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Anaemic Crises in Patients with Sickle-cell Anaemia

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Summary

Sodeinde O, Ambe J P, Fatunde OJ. Anaemic Crises in Patients with Sickle-cell Anaemia: *Nigerian Journal of Paediatrics* **1997; 24: 55.** In order to determine the relative frequencies of the different causes of severe anaemia among patients with sickle cell anaemia (SCA), 104 consecutive patients with SCA presenting over an eight-month period with severe anaemia (PCV < 15 percent) were studied at the children's emergency ward, University College Hospital, Ibadan. They accounted for 8.2 percent of all admissions and 24.2 percent of those who had severe anaemia. Among the patients with SCA, hyperhaemolytic, acute splenic sequestration and aplastic crises constituted 49, 20 and 12.5 percent of the anaemic crises, respectively. Ten patients (9.6 percent) showed mixed features and could not be definitely classified. The frequency rate of glucose-6-phosphate dehydrogenase (G-6-PD) deficiency was similar between patients with hyperhaemolytic and those with other forms of anaemic crisis, a finding which suggests that G-6-PD deficiency neither aggravates nor ameliorates haemolysis in SCA. The mortality in the series was 8.7 percent. Six of the patients who died had hyperhaemolysis while the other three had acute splenic sequestration crisis. Five of these deaths occurred despite emergency blood transfusion.

Introduction

SICKLE cell anaemia (SCA) is the homozygous form of sickle cell disease (SCD), which presents with a chronic familial, haemolytic anaemia.[1] The incidence of infection and anaemic crisis are greatest among patients below the age of five years and this is evident from the frequent clinic visits and hospitalization.[2,3] Infections and anaemic crisis, among others, are common causes of death in children with SCA.[4] The symptomatology of SCA is protean and variable in severity, but its salient features include jaundice, weakness, easy fatiguability and painful episodes. Four types of crisis are recognized namely: acute splenic sequestration (ASS), aplastic, vaso-occlusive or infarctive and hyperhaemolytic crises.[5,6] Patients with SCA usually maintain a haemoglobin concentration of 5.0-10.0g/dl (PCV 15-30 percent),[6] but any of the crises, except vaso-occlusive, may result in severe and life-threatening anaemia. The size of the SCA problem in Nigeria is large, but the relative frequencies of the different forms of anaemic crises and the associated morbidities in children with SCA have not been well-documented.[7] Virtually all the published data from other parts of the world have been from malaria-free areas and would be difficult to extrapolate to our situation. The present study was therefore, carried out in order to provide requisite information on this aspect of SCA.

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Patients and Methods

The present study was undertaken at the Children's Emergency Ward (CHEW), University College Hospital (UCH), Ibadan, over a period of eight months. The study was approved by the Ethical Committee of the hospital. Patients with SCA presenting at the CHEW were recruited into the study if they satisfied the following criteria: packed cell volume (PCV) < 15 percent, age range six months to 15 years, no blood transfusion in the pre-

ceding three months, haemoglobin types confirmed, using cellulose acetate electrophoresis.[8]

The patients were admitted to the study after obtaining informed oral parental/guardian consent. Where available, steady state PCV and splenic size were recorded in addition to age and sex. Blood pressure, presence or absence of jaundice in addition to a history of deepening jaundice if present before presentation, were also noted. Spleen sizes (in supine position) were measured on admission and after blood transfusion, if given.

On admission, serum bilirubin, PCV, blood films for malaria parasites and the reticulocyte index (RI)[9,10] were determined. RI was determined by the following formula: RI = (Reticulocyte count) x (Patient's PCV/Reference PCV). The reference PCV used for SCA patients in this study was 30 percent. Bone marrow aspiration was done where RI was less than 1.0.[11] Glucose 6-phosphate dehydrogenase (G-6-PD) deficiency was sought by the fluorescent spot test.[8] As a quality assurance measure to correct for the wide variations in PCV among the patients, all blood specimens were first washed in normal saline (by centrifugation) and the supernatant removed. A volume of fresh saline was then added that was equal to the volume of the red cell pellet, thus adjusting the PCV of the resulting red cell suspension to approximately 50%. This red cell suspension was used for the fluorescent spot test.[8]

The following definitions were used: hyperhaemolytic crisis[6] was defined as reticulocytosis (i.e. RI > 1.0), scleral icterus recently reappeared or deepened, and raised serum bilirubin (>4mg/dl total serum bilirubin); acute splenic sequestration (ASS) crisis[12] was defined as splenic enlargement by > 2.0cm relative to the latest steady state measurement less than six weeks earlier, with or without hypovolaemia, or a clear reduction by > 2.0cm within 24 hours of transfusion, and RI > 1.0, while aplastic crisis[8,10] was defined as reticulocytopenia (RI < 1.0) with no evidence of recent splenic enlargement or post-transfusion reduction in size, and marrow erythroid hypoplasia, where consent for bone marrow aspiration was given.

Uncrossmatched but ABO- and Rhesus-compatible packed cells blood transfusion was carried out usually within 30 to 60 minutes of arrival in hospital if PCV was 10 percent or less. For higher PCV values (i.e. 11-14 percent), a full (2-hour) crossmatch or a 1-hour crossmatch was done, depending on the physician's assessment of how severely ill the patient was on general examination. Regardless of PCV, the presence of incipient or established cardiac failure was an indication for uncrossmatched blood transfusion.

Data analysis was by SPSS (statistical package for the social sciences) on a personal computer. Continuous variables were analyzed using Students' 't'-test and categorical ones by the chi-square test. Yates correction and Fisher's exact test were used as appropriate. Statistical significance was set at $p < 0.05$.

Table I

Distribution of Types of Crisis According to Age Group in 104 Patients with SCA

Type of Crisis	*Age group in years (%)*			*Total (Percent)*
	0.5-4	*5-9*	*10-15*	
Hyperhaemolytic	16(34.8)	23(59.0)	12(63.2)	51(49.0)
ASS	13(28.3)	11(28.2)	5(26.3)	29(27.9)
Aplastic	11(23.9)	1(2.5)	2(10.5)	14(13.5)
Indeterminate	6(13.0)	4(10.3)	-	10(9.6)
Total	46(100)	39(100)	19(100)	104(100.0)

Eleven (78.6 percent) of the 14 patients with aplastic crisis were aged <5 years, compared with 16(31.4 percent) of 51 patients with hyperhaemolytic crisis, 13(44.8 percent) of 29 with ASS and 6(60 percent) of 10 patients with indeterminate crisis ($X^2 = 11.12$; df = 3; p = 0.01).

Results

One thousand, two hundred and sixty-one patients (aged 6 months to 15 years) were admitted to the CHEW during the study period. Severe anaemia accounted for 423 (33.5 percent) of these admissions, of which 104 (24.6 percent) had SCA. Of the 104 patients who met the study criteria, 53 were males and 51 females [M:F = 1.04]. Table I shows the age distribution according to the types of crisis. Hyperhaemolysis was the commonest; the type of crisis could not be determined in 10 (9.6%). The mean age of the 104 patients was 6.48 ± 3.9 years (range 10 months to 15 years). Children with ASS were significantly younger than the other three groups (p = 0.01). Nineteen (18.3 percent) of the SCA patients studied were presenting for the first time; 16 (84.2 percent) of these 19 were less than five years old. Table II shows the clinical features

of the patients and the various forms of anaemic crisis. Fever (oral temperature > 37.5°C) was the commonest feature. In addition, jaundice was approximately four times as common in hyperhaemolytic crisis as in the other types of crisis, while hepatosplenomegaly was about thrice as common in ASS (in 93 percent) compared to hyperhaemolytic (37.3 percent) and aplastic (28.6 percent).

Table II

Clinical Signs in SCA Children with Anaemic Crisis

Signs	*Number of Patients (%)*			
	Hyperhaemolytic (n=51)	*ASS (n=29)*	*Aplastic (n=14)*	*Indeterminate (n=10)*
Fever+	47(92.2)	22(75.9)	8(57.1)	8(80)
Jaundice	45(88.2)	9(31.0)	3(21.4)	-
Hepatosplenomegaly	19(37.3)	27(93.1)	5(35.7)	5(50)
Hepatomegaly	29(56.9)	-	4(28.6)	2(20)
Shock	-	7(24.1)	-	3(30)
Heart failure*	3(5.9)	9(31.0)	-	3(30)
Pulmonary signs**	10(19.6)	14(48.3)	3(21.4)	-

+ Oral or rectal temperature > 37.5°C
* Tachycardia, tachypnoea and soft, tender hepatomegaly
** Dyspnoea and crepitations
ASS = Acute splenic sequestration

Malaria parasitaemia was present in 36/51 (70.6 percent), 17/21 (80.9 percent), 8/14 (57.1 percent) and 7/10 (70 percent) of the haemolytic, ASS, aplastic and indeterminate groups, respectively. Thus, malaria showed no statistical association with any type of anaemic crisis ($X^2 = 2.32$; $p = 0.51$). Table III shows that G-6-PD deficiency rates were similar among hyperhaemolytic patients compared with the other SCA patients as a group. They were taken as a group because the numbers of patients with the other individual types of anaemic crisis are too small for meaningful comparison with the hyperhaemolytic patients especially after the necessary separation of males from females, because of the X-chromosome linkage of the G-6-PD gene. Furthermore, as another common hereditary cause of haemolytic anaemia, G-6-PD deficiency is more relevant to the hyperhaemolytic crisis patients than patients with other forms of anaemic crisis. The steady state PCV of SCA patients (21.67 ± 3.4 percent) was significantly higher than the PCV of the same patients on admission (12.1 ± 2.5 percent)($p < 0.001$). There was no significant relationship between the PCV and the types of crisis ($p > 0.05$). Of the 14 patients with aplastic crisis, six had successful bone marrow aspiration, three had dry taps while the parents refused consent in five. The findings in all six patients were erythroid hypoplasia, with cellularity less than 25 percent of normal, and a high myeloid-erythroid ratio. Two patients had megaloblastic erythropoiesis and one had microcytic hypochromic erythroid cells.

Mortality rate was 9/104 (8.7 percent); six of the nine had hyperhaemolysis, while three had acute splenic sequestration crisis. Four patients died before emergency transfusion could be effected and the remaining five did so despite prompt transfusion. Thus, prompt blood transfusion most probably prevented death in 95 percent of the patients who received it.

Table III

Glucose-6-Phosphate Dehydrogenase (G-6-PD) Deficiency among 104 Patients with SCA and Anaemic Crises

Type of Crisis and Sex	*No. of Patients*	*No. (%) G6PD deficient*
Hyperhaemolytic		
Males*	26	3 (11.5)
Females	24	0 (0.0)
Others		
Males*	25	3 (12.0)
Females	29	1 (3.4)

* Hyperhaemolytic versus other crises: Yates $X^2 = 0.70$; $p = 0.65$ (Fisher's exact test).

Discussion

Severe anaemia accounted for 33.5 percent of all the admissions in patients aged six months to 15 years during the eight-month period of this study. Malaria may have contributed to the higher case load of anaemia in this study, especially in those presenting for the first time. In addition, it is widely believed that the burden of admissions from gastroenteritis and measles has been reduced in most hospitals in Nigeria because of the oral rehydratin therapy and the expanded programme on immunization, respectively. Therefore, common illnesses that are not vaccine-preventable would tend to become relatively more prominent.

Acute splenic sequestration crisis occurred

equally in under-five and 5-10-year old children in the present study, in contrast to the observations in Jamaica[5] where ASS is commonest in under-fives, with 76 percent of first attacks occurring before the age of two years. This difference might be explained by the fact that ASS can only occur in a non-fibrotic spleen which can still be stretched. Furthermore, it has been reported that in patients with SCA residing in malaria-endemic areas, splenomegaly persists into later childhood.[13] By contrast, Jamaica is a malaria-free country. Our findings indicate that in malaria-endemic countries, ASS remains common in older SCA children. Regarding prognosis, ASS has a high recurrence rate [5,14,15] and subsequent attacks may be fatal. Elsewhere, parents have been trained to detect such splenomegaly and rush the child to hospital.[16] It remains to be seen whether, with the low literacy level, especially of mothers, this approach can be successful in our country.

About one in five of our patients were being diagnosed as SCA patients for the very first time. In other words, our health care delivery system had failed to detect them before they developed life-threatening anaemia. This indicates that much still needs to be done by way of early case-detection in SCA. As has been shown, 49.0 percent of the patients in the present series had hyperhaemolytic crisis. However, since we did not have the steady (stable) state values for reticulocyte counts and serum bilirubin for these patients, it was difficult to be certain of the diagnosis in all of them, on strict scientific grounds. However, the combination of clinical criteria and limited laboratory data used in this study is about all that is usually available in most clinical settings in Nigeria, where SCA patients are looked after. The presence of G-6-PD deficiency in the same environment as a common cause of episodic bouts of acute haemolytic anaemia naturally raises the question of how it interacts with SCA. Previous studies have shown that G-6-PD deficiency neither ameliorates nor aggravates the overall clinical course/severity of SCA.[17-19] However, the specific interaction between hyperhaemolytic SCA crises and G-6-PD deficiency has remained an open question. If G-6-PD deficiency ameliorates or aggravates haemolysis in SCA, then the former should be significantly less or more common, respectively, in hyperhaemolytic SCA crises. Although the numbers are relatively small, the laboratory quality assurance measures adopted allow one to be quite confident of the G-6-PD screening (fluorescent spot test) results, particularly in the males. Thus, our data provide no support for amelioration or aggravation of haemolysis in SCA by G-6-PD deficiency.

Aplastic crisis was commoner in our pre-school children unlike in the Jamaican study,[5] where it was predominant in 5-10-year old children. The lower peak age of aplastic crisis in our patients could be explained by an earlier exposure to infections due to unhygienic environments or that the aetiological agent is different from the human parvovirus. This possibility is particularly important since malaria parasitaemia is virtually always associated with reticulocytopenia. This fact underlines the need for studies of human parvovirus infections among Nigerian SCA patients. Emergency transfusion with uncrossmatched but ABO- and Rhesus- compatible blood, usually within half to one hour of arrival in hospital, was life-saving in 95/100 of these patients. All necessary steps should be taken to maintain and improve upon the capability for rapid reaction to transfusion emergencies, including the collection and processing of adequate quantities of blood for transfusion and the training of blood bank and other hospital personnel.

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