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Original Article

Pattern of anaemic crises in Paediatric Sickle Cell Anaemic Patients seen at the University of Maiduguri Teaching Hospital, North-eastern Nigeria

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Abstract

Background: Sickle cell anaemia (SCA) is the commonest haemoglobinopathy worldwide. The main presentation is chronic anaemia often exacerbated during periods of rapid destruction of red blood cells, marrow failure, or acute sequestration. Blood transfusion is often needed to save lives; unfortunately, this is often not available. **Objectives:** This study aimed at identifying the pattern of anaemic crises, the age group with the highest frequency and associated morbidities. **Methodology:** This was an analytical observational study that examined patterns of anaemic crises in children with SCA. Patients who that fulfil the inclusion criteria were recruited consecutively. Standard laboratory methods as described by Dacie and Lewis were employed in the evaluation of specimens. **Results:** One hundred patients in anaemic crisis, comprised 53 males and 47 females, given an M: F ratio of 1.1:1, and 100 SCA patients age and sex-matched in steady-state. The mean ± SD age of cases was 7.2 ± 3.5 while that of controls was 6.82 ± 3.98, there was no difference between the ages $p = 0.53$. The highest incidence of anaemic crisis was seen among those aged 10 to 16 years. Malaria was the commonest morbidity among all types of anaemic crises. There was no association between types of morbidity and anaemic crisis p = 0.42**. Conclusions:** Haemolytic crisis was the most common anaemic crisis; acute splenic sequestration was commoner in the under-fives. Children older than 10 years were at greatest risk of anaemic crisis. Malaria was the commonest associated morbidity.

Keywords: *Anaemia, Crisis, Maiduguri, Paediatrics, Sickle cell.*

Introduction

Sickle cell anaemia (SCA) is the commonest variant of haemoglobin disorders inherited from both parents in an autosomal recessive fashion. The disorder is characterized by chronic anaemia and hand-and-foot syndrome in the first few years of life. The ongoing anaemia is exacerbated by infections. During this period, there may be rapid red blood cell destruction, failure of the erythroid cell line in the bone marrow, or acute sequestration episodes.[1] Three major types of anaemic crises are recognised in SCA: aplastic, acute sequestration, and hyper-haemolytic anaemic crises. The hyper-haemolytic anaemic crisis is less commonly reported in literature emanating from temperate climates.[2-4] Unfortunately this continues to be a major problem among patients with SCA in tropical Africa where the disease's natural history is somewhat complicated with infectious diseases and recurrent episodes of malaria infestation.[5-7] These

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three major types listed above could lead to severe anaemia in children with SCA. The average haemoglobin concentration in patients with SCA in Nigeria is 7.2 g/L.[8] This is the level that is considered to be severe anaemia that will warrant blood transfusion. These children with severe anaemia are seen in the emergency paediatric unit (EPU) mostly in a moribund state and die before securing blood for transfusion. Therefore, SCA is not only a major cause of morbidity but also mortality among children with this disorder. Blood transfusion is often needed to save the lives of children presenting with anaemic crises; but is often unavailable in many hospitals, especially outside the tertiary hospitals. A poor donor drive, lack of storage facilities, and poor power supply are compounding factors for blood availability. Infections, which often coexist, or precipitate the anaemic crises, influence the outcome of the disease, even after blood transfusion, often resulting in poorer outcomes.[9,10,11] With this fact borne in mind, and associated morbidities of anaemic crises are arduously sought for and addressed early enough, a better outcome becomes highly likely. Studies on sickle cell anaemic crises have been done in other parts of the country.[1, 9] However, no similar studies were done in North-eastern Nigeria. This study, therefore, was aimed at identifying the pattern of anaemic crises in SCA patients at the University of Maiduguri Teaching Hospital (UMTH), the age group with the highest frequency of anaemic crises, and the morbidities associated with anaemic crises in SCA patients at the UMTH.

Materials and Method

Study design

The study was an analytical observational study that examined the pattern of anaemic crises in paediatric sickle cell anaemic patients. The study was conducted at the Emergency Paediatric Unit (EPU), Paediatric Outpatient Clinic, and the Paediatric Medical Ward of the University of Maiduguri Teaching Hospital, Maiduguri, Borno State, Nigeria.

Study participants

Patients with severe anaemia (PCV <15%) between six months and 16 years admitted into the wards were recruited consecutively into the study after consent was obtained. All cases were seen and evaluated at admission. They were reviewed daily during admission until discharge and were subsequently followed up at the sickle cell clinic at one, four, eight and 12 weeks after discharge, or for longer periods when necessary. A case report form was used to obtain the history of clinical symptoms from the patients, parents, or guardians. A physical examination was carried out to document the presence or absence of hepatomegaly and splenomegaly. The liver was measured from the right costal margin along the mid-clavicular line, and the spleen along its axis. The steady-state parameters (PCV, spleen and liver sizes) for each of the cases were used as their control in determining the type of anaemic crisis. For patients that have recently received a blood transfusion, the determination of the steady-state parameters (where this had not been done before) was deferred until three months later. For newly diagnosed or transferred patients, their steady-state PCV, spleen and liver sizes were determined during the follow-up visits.

The presence of other co-morbidities in the cases, such as malaria, vaso-occlusive crisis (VOC), and acute respiratory infection (ARI) among others, were taken as associated morbidities. The diagnoses of associated morbidities were made based on standard literature. Patients with PCV <15% were transfused as soon as blood was made available. Those with fever or other associated morbidities were evaluated appropriately, and placed on the appropriate treatment and medications.

Age and sex-matched SCA patients in steady state were recruited as controls; and since they are in steady state, and, therefore, had no complaints during follow-up visits, their steady-state parameters such as the PCV, spleen and liver sizes, were for this study taken as morbidities.[12]

Study procedure

Five millilitres of blood sample was drawn by venepuncture using standard techniques into an ethylene-diamine-tetra-acetic acid (EDTA) bottle for evaluation FBC and reticulocyte count; blood film for malaria parasite, and haemoglobin genotype, where this has not been established previously. Other investigations such as blood culture, urine microscopy, culture, sensitivity test (MCS), lumbar puncture and radio-graphs, were carried out using standard methods where indicated by patients' clinical condition. These investigations

were carried out in the Hospital's main laboratories by the designated laboratory scientists. Standard laboratory methods as described by Dacie and Lewis[28] were employed in the evaluation of the haematological specimens.

Anaemic crises were classified in this study into six types, based on the following observations:

1. **Hyperhaemolytic crisis:** Significant fall in Hb level by 3g/L from steady state Hb level, reticulocytosis, with recently appearing or deepening jaundice, and/or raised serum bilirubin.[9]
2. **Aplastic crisis:** Precipitous fall in Hb level and reduced or absent reticulocytes in the peripheral blood.[13-15]
3. **Acute splenic sequestration crisis:** A decrease of at least 2g/dl from the steady state Hb concentration, evidence of increased erythropoiesis such as markedly elevated reticulocyte count, and an acutely enlarging spleen.[14,16-18]
4. **Aplastic-haemolytic crisis**: co-existence of hyperhaemolysis with reticulocytopenia[19]
5. **Aplastic-sequestration crisis**: occurrence of reticulocytopenia, acutely enlarging spleen, and absence of jaundice.[13]
6. **Recovery phase of the aplastic crisis:** reticulocytosis with severe anaemia, absent jaundice, and splenomegaly.[20,16,21-23]

Steady State: Was defined as the period of relative well-being, when the patient is free from pain, infection or other disease process,[1] for at least three weeks since the last clinical event and three months or more since the last blood transfusion.[24]

Crisis: the sudden onset, and occasionally fatal outcome of the disease that periodically interrupts the steady level of fitness in patients with sickle cell anaemia.[25,26]

Data analysis

Results obtained from the study were recorded in a proforma as soon as cases were seen and were coded and analysed using SPSS software (version 16). The frequencies of the data generated were displayed using tables, bar charts, pie charts and graphs as appropriate. The means, ranges and standard deviations of variables were also generated. These were compared among the different types of anaemic crisis using the Student's t-test and Chi-square as appropriate. Statistical significance was set at $p<0.05$.

Ethical considerations

Ethical clearance was obtained from the Ethics and Research Committee of the University of Maiduguri Teaching Hospital (ADM/TH/75/Vol.II). A written (signed) informed consent was obtained from the parents/caregivers, with the liberty to deny consent or opt out of the study at any stage. Such a decision did not affect the quality of care rendered to the patient. For those that could not read, the content of the consent form was explained to them in a language they could understand.

Results

Demographic and clinical characteristics of the study population

One hundred patients in anaemic crisis, comprised 53 males and 47 females, given an M: F ratio of 1.1:1, and 100 SCA patients were age and sex-matched in steady state. The ages of the subjects ranged between six months and 16 years. The mean ±SD age of the SCA patients in crisis was 7.2 ± 3.5 while that of the steady state was 6.8 ± 3.98. There was no statistically significant difference between the ages (t = -0.636, = 0.525). The highest incidence of the anaemic crisis was seen among those aged 10 to <15 years. The demographic characteristics distribution of the study population is shown in Table 1.

Table 1: Demographic characteristics of the study population (n = 100)

Variables	SCA crisis N (%)	Steady state N (%)
Age (years)		
< 5	22 (22)	33 (33)
5 - < 10	27 (27)	43 (43)
10 - < 15	43 (43)	24 (24)
? 15	8 (8)	0 (0)
Sex		
Male	53 (53)	57 (57)
Female	47 (47)	43 (43)

N = frequency

Fever was documented in 75(75%) of cases, while paleness was the presenting symptom in 2(2%) patients. One patient complained of weakness as a presenting symptom. The frequency of clinical presentations in children with anaemic crises is summarized in Table 2.

Table 2: Frequency of clinical features among cases with anaemic crises

Variables	Frequency*	%
Fever	75	75
Hepatomegaly	64	64
Jaundice	42	42
Cough	41	41
Bone Pain	34	34
Headache	21	21
Abdominal Pain	20	20
Breathlessness	18	18
Splenomegaly	16	16
Easy fatigability	16	16
Vomiting	15	15
Catarrh	12	12
Dizziness	9	9
Palpitation	8	8
Carpopedal spasms	6	6
Paleness	2	2
Weakness	1	1
Chronic leg ulcer	1	1
Dysuria	1	1
Dark urine	1	1
Chest pain	1	1
Excessive cry	1	1
Convulsion	1	1
Body rash	1	1

**Frequency not summing up to 100% because many patients had more than one symptom at presentation.*

Proportions of patients with a previous history of blood transfusion were similar in both cases (43%) and controls (30%). The steady-state PCV, splenic and liver sizes were compared between the cases and controls (Table 3). Steady-state PCV was found to have a statistically significant difference.

Table 3: Steady-state parameters of SCA crisis cases and controls

Variables	SCA crisis		Controls		X	*p-value*
Steady-state PCV (%)	**Freq**	**%**	**Freq**	**%**		
16 - 20	56	56	31	31		
21 - 25	43	43	61	61	15.74	0.0004
>25	1	1	8	8		
Total	**100**	**100**	**100**	**100**		
Steady-state Spleen (cm)						
None	93	93	94	94		
1-5cm	6	6	5	5	0.0962	0.953
6-10cm	1	1	1	1		
Total	**100**	**100**	**100**	**100**		
Steady-state Liver (cm)						
None	74	74	71	71		
1 – 5cm	24	24	27	27	0.2826	0.868
6 - 10cm	2	2	2	2		
Total	**100**	**100**	**100**	**100**		

Figure 1 shows the pattern of anaemic crises. The haemolytic crisis was the commonest form of anaemic crisis encountered.

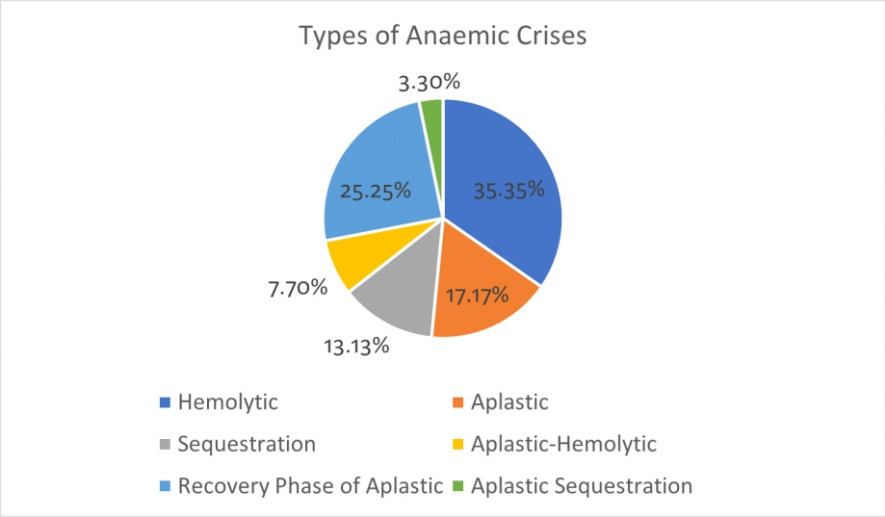

Fig 1: Pattern of anaemic crises: Frequencies of occurrence (N, %)

Associated Morbidities among sickle cell anaemic patients in anaemic crisis

Malaria was seen in 64 (64%) cases as a comorbidity among sickle cell anaemic patients in anaemic crises, followed by acute respiratory infection (ARI). The least encountered morbidities included urinary tract infection (UTI), and chronic leg ulcer, among other morbidities. Table 4 shows the morbidities encountered in patients with anaemic crises.

Table 4: Associated morbidities among sickle cell anaemia patients in anaemic crisis

Diagnosis	No. of Cases*
Malaria	64
ARI	30
VOC	9
CCF	60
steomyelitis	6
Tetany	6
CVA	5
Septicaemia	4
CKD	3
HBV infection	2
Chronic leg ulcer	1
UTI	1
Cellulitis	1
Acute diarrhoeal disease	1
Measles	1
Febrile convulsion	1

** Some patients had more than one diagnosis; hence number of cases is greater than 100.*

ARI, acute respiratory infection; HBV, hepatitis B virus; VOC, vaso-occlusive crisis; CCF, congestive cardiac failure; CKD, chronic kidney disease; CVA, cerebrovascular accident; UTI, urinary tract infection.

Association between demographic variables and types of anaemic crises

Haemolytic and aplastic crises were more frequent among children aged 10 - <15 years with the incidence of 45.7% and 41.2% respectively. Sequestration crisis on the other hand was more frequent among children <5 years, with an incidence of 46.2%. A significant statistical association exists between age and type of anaemic crisis, $p = 0.019$ (Table 5).

Table 5: Association between demographic variables and types of anaemic crises

Demographic Variable	Frequency of type of Anaemic Crises N, (%)					
	HM	**AP**	**SQ**	**AP-HM**	**RP-AP**	**AP-SQ**
Age (yrs)*						
0 - <5	7(20.0)	6(35.1)	6(46.2)	1(14.3)	2(8.2)	0(0.0)
5 - <10	11(31.4)	3(17.6)	2(15.4)	3(42.9)	7(28.0)	1(33.3)
10 - <15	16(45.7)	7(41.2)	5(38.5)	2(28.6)	13(52.0)	0(0.0)
≥ 15	1(2.9)	1(5.9)	0(0.0)	1(14.3)	3(12.0)	2(66.7)
Total	**35**	**17**	**13**	**7**	**25**	**3**

χ^2-value = 28.39, ***p* -** 0.019

HM, haemolytic; AP, aplastic; SQ, sequestration; AP-HM, aplastic-haemolytic; RP-AP, the recovery phase of aplastic; AP-SQ, aplastic-sequestration.

Association between morbidities and type of anaemic crisis

Malaria was the commonest morbidity among all types of anaemic crises, accounting for 34.5% of the morbidities recorded among those with haemolytic crises and 63% in the recovery phase of the aplastic crisis. ARI also had a similar pattern across all types of anaemic crises. There was no significant association between the type of morbidity and type of anaemic crisis $\chi^2 = 3.92, p = 0.42$ (Table 6).

Table 6: Association between morbidities and type of anaemic crisis

Morbidities	Haemolytic n (%)	Aplastic n (%)	Sequestration n (%)	χ^2	*p*
Malaria	19(34.5%)	13(50%)	7(36.8%)	3.924	0.416
ARI	11(20%)	7(26.9%)	5(26.3%)		
Others	25(45.5%)	6(23.1%)	7(36.8%)		
Total	**55 (100)**	**26 (100)**	**19 (100)**		

Others include: Vaso-occlusive crisis, (9); osteomyelitis(6); congestive cardiac failure (6); tetany (6); cerebrovascular disease (5); septicaemia (4); chronic kidney disease (3); hepatitis B virus infection (2); urinary tract infection (1), cellulitis (1); acute diarrhoeal disease (1); febrile convulsion (1); Measles (1); chronic leg ulcer (1). ARI, acute respiratory infection.

Discussion

The haemolytic crisis was the commonest type of anaemic crisis encountered in this study, with a frequency of 35%. This is similar to the findings in South-eastern Nigeria,[1,5] South-western Nigeria,[9] and Central India.[27] Our finding of haemolytic crisis to be the commonest is also in concordance with Akinyanju's finding that haemolytic anaemia is more commoner in children than in adults,[31] and also with those of other researchers who reported a steady decline with age in the incidence of both VOC and hyperhaemolytic crisis.[1,5] Haemolytic crisis is, however, reported to be rare by other workers.[4,25,26,28-30] It was the least type of crisis in Olabode's study at University College Hospital Ibadan Southwestern Nigeria[30] probably because his subjects were mostly adults, and just like in the Western world, the prevalence of malaria and other infections which commonly precipitate haemolysis in SCA patients are a less frequent finding.[32]

The aplastic crisis was found to be the second most common crisis in this series. This is slightly higher than a study in Ibadan, where it accounted for 12.5% of cases.[9] It was, however, not the encounter in several Nigerian studies.[5,33,34] Kaine did not report an aplastic crisis because bone marrow aspiration (BMA) was not done to confirm marrow aplasia.[5] However, the diagnosis of aplastic crisis has been defined without requiring BMA as "a precipitous fall in Hb level and reduced or absent reticulocytes in the

peripheral blood.[13-15] These cases might have simply been missed out. In our series, none of the patients who had acute splenic sequestration crisis (ASSC) were in shock. This finding is inconsistent with the report by Topley *et al*.,[16] These would represent minor episodes of the disease spectrum, in which shock is not a feature.[16] Minor episodes of ASSC may precede and possibly be of predictive value for later more severe or even fatal attacks, hence the need for close supervision of children with such a history.[35] Acute splenic sequestration crisis was found to be more frequent in children less than five years where almost half of the cases occurred. This finding is similar to the Jamaican study where it was found to be commoner in the under-fives.[16] Similar findings have been reported in children between the ages of two months and four years, with a peak age incidence between six months and three years.[36,37] Acute splenic sequestration crisis is common in this age group because autosplenectomy, which usually occurs between the ages of six and eight years, has not yet occurred.[38] Beyond this age, it is found only rarely. Acute splenic sequestration crisis however, has been reported to occur at any age in childhood in those who have not had splenic infarction,[39] in those with high levels of HbF,[40] and in adults with splenomegaly, particularly those with HbSC disease or β-thalassemia.[26,40]

This was also demonstrated in this study as ASSC was found to be common in the age group 10-<15 years, where it accounted for almost forty per cent of cases. These patients may have had splenomegaly from the persistent stimulatory effect of malaria, or due to a high HbF level (which was not measured in this study). The finding of ASSC in this study might have been exaggerated by the presence of splenomegaly, which is a common feature of infections known to precipitate anaemic crises, principally malaria and septicaemia. These infections might have been responsible for both the anaemia and splenomegaly.

The anaemia seen in 35% of patients in this study had mixed features that did not fit into any of the three major recognised types of anaemic crises. This finding is higher than that which was observed previously[20] which could be attributed to the inclusion of those in the recovery-phase-of-aplastic crisis. These have been designated 'indeterminate' or 'mixed anaemic crises' (MAC). They include aplastic-haemolytic,[19] aplastic-sequestration, and recovery-phase-of-aplastic crises.[20]The significance of the MAC is not certain, but they are associated with a high relative risk of *Salmonella* bacteraemia compared with those with pure anaemic crises.[20]

This observation contrasts the finding in this study where no significant association was found between morbidity and type of crisis. The observed association in the aforementioned study might have been influenced by the ten cases of *Salmonella* bacteraemia found, compared with only two in this study.

This study reveals a significant proportion of patients in the recovery-phase-of-aplastic crisis. It remains to be determined if these patients in future can do without blood transfusion because, of the three patients who were not transfused, only one of them was in the recovery phase of an aplastic crisis and their mean PCVs at admission were not significantly higher than those with other crisis types.

It was demonstrated that the age group at the greatest risk of anaemic crises in this study was 10 to less than 15 years old, this finding differs from that of Juwah[1] where the peak age of anaemic crises was two to 4-year-old despite having a similar methodology of consecutive patient recruitment. The reason for this was not clear; it was also not in keeping with the observation that the incidence of anaemic crises decreased with increasing age.[5] It, however, agrees with the marrow 'burn-out' phenomenon that reported the severity of anaemia in sickle cell disease to gradually increase with age. Bone marrow 'burn-out' is expected to become a greater issue as better general medical care and new therapies prolong the lives of patients with SCA.[41]

This study reveals that the commonest comorbidity in SCA patients presenting in anaemic crises was malaria, which was seen in 64% of cases; followed closely by respiratory tract infection (comprising both upper respiratory tract infection and pneumonia) seen in 30% of cases. The finding of malaria as the commonest associated morbidity was similar to the findings of earlier researchers in Ibadan and Abuja, Nigeria,[11,33] but differs from those of Juwah[1] and Kaine[5] where malaria was found to be uncommon as it was seen in less than 22% of

patients. In the Enugu study, Juwah[1] concluded that malaria might have played a role in precipitating some of the hyper-haemolytic crisis and suggested that prophylaxis with pyrimethamine may be inadequate, the same drug used in Kaine's patient. The period of study could have accounted for the observed difference in these two studies from the same institution. Probably resistance to pyrimethamine might have developed during Juwah's study, evident from the fact that pyrimethamine is no longer recommended for prophylaxis, even in pregnant women. The absence of malaria as morbidity in Mann's study[19] is not surprising, because it was carried out in a malaria-free area.

We observed that malaria had no association with the type of anaemic crises, this is similar to Ambe *et al* findings,[11] However, this finding is at variance with the finding by Juwah,[5] where it was suspected to have precipitated haemolysis. The reason for this suspicion was not clearly stated but could have been because his study documented the presence of increased haemolysis by incorporating increased urobilinogen level with polychromasia, in addition to reticulocytosis and increased serum bilirubin.

It should be noted as previously observed, that the mere co-existence of infections and crises cannot not be regarded as a proof of causation.[5,42] This is further buttressed by finding no infectious cause in 43% of patients with fever after a detailed bacteriological and serological study of 180 episodes of fever in 22 patients.[12] It may, however, seem reasonable to attribute causation to malaria in febrile children with malaria parasitaemia in the absence of any focus to suggest other infections; although viral infections or even bacteraemia might as well be responsible. It is noteworthy that 10% of the patients had no illness at presentation (no morbidity) in this series. These patients were aged eight years and above, and 60% of them were in the recovery-phase-of-aplastic crises, and nearly all of them (90%) have been transfused previously. A tendency towards repeated blood transfusion was observed among older patients in our series. This is similar to the finding of a retrospective study of the morbidities in SCA in Port Harcourt where two-thirds of the older age group of patients had been transfused between 1-7 times.[43]

Conclusion

Haemolytic crisis was the commonest anaemic crisis encountered followed by aplastic crisis followed by mixed anaemic crises. The most commonly associated comorbidity was malaria. There was also a significant association between age and type of anaemic crises, as ASSC was commoner in the under-fives and children older than 10 years were at greatest risk of anaemic crisis.

Competing interests

The authors have declared that no competing interests exist.

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