ORIGINAL ARTICLE

Types of anaemic crises in paediatric patients with sickle cell anaemia seen in Enugu, Nigeria

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Background: Anaemic crises in paediatric patients with sickle cell anaemia are major causes of morbidity and mortality. Some children admitted to hospitals' emergency rooms or paediatric wards of the hospitals with severe anaemia die before blood transfusion.

Aims and Methods: A total of 108 episodes of anaemic crises were prospectively evaluated in 108 patients with sickle cell anaemia attending the paediatric sickle cell clinic of the University of Nigeria Teaching Hospital, Enugu, Nigeria.

Results: Hyper-haemolytic crises were the commonest types of anaemic crises in the patients studied. The mean haemoglobin concentration of 44.66 (SD 6.42) g/l in crises was significantly lower than the mean steady state level of 78.69 (SD 8.50) g/l. Reticulocytes, unconjugated serum bilirubin concentrations, and the presence of nucleated red blood cells were also increased. About 4.6% of patients were not jaundiced at presentation even though they were profoundly anaemic. Their haematological indices gradually returned to normal without marked changes in their serum bilirubin concentrations. These patients were probably in the early recovery phase of aplastic crises. The classical presentation of acute splenic sequestration crisis with a rapidly enlarging spleen and hypotension was not observed. This was probably because of its precipitate nature and accompanying circulatory collapse, which carried a high mortality rate. Minor forms of sequestration crises may have occurred in the liver and spleen.

Conclusions: Malaria appeared to have played a role in precipitating some of the hyper-haemolytic episodes. Further studies to elucidate this role are required so that appropriate recommendations regarding malaria prophylaxis can be made in patients with sickle cell anaemia.

Sickle cell anaemia is one of the variants of disorders of haemoglobin synthesis inherited from both parents in an autosomal recessive fashion. It is characterised by chronic anaemia and/or hand foot syndrome in the first few years of life. This anaemia is exacerbated during periods of rapid red blood cell destruction, failure of the erythroid cell line in the bone marrow, or in acute sequestration episodes.

Nigeria, with a population of about 120 million, is the most populous country in Africa.[1] It has the largest concentration of patients with sickle cell anaemia in the whole world.[2] The disorder is uniformly distributed among its various ethnic groups. The prevalence of the carrier state (Hb AS) is about 25%.[3 4] About 2% of newborn babies suffer from sickle cell disease, mainly Hb SS and SC diseases.[5] In Eastern Nigeria where sickle cell haemoglobin SC disease is uncommon, Kaine and Udeozo[6] estimated that 30 000 Igbo preschool children suffer from sickle cell anaemia. This enormous number is likely to place a burden on the health care delivery system that is not adequately equipped to deal with the problem.

Four major types of crises are recognised in sickle cell anaemia: aplastic, acute sequestration, hyper-haemolytic, and vaso-occlusive crises. Hyper-haemolytic crises are less commonly reported in literature from the temperate climates.[7–9] This continues to be a major problem among patients with sickle cell anaemia in tropical Africa where the natural history of the disease is somewhat complicated with recurrent episodes of malarial infection.[10–12] Apart from the vaso-occlusive crises, the first three listed above could lead to severe anaemia in patients with sickle cell anaemia. In Nigeria, the average haemoglobin concentration in patients with sickle cell anaemia is 72 g/l.[13] At the University of Nigeria Teaching Hospital, Enugu, such patients are not normally transfused until the haemoglobin concentration falls below 50 g/l, unless they also have features of circulatory collapse. This level is considered to be severe anaemia. The majority of these children are seen in the children's emergency room (CHER) in a moribund state and die before blood transfusion. Sickle cell anaemia is therefore not only a major cause of morbidity but also of mortality among those affected with the problem.

This study was designed to identify: (1) the commonest types of anaemic crises in those patients with sickle cell anaemia attending the paediatric sickle cell clinic of the University of Nigeria Teaching Hospital, Enugu; and (2) where possible, the immediate precipitating factor(s) of anaemic crises in these patients.

METHODS

The methodology for this study has been described elsewhere.[14] This study was carried out at the University of Nigeria Teaching Hospital, Enugu, Eastern Nigeria. Enugu lies in the equatorial rain forest belt and was the former capital of Eastern Nigeria. The paediatric sickle cell clinic serves Enugu and its environs. Before patients are accepted into the clinic, their haemoglobin genotypes are confirmed with cellulose acetate haemoglobin electrophoreses and sickling tests to rule out undetected coexisting abnormal haemoglobins. Their glucose-6-phosphate dehydrogenase (G6-PD) status is also determined. On average, patients are seen in the sickle cell clinic 4–6 times annually. Those with acute medical problems are managed in the paediatric wards or the CHER. During each clinic visit, an interval history is obtained and a full physical examination performed noting the presence of pallor, jaundice, hepatomegaly, and splenomegaly. The liver was measured from the coastal margin along the mid-clavicular line, while the spleen was measured along its long axis of enlargement, also from the

mid-clavicular line. Blood is then drawn from a peripheral vein for FBC, blood smears including thick and thin films for malaria parasites, MCH, MCV, reticulocyte count, and split bilirubin levels. All the patients are routinely placed on folic acid 5 mg daily and the antimalarial drug pyrimethamine 12.5–25 mg weekly. Patients are given enough of the drugs from the hospital pharmacy to last them until their next clinic appointment.

Definitions

- *Steady state*: this is defined as that period when the patient with sickle cell anaemia is free of infection, pain, or other disease processes.
- *Aplastic crisis*: significant change in blood picture characterised by a precipitous fall in the haemoglobin level (>20 g/l beyond steady state level) and reduced (<1%) or absent reticulocytes in the peripheral blood. The total white blood cell or platelet counts may or may not be affected. In addition, there is no significant increase in the unconjugated fraction of serum bilirubin.
- *Acute sequestration crisis*: significant change in blood picture characterised by a precipitous fall in the haemoglobin level and accompanied by a rapidly enlarging spleen or liver (greater than 2 cm from the steady state level) and reticulocytosis above the steady state level for each individual patient. Signs of acute circulatory insufficiency such tachypnoea, tachycardia, and hypotension may or may not be present.
- *Hyper-haemolytic crisis*: significant change in blood picture characterised by a precipitous fall in the haemoglobin level associated with jaundice, marked reticulocytosis, and polychromasia on the blood smear, increased unconjugated hyperbilirubinaemia, and increased urobilinogen content in urine above the steady state level for each individual patient.

Inclusion criteria

(1) All paediatric patients (<16 years) with sickle cell anaemia (Hb SS) admitted to the paediatric wards or the children's emergency room of the University of Nigeria Teaching Hospital, Enugu, who met the criteria for anaemic crises.

(2) All newly diagnosed paediatric patients (<16 years) with sickle cell anaemia (Hb SS) admitted to the children's emergency room or the paediatric wards of the University of Nigeria Teaching Hospital, Enugu with severe anaemia (haemoglobin <50 g/l), requiring blood transfusion. All such patients were then followed up in the paediatric sickle cell clinic for a period not less than three months from date of diagnosis in order to establish their steady state parameters.

Exclusion criteria

(1) All newly diagnosed paediatric patients (<16 years) with sickle cell anaemia (Hb SS) admitted to the children's emergency room or the paediatric wards of the University of Nigeria Teaching Hospital, Enugu, with severe anaemia requiring blood transfusion but who were either lost to follow up or could not be followed up for periods greater than three months from the date of diagnosis.

(2) All paediatric patients (<16 years) with sickle cell anaemia (Hb SS) that met the definition of anaemic crises but whose steady state haematological indices or serum bilirubin concentration could not be established during the study period.

(3) All paediatric patients with sickle cell anaemia (Hb SS) who showed features consistent with hypersplenism.

Treatment

Patients with anaemic crises were admitted either to CHER or the paediatric wards for blood transfusion. All such patients admitted between 1 September 1994 and 30 April 1995 were recruited for the study. A master list of all the patients seen during the study period containing hospital number, name, date of birth, and sex was compiled.

On admission, the patient's full medical history was recorded using the study protocol. The findings on physical examination were also documented. All the patients were initially treated with adequate doses of the antimalaria drug, chloroquine. Those who failed to respond adequately within 48 hours with complete resolution of fever, improvement in clinical symptoms, and absence of malaria parasites on thick and thin blood film preparations were presumed septic and went on to have a septic screen done. This included blood and urine cultures as well as repeat thick and thin blood films for malaria parasites. They were then treated with broad spectrum antibiotics, initially a combination of benzylpenicillin and gentamicin pending the culture results. Other antimalarial drugs were given if malaria parasites were still present on the repeat blood film examinations. If a patient presented with fluctuant bony swelling, this was aspirated for culture and sensitivity. A chest *x* ray examination and lumbar puncture were performed where indicated.

The range and mean (SD) were calculated for all the variables. The Z test for comparing sample means, χ^2 for proportions, and χ^2 test of goodness fit test, were employed where applicable. The steady state parameters of all the patients studied were used as controls. Standard laboratory methods were employed in evaluation of all the laboratory parameters.[15] Informed consent was obtained from the patients/parents/guardians where applicable of all those included in the study. The approval of the hospital ethics committee was also obtained.

RESULTS

Between 1 September 1994 and 30 April 1995, 447 patients were seen in the paediatric sickle cell clinic of the University of Nigeria Teaching Hospital, Enugu, Nigeria. They comprised 239 males and 208 females (M:F ratio 1.15:1.0). One hundred and twenty three patients (108 old and 15 newly diagnosed) were seen on 126 occasions with anaemic crises, one patient having presented with a recurrent episode and another patient with two recurrent episodes. Fifteen patients (12 old and three newly diagnosed) did not meet the study criteria and so were excluded from the study. One hundred and eight patients (60 males and 48 females; M:F ratio 1.25:1.0) with 108 episodes of anaemic crises were therefore available for analysis. The mean age of the patients studied was 7.39 (4.66) years. All the patients studied had the SS haemoglobin genotypes. Twelve patients (nine males and three females) were in addition G6-PD deficient. Nearly all the patients had urobilinogen in their urine, both in the steady state and in anaemic crises. The mean duration of illness before presentation was 3.37 (0.65) days. The majority of the patients were febrile on admission with a mean temperature of 38.7 (0.26)℃. Seventy seven per cent of them became afebrile after blood transfusion and antimalaria treatment. Nineteen patients, three of whom were in addition G6-PD deficient, had malaria parasites on their blood films. There were two deaths during the study period.

Hyper-haemolytic crises were the commonest types of anaemic crises observed in this study. More than 90% of the patients had a profound fall in their haemoglobin levels, in

Table 1 Characteristics of sickle cell patients with possible aplastic crises in the steady state and in anaemic crises

Steady state							Crises					
Age (y)	Hb (g/l)	Liver size (cm)	Spleen size (cm)	Retic. count	Tot. bil.	MP	Hb (g/l)	Liver size (cm)	Spleen size (cm)	Retic. count	Tot. bil.	MP
1.6	74	0.0	0.0	4.5	18.4	Neg	49	1.0	1.0	15	22.3	Pos
2.5	73	0.0	0.0	10	15.3	Neg	45	1.0	0.0	31	14.2	Neg
1.8	75	0.0	1.2	8.2	25.3	Neg	52	1.0	1.0	16	30.4	Neg
2.6	82	1.0	1.4	8.5	20.6	Neg	50	1.8	1.4	20	25.1	Neg
5.5	84	3.5	1.8	6.4	50.4	Neg	52	4.0	2.1	21	49.2	Neg

Tot. bil., total bilirubin level (μmol/l).
Retic. count, reticulocyte count (%).
MP, malaria parasite.

association with jaundice, reticulocytosis, polychromasia, unconjugated hyperbilirubinaemia, and increased nucleated red blood cells in circulation. The classical presentation of acute splenic sequestration crisis with a precipitous fall in the haemoglobin level, a rapidly enlarging spleen or liver (>2 cm), and hypotension was not observed. Five patients (4.6%) were probably in the early recovery stage of aplastic crises (table 1). They were not clinically jaundiced even though they were profoundly anaemic at presentation. Also their serum bilirubin concentrations, and liver and spleen sizes were not very different from their steady state values. They had pronounced reticulocytosis, however.

Table 2 presents the haemoglobin levels in the steady state and in anaemic crises. The mean steady state haemoglobin level was 78.69 (8.50) g/l. This was significantly higher than the mean level of 44.66 (6.42) g/l in crises ($p < 0.05$). Table 3 shows the reticulocyte counts in the steady state and in crises. The mean reticulocyte count in crises in this study was 14.39 (6.40)%. This was significantly higher than the mean steady state value of 6.41 (2.45)% ($p < 0.05$). Nearly all the patients studied had reticulocyte indices of greater than one, both in the steady state and in crises, indicating optimal bone marrow response. The mean MCV in the steady state was 84.5 (5.6) fL. This increased slightly in anaemic crises, mean MCV 86.7 (4.2) fL ($p > 0.05$). Jaundice was present in 95.4% of the patients in crises compared to 58.5% of the patients in steady state. This observation was statistically significant ($\chi^2 = 41.2$, $p < 0.05$). Table 4 presents the split serum bilirubin levels in the steady state and in crises. The mean total serum bilirubin concentration in the steady state was 45.28 (18.62) μmol/l. This was significantly lower than the mean level in crises of 90.83 (22.82) μmol/l ($p < 0.05$). There was, however, no significant difference in the conjugated levels of serum bilirubin concentrations, both in the steady state and in crises ($p > 0.05$). Table 5 shows the liver and spleen sizes in the steady state and in crises. Both mean values were significantly increased in crises (liver: 3.52 (1.68) cm; spleen: 2.00 (1.90); $p < 0.05$).

DISCUSSION

This study has shown that hyper-haemolytic crises were the commonest types of anaemic crises seen in paediatric patients with sickle cell anaemia attending the University of Nigeria Teaching Hospital, Enugu, Nigeria. A profound fall in the haemoglobin level (mean haemoglobin 44.66 (6.42) g/l) was usually heralded by fever (mean temperature 38.7 (0.26)℃). Jaundice was present in 95.4% of the patients. Haematological indices revealed marked reticulocytosis (mean 14.39 (6.40)%) beyond the steady state levels (mean 6.41 (2.45)%), polychromasia on blood smears, and increased presence of nucleated red blood cells in the peripheral blood. The total serum bilirubin concentration was also significantly increased in crises (mean 90.83 (22.82) μmol/l) above the steady state levels (mean 45.28 (18.62) μmol/l). There were no appreciable increases in the levels of conjugated serum bilirubin, suggesting that the increase in total serum bilirubin concentrations must have been accounted for solely by unconjugated hyperbilirubinaemia. The urinary urobilinogen levels did not show any appreciable differences in the steady state and in anaemic crises, probably because only qualitative measurements were performed. These are the hallmarks of haemolysis. Other authors working in tropical Africa have also come to similar conclusions.[5 16 17]

These results are contrary to most reports in the literature from temperate climates.[7–9] Hyper-haemolytic crisis continues to be a major problem in tropical Africa where the clinical course of the disease is somewhat complicated with recurrent episodes of malaria infections.[10–12] In a comparative analysis of the haematocrit values in Nigerian and Californian children with sickle cell anaemia, Oyejide and colleagues[18] noted that there might be differences in the types of crises that occurred in both environments. Since there were no significant differences between the mean haematocrit values in the steady state and in crises among the Californian

Table 2 Haemoglobin levels of patients in the steady state and in anaemic crises

Haemoglobin (g/l)	Steady state No. patients	Crises No. patients
30–40	0 (0.00)	18 (16.7)
40–50	0 (0.00)	69 (63.9)
50–60	0 (0.00)	21 (19.4)
60–70	21 (19.5)	0
70–80	47 (43.5)	0
80–90	28 (25.9)	0
90–100	12 (11.1)	0
Total	108 (100%)	108 (100%)

The figures in parentheses indicate percentages.
$Z = 130.9$; $p<0.05$.

Table 3 Reticulocyte counts of patients in the steady state and in anaemic crises

Reticulocyte count (%)	Steady state No. patients	Crises No. patients
2–7	75 (69.4)	13 (12.1)
7–12	29 (26.9)	26 (24.1)
12–17	4 (3.7)	37 (34.2)
17–22	0	23 (21.3)
22–27	0	3 (2.8)
27–32	0	6 (5.5)
Total	108 (100%)	108 (100%)

The figures in parentheses indicate percentages.
$Z = 36.6$; $p<0.05$.

Table 4 Total and conjugated serum bilirubin concentrations of patients in the steady state and in anaemic crises

	Steady state		Crises	
Bilirubin (μmol/l)	Total No. patients	Conjugated No. patients	Total No. patients	Conjugated No. patients
0.0–17.1	12 (11.1)	34 (31.5)	0	29 (26.9)
17.1–34.2	23 (21.3)	59 (54.6)	2 (1.9)	67 (62.0)
34.2–51.3	37 (34.3)	15 (13.9)	2 (1.9)	12 (11.1)
51.3–68.4	31 (28.7)	0	5 (4.6)	0
68.4–85.5	3 (2.8)	0	21 (19.4)	0
85.5–102.6	0 (0)	0	57 (52.7)	0
102.6–119.7	2 (1.8)	0	15 (13.9)	0
119.7–136.8	0 (0)	0	6 (5.6)	0
Total	108 (100%)	108 (100%)	108 (100%)	108 (100%)

The figures in parentheses indicate percentages.
Total bilirubin: $Z = 42.5$; $p < 0.05$.
Conjugated bilirubin: $Z = -1.05$; $p > 0.05$.

children, they postulated that vascular occlusive crises appeared to be the more prevalent type of crises in that environment. In Nigerian children however, sudden and severe anaemia accompanied by features of imminent heart failure suggested aplastic or sequestration crises.

Malaria infection has been particularly implicated as causing hyper-haemolysis in patients with sickle cell anaemia.[10 12 18] Its role in causing hyper-haemolytic crises in the patients in this study could not be fully evaluated. All the patients were on routine antimalarial prophylaxis. In spite of this, about 17.6% of the patients had malarial parasites in their blood films. Seventy seven per cent of these patients became afebrile 48 hours after blood transfusion and antimalarial treatment. It is therefore possible that malaria infection might have played a role in precipitating anaemic crises in some of these patients, but because of prior antimalarial treatment taken at home before presenting to the hospital, malaria parasites may not be seen in the peripheral blood.[16] In Nigeria, antimalarial drugs could be freely purchased over the counter without medical prescriptions. The apparent reticulocytopenia in relation to very low haemoglobin levels observed in some of the patients in anaemic crises can also be explained by acute malaria infection. Some authors had noted that reticulocytosis following anaemia caused by acute malaria infection was usually very brisk, but this did not occur until after complete clearance of malaria parasites. If parasite clearance was delayed, the reticulocyte count did not rise despite a severe progressive fall in haematocrit.[19 20] It is therefore possible that the observed relative reticulocytopenia on admission in some of the studied patients may have been as a result of the presence of malaria parasites in their peripheral blood.

Bone marrow aspirations were not performed on any of the patients in this study. It is therefore difficult to determine the relative roles of bone marrow aplasia/hypoplasia in causing anaemic crises in the patients studied. A similar study in the same institution failed to document any case of aplastic crises in patients with sickle cell anaemia.[11] In this study, about 4.6% of the patients were not jaundiced at presentation. Their serum bilirubin concentrations were only slightly raised in crises beyond their steady state levels. However, they had pronounced reticulocytosis, polychromasia, and increased nucleated red blood cells beyond their steady state levels. Diggs[7] noted a similar picture in one of his patients. In explaining this, McIver and Parker-Williams[21] suggested that a few of those patients in whom there was a gradual return of the haematological indices to normal but without significant changes in their serum bilirubin concentrations were probably in the early recovery phase of aplastic crises. Aplastic crisis is a self limiting condition.[7 22] The timing of haematological investigations is critical to making a diagnosis. Some patients might have been missed due to late presentation to the hospital. In this study, some patients presented as late as eight days after the onset of illness. It is therefore possible that these patients who were severely anaemic at presentation but not significantly jaundiced may have been in the early recovery stage of aplastic crises. Viral studies were not performed on any of the patients, as there were no facilities for this.

The classical presentation of acute splenic sequestration crisis as reported from the USA and West Indies[8 23–25] was not observed in this study. This may have been due to its precipitate nature and accompanying circulatory collapse, which carried a high mortality rate. These may not permit

Table 5 Liver/spleen sizes of patients in the steady state and in anaemic crises

	Steady state		Crises	
Organ size (cm)	Liver No. patients	Spleen No. patients	Liver No. patients	Spleen No. patients
0.0–2.0	28 (25.9)	81 (75.0)	19 (17.6)	74 (68.5)
2.0–4.0	40 (37)	13 (12.0)	39 (36.1)	15 (13.9)
4.0–6.0	28 (25.9)	8 (7.4)	40 (37)	11 (10.2)
6.0–8.0	12 (11.2)	3 (2.8)	10 (9.3)	5 (4.6)
8.0–10.0	0	3 (2.8)	0	3 (2.8)
Total	108 (100)	108 (100%)	108 (100)	108 (100%)

The figures in parentheses indicate percentages.
Liver: $Z = -6.54$; $p < 0.05$; spleen: $Z = -2.08$, $p < 0.05$.

timely presentation at the hospital and death invariably occurred at home, especially in a situation where prompt transportation to the hospital was not readily available. In a study of the morbidity pattern of homozygous sickle cell anaemia, Kaine[11] did not find any case of acute splenic sequestration crises among her patients. However Akinyanju and colleagues[10] in Lagos, had noted that splenomegaly was significantly associated with severe anaemia in patients with sickle cell disease. They concluded that this probably reflected the well known blood sequestrating propensity of that organ. In this study, both the liver and spleen were significantly enlarged beyond their steady state levels in anaemic crises. However, none of them met the strict criteria for acute sequestration crises at presentation. Also none of these patients were hypotensive on admission. Acute sequestration in the spleen or liver is however a continuum from the very mild to the most severe. It is therefore possible that minor forms of sequestration crises may have occurred in the spleen and liver. On the other hand, patients with sickle cell anaemia are prone to various types of infections including malaria, which are endemic in this environment. These infections are frequently associated with hepatosplenomegaly.

Twelve patients included in this study were G6-PD deficient. It is difficult to determine the relative role the deficiency of this enzyme played in causing hyper-haemolysis among the patients studied. Jaundice was present in all 12 patients at presentation. In addition, three of them had malaria parasites in their blood films. None of these patients presented with the classical ''coca-cola'' coloured urine or presence of Heinz bodies on reticulocyte preparations that are so characteristic of this condition. The observed low mortality in this study of 2.8% could be attributed to the prompt blood transfusions that were made available to most of the patients.

In conclusion, there appeared to be differences in the types of anaemic crises seen in paediatric patients with sickle cell anaemia between the temperate climates and tropical Africa. This study has shown that hyper-haemolysis does occur and was the commonest type of anaemic crises in paediatric patients with sickle cell anaemia seen in Enugu, Nigeria. Though the majority of these patients were presumed to be on antimalarial prophylaxis, the data from this study seemed to suggest that malarial infection might have played a role in precipitating some of the crises in the patients studied. Further studies are needed to elucidate this role, so that appropriate recommendations can be made regarding malaria prophylaxis in patients with sickle cell anaemia in this environment. These will include a much more detailed intensive search for other causes of fever in patients with sickle cell anaemia, including viral infections. The studies should also include carefully designed randomised clinical trials to assess the efficacy of the currently used antimalarial prophylaxis, the long term risks of introducing new drugs, and their cost implications. The widespread use of newer drugs will be severely hindered if they are found to be either too toxic or very expensive. The current practice of administering weekly pyrimethamine prophylaxis may be inadequate as about a fifth of the patients studied still had malaria parasites in their blood films at presentation. Physicians looking after sickle cell patients are also encouraged to establish baseline data on the steady state parameters on their patients so that a departure from normal can easily be appreciated.

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