



Haemostatic Disorders in Sickle Cell Disease Subjects in Nigeria: A Review of Literature

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Authors' contributions

This work was carried out in collaboration between all authors. Authors KA, MI and TE designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors OI, UG and EB managed the analyses of the study. Authors EE and HA managed the literature searches. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Background: Sickle cell disease (SCD) is an autosomal recessive disorder that is characterised with chronic anaemia and painful crisis. SCD is associated with hypercoagulability or prothrombotic state that can predispose to thromboembolic complications with increasing morbidity and mortality.
Aim: This study aimed to show the various documented haemostatic disorders and possible thromboembolic complications among SCD subjects in Nigeria.
Methods: A comprehensive literature search was performed using the internet search engines linked to academic databases including Pubmed, Google Scholar, Ebsco, Hinari, Scopus, etc. Studies involving hemostatic disorders in Nigeria were thoroughly searched, and the references of such articles were also searched for any probable relevant information.

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Findings and Conclusion: There is a paucity of information on this subject in Nigeria, and there are inconsistencies in the available studies. Haemostatic disorders in sickle cell disease are conditions that are associated with increased mortality and morbidity. Further research on the level of natural anticoagulant is required to verify the correlation between haemostatic disorders and thromboembolic complications in SCD subjects in Nigeria.

Keywords: Haemostatic disorders; sickle cell disease; hypercoagulability; Nigeria.

1. INTRODUCTION

Sickle Cell Disease (SCD) is an autosomal recessive heterogeneous monogenetic disorder, caused by the inheritance of sickle cell gene either homozygous or heterozygous with another interacting gene.

The homozygous state is referred to as sickle cell anaemia (SS), where the red blood cells lacking normal adult haemoglobin are replaced by sickle cell haemoglobin [1]. This phenotype expresses severe haemolytic anaemia among other manifestations¹. The sickle cell trait is a heterozygous state (AS), where the red blood cells contain both normal adult haemoglobin (HbA) and sickle cell haemoglobin rarely have a phenotypic expression of clinical significance¹. There is also the double heterozygous state in an allele carrying HbS, and the other allele carrying other abnormal haemoglobins such as HbC, HbE or alpha or beta chain quantitative variant (thalassaemic gene Hb products) [1].

2. EPIDEMIOLOGY

SCD is the most common genetic disorder worldwide. The global prevalence of SCD is 20 – 25 million, and about 12 – 15 million affected persons are in sub-Saharan Africa [2]. In Nigeria, more than 150,000 children are born with the disease annually, while 4 million people are said to have sickle cell trait. The overall prevalence of SCD in Nigeria is estimated to be 2% however there are slight variations from one region to another [2]. Nwogoh et al. [3], in a hospital-based retrospective study in Benin City, South-South Nigeria reported a prevalence of SCD to be 2.4% and a sickle cell trait prevalence of 23%. Dosunmu et al. [4], in South West, Nigeria reported a prevalence of 2.4% for SCA and 25% for sickle cell trait.

In another study conducted in Eastern Nigeria, Kaine and Udeozo estimated that 30,000 Igbo pre-school children suffer from sickle cell anaemia [5].

3. CLINICAL SPECTRUM OF SICKLE CELL DISEASE

Sickle cell disease is a heterogeneous disorder with highly variable clinical spectrum. The clinical state ranges from chronic anaemic steady state to acute complications (otherwise referred to as crises) and chronic complications.

3.1 Steady State

This is defined as a period when a patient with sickle cell anaemia is free of infection, pain or any evidence of active disease at least one month prior to the next clinical visit and three months after blood transfusion [1].

3.2 Crises

These are acute exacerbations of the features of sickle cell disease. There are four major clinical spectra which include the vaso-occlusive crisis, aplastic crisis, acute sequestration crisis and hyper haemolytic crisis [1].

3.3 Pathogenesis of Vaso-occlusive Crisis

It is known that under hypoxic conditions, deoxygenation triggers a hydrophobic interaction between the mutated haemoglobin (HbS) molecules, resulting in the polymerisation of HbS and sickling of the RBCs. Sickling alters the cell membrane properties, reducing cellular flexibility and leads to unusual cell adherence to vascular endothelium. Studies further suggest that sickling alters the RBCs membrane properties including a significant up regulation of different endothelial adhesive molecules, for example, VCAM, selectins, and integrins. These mediate the adhesion of endothelium and subendothelial matrix to sickle RBCs via the exposure of phosphatidylserine and very late antigen 4 (VLA₄) on the sickle RBCs [6].

Dysregulation of cation homeostasis resulting from the activation of some ion channels, such as the K-Cl cotransport system and the Ca-

dependent K-channel in particular leads to a loss of potassium and cellular dehydration which increases the intracellular Hb concentration, thereby favouring deoxy-HbS polymerisation [6].

Although the molecular basis for SCD is well characterised, the mechanism underlying vaso-occlusive crisis (VOC) have not been fully elucidated. HbS RBC is said to be the initiator and propagator of VOC via adhesive interaction with the endothelium [7]. Sickle haemoglobin causes damage to the red cell membrane via auto-oxidation and formation of precipitate on the inner surface of the red blood cell membrane due to the damage to the membrane proteins and lipids via iron-mediated oxidants [8]. This membrane damage causes the irreversible sickling and rigidity with a propensity to adhere [7]. This sickled red blood cell surface possesses some adhesion molecules which can either interact directly with the endothelial cell such as the VCAM1, without the assistance of plasma protein8, while others require a soluble bridge molecule such as the von Willebrand factor and thrombospondin [7,8]. The sickled red blood cell adhesion molecules such as, the BCAM/LU, $\alpha 4\beta 1$ have also been reported to interact with subendothelial matrix proteins (lamina vWF). These interaction between SS RBC and vascular endothelia may lead to the generation of oxygen radicals by the endothelial cells, and oxidant-dependent activation of transcription factor NF- $\kappa\beta$, which causes the up regulation of the transcription of various genes including adhesion molecules like p-selectin, e-selectin, VCAM-1, ICAM-1 and epinephrine on the surface of the endothelium which participate in VOC [9,10]. Thus, apart from the SS RBC initiating and propagating of VOC, circulating leucocytes and platelets also play a pivotal role in the process of VOC [10]. The damaged SS RBC and activated endothelial cell produce a pro-inflammatory environment that is exacerbated during crisis [8]. Ischaemic reperfusion injury, release of free haemoglobin and increased production of placental growth factor contribute to the inflammatory vasculopathy [8]. The level of the placental growth factor, which is an angiogenic growth factor produced by erythroblasts are elevated in the plasma of individuals with SCD. Monocytes from SCD are activated in response to placental growth factor releasing an increased level of TNF- α , IL-1, and other chemokines [11]. Ischaemia reperfusion injury secondary to ongoing, intermittent microvascular occlusion exacerbate chronic inflammation in SCD by increasing oxidants production thereby

enhancing leucocyte adhesion to the endothelium followed by extravasation into the tissues [11].

Intravascular haemolysis results in the release of cell-free haemoglobin, which translocates between the space between the endothelium and the smooth muscle cell causing depletion of nitric oxide in plasma and subendothelial space [8,12]. The release of oxidants and hemein which binds to the transcriptional repressor Bach-1 regulates transcription of haem-oxygenase and other antioxidants, thereby contributing to inflammation [12]. Circulating platelets are also chronically activated, and they express high levels of p-selectin, CD-40 ligand and pro-inflammatory cytokines TNF- α , nf-14. Therefore, activation of coagulation is not just a secondary event contributing to increased thromboembolism but also drives inflammation and vascular injury. All these interplays between these processes can initiate and move inflammatory priming that in the presence of a precipitating event can lead to VOC [13].

Chronic haemolysis with the release of plasma free haemoglobin results in scavenging of NO with consequent endothelial dysfunction, which may favour sickle cell adherence. It has also been found to play a role in vaso-occlusive crises. NO is a key component of the vascular endothelium that has vasodilatory, anti-inflammatory, and antiplatelet properties [12]. Another form of acute crisis is the hyperhaemolytic crisis, which has an uncommon but potentially life-threatening complication, involving the destruction of both donor and recipient red blood cells after transfusion [13]. Haemolysis can be rapid and profound and is usually characterised by severe intravascular haemolysis, haemoglobinuria and anaemia to the level of haemoglobin lower than pre-transfusional level. Marked reticulocytopenia may be present [13]. The exact mechanisms responsible for hyperhaemolysis are not fully understood, but suggested mechanisms of hyperhaemolysis include cytokine-mediated haemolysis or uncontrolled macrophage activation [13].

Splenic dysfunction is a major feature of SCD and can manifest as acute splenic sequestration crisis, which is one of the early life-threatening complication seen in patients with SCD [14]. Acute splenic sequestration crisis is defined as acute splenic enlargement with a fall in haemoglobin level at least 20 g/L. There is no known predisposing factor, normal reticulocyte

count and acute intrasplenic sickling traps blood in the spleen leading to a decrease in circulating blood volume [14]. ASSC may also be followed by transient hypersplenism and functional asplenia. Over the time, the spleen loses its function via progressive atrophy; a state known as autosplenectomy and associated with a lifelong susceptibility to infection with encapsulated bacteria. Therefore Hb SS subjects often require daily prophylactic penicillin therapy and appropriate immunisation [14].

Sickle cell crisis can be classified into two sub-phenotypes as observed in patients. According to this classification, patients with viscosity vaso-occlusive sub-phenotype have a relatively high haemoglobin level and experience frequent vaso-occlusive pain crises, acute chest syndrome and osteonecrosis [15]. At the other end of the spectrum are patients with haemolytic endothelial dysfunction sub-phenotype. These patients have high levels of lactate dehydrogenase and a high reticulocyte count, and their clinical picture is characterised by stroke, pulmonary hypertension, priapism and leg ulcers [15].

4. HAEMOSTATIC CHANGES IN SCD

SCD is a hypercoagulability state which exhibits a high level of markers of thrombin generation with depletion of natural anticoagulant proteins, abnormal activation of the fibrinolytic system and increased expression of tissue factor even in non-crisis steady state. In addition, platelet and other cellular elements are also chronically activated. Tissue factor is a primary activator of the coagulation cascade [16]. SCD patients demonstrate elevated levels of whole blood tissue factor pro-coagulant activity [16]. Furthermore, circulating isolated endothelial cells showed increased level of TF antigen, mRNA and activity, and high level of TF-positive microparticle were observed during pain crisis episode compared to steady state disease [15]. TF expression is regulated by extracellular nitric oxide synthesis and activation of NF- κ B pathway in mononuclear cells [17,18]. TF activates coagulation cascade by forming a complex with activated factor VII (FVIIa). This complex activates both FX and FIX, with subsequent thrombin generation, fibrin deposition and activation of platelet [15,17,18].

Markers are supporting the concepts of hypercoagulability and thrombin generation, which causes significant alteration of the haemostatic system characterised by increased vWf, p-selectin expression by platelet,

prothrombin fragment 1.2 and thrombin-antithrombin complex which are increased in SCA, With the depletion of the natural anticoagulant and impaired fibrinolytic activity [19].

In addition, plasma level of D-dimers and fibrin/fibrinogen degradation products are increased in SCD [20].

5. HAEMOSTATIC DISORDER IN SCD PATIENT IN NIGERIA

SCD is a known hypercoagulable and prothrombotic disease state in which there is significant alteration of the haemostatic system, as characterised by increased activation of coagulation proteins, with attendant increase in thrombin-antithrombin (TAT) generation, depletion of natural anticoagulant impaired fibrinolytic activity, increase level of vWF, increase expression of p-selection and platelet adhesion and aggregation. All these predispose to increased thrombosis. There are a paucity of studies that had been done on the haemostatic disorder in SCD subjects in Nigeria and its associated complications [21].

Chinawa et al. [22] revealed a prolongation in PT, APTT but a shortened TT with an increase in platelet level. A similar study was also demonstrated by Ahmed et al. [23] but gave a contrary result to that of Chinawa et al. [22] which showed a normal level of both PT & APTT both in steady state and crises [23]. In another study, which tried to determine the plasma level of some coagulation parameter in HBSC disease patient revealed a shortened APTT with normal PT [24]. Furthermore, another study conducted by Chinawa et al. [25] revealed a negative correlation between haemoglobin and coagulation profile among children in sickle cell anaemia in steady state and crises with prolongation of PT, APTT. Also, another study showed prolongation in PT, APTT with shortened TT [26].

Famodu et al. [27] reported an elevated fibrinogen levels D-dimer in sickle cell disease in a study done in Lagos, Western Nigeria which was also in accordance with the findings of Ajuwon et al. [28]. Furthermore, another study by Ekwere et al. [29] showed a significantly elevated level of fibrinogen and D-D dimer [29]. Shokunbi et al. [28] reported similar finding. An elevated level of D-dimer was also found in sickle cell disease during bone pain crises and in steady state [30].

Other studies also worked on the level of Anti-thrombin III, and revealed a significant reduction [31]. A similar study by Ladu et al. [32] and Kusfa et al. [33] also revealed a reduction in ATIII level. There are several reports on the level of protein C and S, but common among them is a reduction in their level. Iheanacho et al. [34] revealed a low level of protein C in sickle cell subjects seen at the University of Benin Teaching Hospital. Similar study by Ibijola et al. [35] and Kusfa et al. [33] reported significant reduction in protein C level [35]. There is a paucity of study on the level of protein S in SCD subjects, however, studies by el-Hazmi et al. [36] and Schnog et al. [37] reported a significant reduction in both protein S and C level.

6. CONCLUSION

Haemostatic disorder in SCD is a serious condition that is associated with increase morbidity and mortality due to its hypercoagulable and prothrombotic state. There is a scarcity of information on this disorder in our environment with inconsistency in the available studies. More studies with further research on the level of other natural anticoagulant are required to verify the correlation between this disorder and thromboembolic complication in sickle cell disease subjects in Nigeria, and this may promote the development of the targeted therapy.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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