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The spectrum of crises seen among adult sickle cell disease patients at a Nigerian tertiary hospital

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Abstract

Background: Sickle cell disease (SCD) is characterized by frequent crises requiring hospitalization. The objective of this study is to determine the types and frequencies of the various crises in adult sickle cell disease patients.

Methods: This is a cross-sectional study of adult SCD patients accessing emergency care in a Nigerian tertiary hospital over a three-month period.

Results: The mean age and age at diagnosis of the 73 patients seen were 31.8±11.4 and 7.3±6.6 years respectively. HbSC patients were older at diagnosis than HbS patients (14.8±3.6yrs vs 6.5±0.9yrs; *P*=0.007). Steady state haematocrit was significantly higher than haematocrit at emergency visit (24% vs 20.7%; P<0.001). Forty-eight (65.8%) patients had bone pain crisis (BPC), twenty-four (32.9%) had haemolytic crisis with dark brown urine occurring in 14 (58.3%) while 15 (20.5%) had both BPC and haemolytic crises. Nineteen (27.9%) admitted to rarely/never having BPC, 32 (47%) had <1BPC in a year, 13(19.1%) had 1-3 BPC per year while 4(5.8%) had >3 episodes. There was no association between the number of BPC per year and blood transfusion (*P*=0.51) but BPC per year was associated with hospital admission (*P*=0.04). Blood transfusion was also associated with hospital admission (*P*=0.001). The age at diagnosis was associated with the steady state haematocrit (*P*=0.045) but not with BPC per year (P=0.1).

Conclusion: The coinheritance of G6PD prevalent in the community may play a significant role in the associated intravascular haemolysis of the haemolytic crisis. The late age at diagnosis is an urgent call for newborn screening of the disorder.

Keywords: *Age, Bone pain, G6PD, Haemolysis, Newborn screening, Severity*

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Introduction

Acute pain mostly affecting the bones is the commonest and most dramatic presentation of sickle cell disease (SCD). It could occur alone or along

with other acute manifestations of the disorder and it is a major reason for frequent emergency care. Despite significant improvement in the management of SCD, crises in the disorder remain a high cause of morbidity and early mortality [1]. Polymerization of haemoglobin S in the red blood cell is responsible for the chronic haemolytic state, painful vaso-occlusive crisis, and multi-organ damage [2]. The four major types of crises recognized in sickle cell disease are painful vaso-occlusive crisis, haemolytic crisis, sequestration crisis and aplastic crisis. All these crises except the vaso-occlusive crisis could result in a precipitous drop in the haematocrit causing severe anaemia. Haemolytic crisis precipitated by malaria is the commonest anaemic crisis especially in the paediatric age group [3].

Pain control and blood transfusion are therefore the mainstay of therapy for most severe acute crises. Acute chest syndrome (ACS) remains a major cause of death [4,5], and it is associated with prolonged hospitalization [1]. The pathogenesis of ACS has been attributed to infection in children [6] and pulmonary thrombosis in adults [7]. Infections from encapsulated bacteria and malaria parasite are precipitating factors for sickle cell crises in tropical Africa. Vaccination against encapsulated organisms and routine chemoprophylaxis against malaria infection are expected to change this narrative [8]. Both vaso-occlusion and haemolysis can generate and can also be caused by reactive oxygen species (ROS) in a vicious cycle [2]. About a quarter each of our patients rarely have bone pains or ever received blood transfusion [9]. The objective of this study was to determine the frequencies and the interrelatedness of the various crises seen in adult sickle cell disease patients accessing emergency care in our hospital.

Methods

Study site and patients: This prospective, questionnaire based, cross-sectional study was carried out at the Haematology Department of the University College Hospital, Ibadan, a tertiary health facility in South West, Nigeria. Adult sickle cell disease patients (age $\geq$16years) can access emergency care through the Haematology Day Care Unit (HDCU) or the emergency department of the hospital. The HDCU is a three-bed facility which offers emergency care to adult patients with haematological disorders between the hours of 8am and 6pm. Patients present to the emergency department after closure of the HDCU (between 6pm and 8am). Adult SCD patients in any form of crises are promptly treated and subsequently reviewed for admission into the wards or discharged to be followed up at the medical out patient. SCD patients who are seen in the emergency department during call hours (4pm-8am) are either admitted to the wards after a review by haematology resident doctors or discharged home if the crises abated after observation in the emergency room. They could also be sent to the HDCU for further evaluation. All SCD patients accessing care at the HDCU or emergency department would have their packed cell volume (PCV) or full blood count (FBC) determined. Patients were also investigated for malaria parasites, if there are reasons to suspect the infection. Patients requiring blood transfusion are transfused and allowed home if there are no further complications while patients having bone pain crisis are given analgesia, rehydrated and observed for 4-6 hours before a decision to admit to the wards or allowed home is made. All patients seen for emergency care are thereafter given a short clinic appointment of about two weeks to be followed up at the outpatient clinic. Patients recruited for this study were all adult sickle cell disease patients who presented to the HDCU or the emergency department with an acute illness over a three-month period from September to November 2020. The information obtained from the patients were corroborated from the case-note by a trained research nurse who perused the case-notes.

Ethical Consideration:
Ethical approval was obtained for the study from the institutional review board (UI/EC/18/0060). Informed consent was also obtained from the patients.

Data Management and Statistical Analyses
Data were entered and analyzed using STATA 13.0 (StataCorp, College Station, Texas, USA). Bone pain crisis per year (BPC/yr.) was categorized into those who claim they never/rarely have bone pains, those who have 1-3 BPC/yr. and those who had more than 3 BPC/yr. The bone pain crises per year was recoded into two groups; those who never and rarely have bone pains were in one group while the second group consisted of those who have had at least one bone pain crisis in a year. Bone pain was also scored at presentation on a scale of 1-10 which was then re-categorized into mild (1-3), moderate (4-6) and severe (7-10) pain. Jaundice was classified as tinge, mild, moderate and severe. Univariate analysis was done by generating frequencies and proportions and

were expressed as percentages for categorical variables. Quantitative variables were presented as mean and standard deviation. Bivariate analysis was done to test for association between categorical variables using the chi-square test while quantitative variables were compared using the independent t test. The level of significance for all tests was set at 5%.

Only one patient was diagnosed with aplastic crisis and none with sequestration crisis but three patients had vasoocclussive crisis involving the abdomen. Among the patients, 17/42 (40.5%) gave prior history of accessing care at the emergency department, 53/59 (89.8%) had also been hospitalized prior to this admission while 40/53 (75.5%) had received blood transfusion prior to this

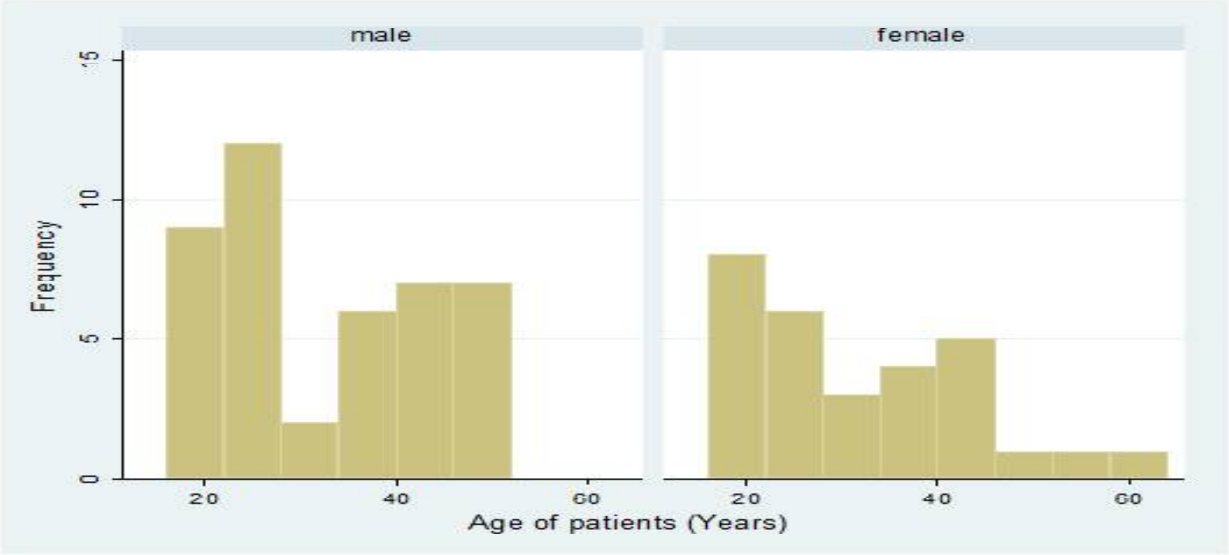

Fig. 1: Age by Gender distribution of Adult Sickle Cell Disease patients assessing Emergency Care at a Tertiary Hospital

Results

Seventy-three patients were seen during the three-month period, there were 44 males and 29 females. The mean age of the patients seen was 31.8±11.4 years with about a third being in the middle age (Figure 1) while the mean age at diagnosis of the disorder was 7.3±6.6 years. The mean age and the age at diagnosis did not differ significantly between male and female patients (32.1yrs vs 31.5yrs and 7.9yrs vs 6.3yrs respectively). The haemoglobin types of the patients were HbSC (8 (11%)), HbSS (64 (87.7%)), one patient did not have his/her haemoglobin type recorded but was included in the analysis. HbSC patients were older at diagnosis than HbS patients (14.8±3.6yrs vs 6.5±0.9yrs; *P*=0.007). Seventeen (23.3%) of the patients presented at the emergency department while 56 (76.7%) presented at the haematology day care unit. The mean steady state haematocrit of the patients was significantly higher than the mean haematocrit at presentation for emergency care 24% vs 20.7% (P<0.001). Forty-eight (65.8%) patients presented with bone pain crisis alone (BPC), twenty-four (32.9%) had haemolytic crisis with history of dark brown urine (suggestive of intravascular haemolysis) in 14 (58.3%) while 15 (20.5%) had both BPC and haemolytic crises.

admission. Nineteen (27.9%) admitted to rarely having bone pains, 32 (47%) had less than one BPC on the average in a year, 13(19.1%) had 1-3 bone pain episodes in a year while 4(5.8%) had more than three episodes in a year **(Table 1)**. When asked how often they have BPC which was treated at home without the need to visit the hospital; 54 (80.6%) claim they have such pain occasionally, 4(6%) claim they never had such pain, 6(9%) have similar pain once a month while one patient each have such pain fortnightly, weekly or daily. Categorization of the pain score as mild, moderate and severe showed that at presentation; 7/61(11.5%) presented with mild pain, 15/61(24.6%) had moderate pain, 26/61 (42.6%) had severe pain while 13/61(21.3%) had no bone pain. There was no association between the bone pain score and the number of BPC in a year (*P*=0.50) nor with whether or not a patient had haemolytic crisis (*P*= 0.23), neither was there a relationship between the number of BPC per year and frequency of blood transfusion (*P*=0.51) **(Table 1)**. However, there was a significant relationship between the number of BPC per year and if a patient was ever admitted to a hospital (*P*=0.04) and between if a patient was ever transfused and admitted to the hospital (*P*=0.001).

Table 1: Association between bone pain crisis, age and transfusion requirements in adult sickle cell disease patients

Parameters	Number of BPC per year None (n=19)*	<1/year (n=32)	1-3/year(n=13)	>3/year(n=4)	*P* value
Mean age at diagnosis (years)	7.3±8.0	6.7±6.9	8.6±5.3	8.3±1.5	0.13
Mean Age (years)	33.8±12.9	29.1±10.3	34.8±9.8	26.3±9.5	0.23
Number of blood units transfused till date	3.5±1.9	3.7±2.6	6.1±3.3	2.5±0.6	0.046
Mean steady state PCV	23.4±4.1	24.5±4.2	24.2±3.9	23.8±5.6	0.87
Mean PCV at admission	18.8±4.9	21.7±5.7	21.7±5.8	20.5±6.3	0.91
Mean bone pain score	1.4±1.2	2.0±1.2	2.1±1.2	1.8±1.3	0.99

PCV: packed cell volume, BPC: Bone pain crisis
** Patients who rarely or have never had bone pains*

Table 2: Association between the degree of jaundice and transfusion requirements in adult sickle cell disease atients

Parameters	Degree of Jaundice None	Tinge	Mild	Moderate	Severe	*P* Value
Mean steady state PCV	24±1.4	24.3±3.7	22.6±2.4	5.8±4.2	21.6±4.8	0.61
PCV at admission	22.2±5.1	18.7±4.9	17.6±3.9	21.1±6.6	20.2±4.3	0.19
Number of blood Units transfused till date	4.5±3.0	2.3±0.5	3±1.9	3.9±2.2	4.2±3.0	0.07

PCV: packed cell volume;

The number of blood units transfused was not associated with the number of BPC per year (*P*=0.39) **(Table 1)** nor the degree of jaundice (*P*=0.4) **(Table 2)**. The recoded bone pain crisis per year did not significantly alter its association with bone pain score (*P*=0.86), need for blood transfusion

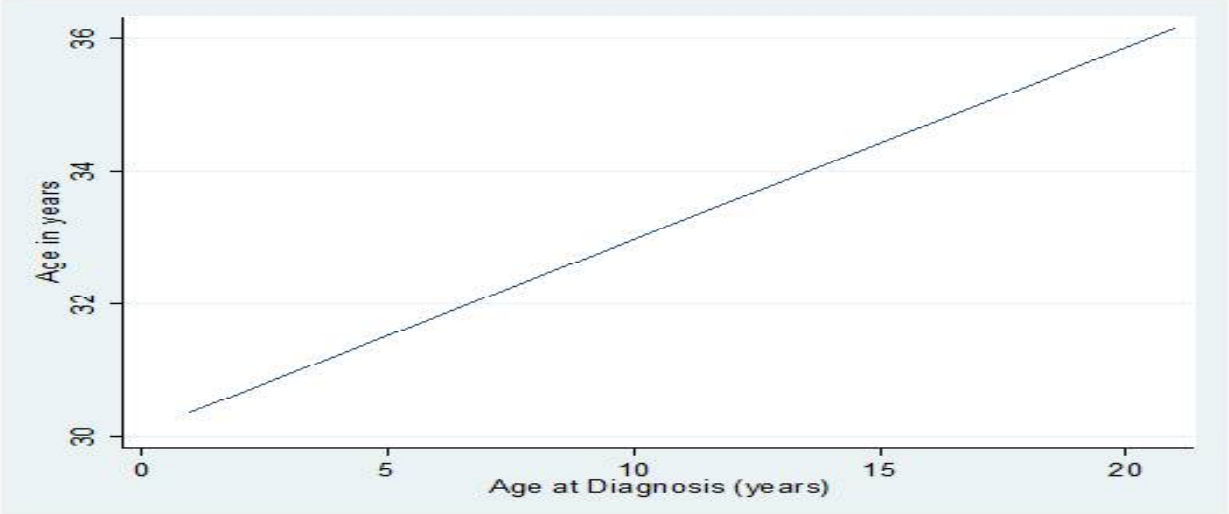

Fig.2: Relationship between age at diagnosis and age at presentation for emergency care in adult sickle cell disease patients

(*P*=0.1) or hospital admission (*P*=0.11). The age at diagnosis was a good fit for the age of the patient (figure2), showing a linear relationship between the patient's current age and age at diagnosis. The mean age at diagnosis was higher for patients with more frequent BPC per year (*P*=0.1) (figure 3) and associated with the steady state haematocrit (*P*=0.045). The three patients who died during the study period were two females and one male with a mean age of 49.7years at death.

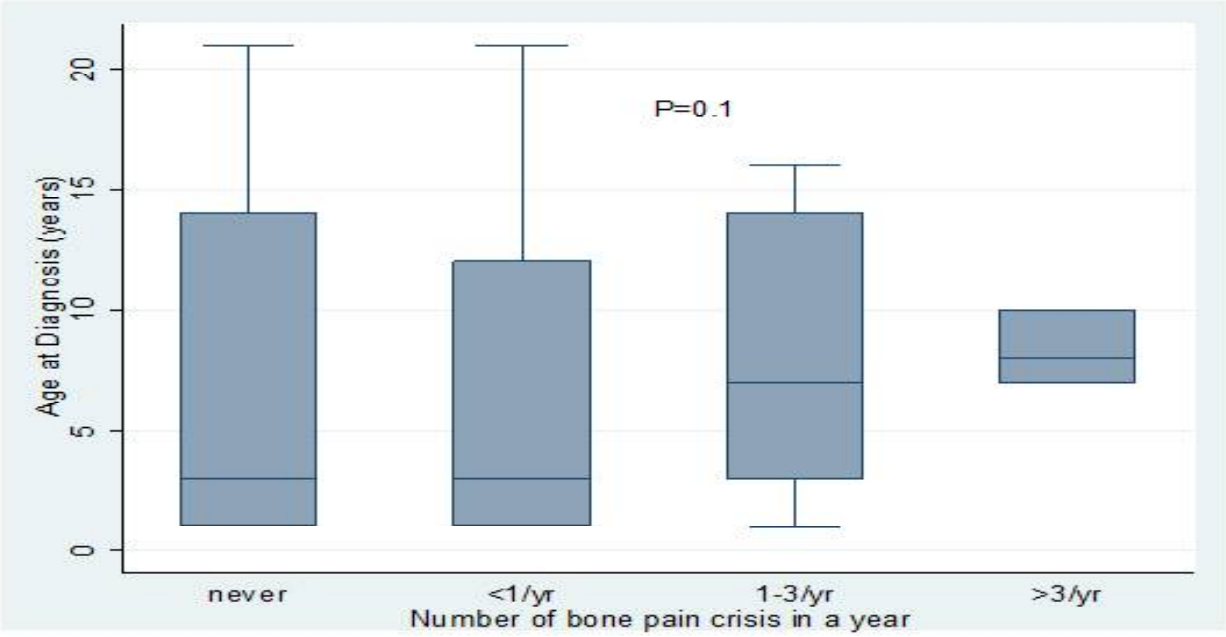

Fig.3: The effect of age at diagnosis on number of bone pain crisis in a year in adult sickle cell disease patients

Discussion

This study shows that bone pain crisis remains the hallmark of sickle cell disease and accounts for more than 80% of why patients access emergency care. Half of the patients were seen in haemolytic crisis and a history of dark brown urine (haemoglobinuria) suggesting intravascular haemolysis occurred in half of those presenting with haemolysis. Sequestration and aplastic crises appear uncommon in adult sickle cell disease patients. It also appears that both bone pain and haemolytic crises occur independently of each other, but a patient is more likely to be admitted to the ward for blood transfusion than for bone pains. The age of the patient at the diagnosis of the disorder is in congruence with the current age of the patient, showing that the older the age at diagnosis the older the age of the patient. The late age at diagnosis would suggest a delay in diagnosis and a milder course of the disease.

As low as six percent (1 in 16) of the patients had more than 3 painful episodes in a year, which is in agreement with a mild to moderate disease in our population of patients, a finding similar to what was seen in paediatric patients [10]. This however, would be contrary to the severe disease phenotype described for the Benin haplotype, a phenotype mostly prevalent in the country [11]. Therefore, the small percentage of patients with severe painful episodes could a mean early death in infancy. Also, this small percentage with severe painful crisis will preclude the use of hydroxyurea in most of our patients since its use is recommended in patients with three or more painful crises in a year [12]. It is then advisable for patients to be placed on hydroxyurea early in childhood using appropriate criteria. The claim of a quarter of the patients to never or rarely have bone pains and a similar proportion not having been transfused would suggest that the frequency of blood transfusion and frequency of bone pains could be used to categorize SCD patients into two broad phenotypes. The phenotypes would be those in whom haemolysis is more problematic than vasoocclusion and those in whom vasoocclusion has an upper hand. This hypothesis can be confirmed by a cohort study of patients diagnosed early in infancy through newborn screening.

Haemolytic crisis is the commonest anaemic crises and this finding which has also been reported in paediatric patients [3,10] occurred in more than half of our patients. Half of the patients with haemolytic crisis also gave a history of dark brown

urine which is suggestive of intravascular haemolysis. Similarly, unconjugated hyperbilirubinaemia in the presence of increased urinary urobilinogen was observed in paediatric patients [3]. This contrast with reports from temperate climate where haemolysis is not a common occurrence in acute emergencies [13]. The high prevalence of haemolytic crisis has been attributed to malaria infection despite the practice of malaria chemopropylaxis in these patients [13,14]. We then hypothesize that the high occurrence of haemolytic crisis with intravascular haemolysis could be as a result of the high prevalence of G6PD deficiency in the community. Though the prevalence of G6PD was not significantly higher than found in the general population in a recent study [15]. SCD patients with G6PD deficiency were twice more likely to have lower enzyme activity than deficient controls, also deficient patients, were more likely to have a lower haematocrit than non-deficient patients [16]. We are therefore in support of G6PD deficiency rather than malaria parasitaemia being the likely reason for the high prevalence of haemolytic crisis. This is not only because the patients are mostly on malaria chemoprophylaxis but also because the level of parasitaemia was found to be similar in steady state SCD and healthy controls [8]. Makani et al [16] also observed that malaria infection is uncommon in steady state SCD, though they noted that concomitant malaria infection during hospitalization is associated with a higher likelihood of death. Furthermore, infection by *Plasmodium Vivax* did not significantly affect the haemoglobin levels or bone pain crisis despite a 73% prevalence of parasitaemia in Indian patients [17].

The limitations of this study are that it is a study from a single centre and the relatively small sample size. A cohort study starting in early infancy would be ideal in studying the different phenotypes of the disease rather than a cross-sectional study. The fewer frequencies of both the aplastic and sequestration crises and the absence of acute chest syndrome among the patients could be because of under-diagnosis.

In conclusion, bone pain crisis remains the hallmark of the disease, and the intravascular haemolysis associated with the haemolytic crises may be as a result of the high prevalence of G6PD deficiency in the region. The late age at diagnosis is a likely reflection of the severity of the disease and a call for newborn screening of the disorder which would be helpful in identifying the different phenotypes of the disease.

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