentation with regard to signs and symptoms as in stroke patients without SCA. Risk of a recurrent stroke is as high as 90% among untreated patients with sickle cell associated first stroke.⁶ However, regular, timely transfusion therapy and hydroxyurea therapy may prevent recurrent strokes.

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