Niger J Paed 2013; 40 (1): 34 –39

ORIGINAL

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Morbidity and mortality pattern in hospitalized children with sickle cell disorders at the University College Hospital, Ibadan, Nigeria

DOI:http://dx.doi.org/10.4314/njp.v40i1.6

Accepted: 16th June 2012

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Abstract *Objectives:* To determine the causes of hospitalization and outcome of children with sickle cell disorders at the University College Hospital, Ibadan.
Methods: Case files of patients with sickle cell disease who were admitted between March 2009 and February 2012 were analysed. Data extracted include demographic variables, diagnoses, types of crises, associated infections, complications and outcome of treatment.
Results: There were 174 admissions of 161 children with a male female ratio of 1.3:1. Their ages ranged from nine months to 18 years with a mean of 7.3(4.0) years. Vaso-occlusive crisis was present in 107 (61.5%), hyper haemolytic crisis in 29 (16.7%) and acute splenic sequestration in 12 (6.9 %) of all admissions. Associated infections were septicaemia in 56 (32.2 %), malaria in 49 (28.2 %), acute osteomyelitis in 24 (13.8%), pneumonia in 23 (13.2%), urinary tract infection in 12 (6.9%) and septic arthritis in 10 (5.7%). Haematocrit was less than 15 % in 36 (20.7%) and blood transfusion administered in 68 (39.1%) of admissions. There were three (1.7%) deaths from cerebrovascular accident, adverse reaction to blood transfusion and meningitis.
Conclusion: Prevention and prompt management of crises and infections in sickle cell disease is recommended to reduce morbidity and mortality.

Key words: Admissions, sickle cell, crisis

Introduction

Sickle cell disease is a genetic disorder characterized by chronic haemolysis resulting from premature destruction of brittle and poorly deformable red blood cells. It is caused by the presence of sickle haemoglobin which results from substitution of glutamic acid at the 6th position of its β chains by valine. [1] Apart from chronic haemolysis, other manifestations of sickle cell anaemia are attributable to ischaemic changes resulting from vascular occlusion by masses of sickled red cells. The clinical course of affected children is typically associated with intermittent episodic events, often referred to as 'crises.'[1] Another major problem in children with sickle cell disease is altered splenic function resulting in increased susceptibility to infections by encapsulated organisms, and causing meningitis, septicaemia and other serious infections. Complications of sickle cell disease when severe often require hospitalization.[2]

Nigeria has the highest burden of sickle cell anaemia worldwide with a prevalence of about 20 per 1000 live births annually.[3] In order to plan for health care of affected children, a knowledge of the morbidity pattern is important. Information on the causes and pattern of morbidity of hospitalization may highlight the most severe manifestations with potential for mortality. Such information will be helpful in targeting prevention strategies, healthcare planning and appropriate resource allocation.[4] Studies on hospitalized children with sickle cell disorders in Nigeria have often focused on a single complication such as either patterns of crises alone or patterns of infections [5,6]; few have focused on the overall pattern of morbidity in all hospitalized children showing the relative contributions of different complications .[2] The value of morbidity data in resource allocation is typified by the establishment of a Day hospital for the management of painful crises in the Bronx, New York based on the finding that painful crises were responsible for the highest proportion of hospitalizations. The result was a significant reduction in admissions and length of stay, equivalent to savings of 1.7 million US dollars.[7]

The objectives of this study were therefore to describe the morbidity pattern and outcome of children with sickle cell disorders admitted at the Paediatric wards of University College Hospital Ibadan, Nigeria.

Methods

This was a retrospective descriptive study of children with sickle cell disease admitted into the Paediatric wards of the University College Hospital, Ibadan between March 2009 and February 2012. The University College Hospital is a tertiary hospital located in the city of Ibadan, south western Nigeria. Haemoglobin phenotype of all patients was established by haemoglobin electrophoresis at a pH of 8.6 at the haematology laboratory of the hospital. Proguanil for malaria prophylaxis is routinely used by all patients attending in the Paediatric sickle cell clinic. Pneumococcal vaccines are also routinely prescribed but repeatedly questioning of carers in our clinic indicates that some of them usually receive it following a long interval after prescription due to its relatively high costs. Documentation after vaccination is therefore not consistently done so that an accurate record of the uptake would not be obtained from their case notes. . Penicillin prophylaxis is not routinely given in our hospital.

Data was extracted from the case notes of the patients seen during the study period. Data extracted included demographic variables, haemoglobin phenotype, type of crisis, associated infections and other complications of sickle cell disease. Other information extracted included the haematocrit on admission, number of blood transfusions, duration of hospital admission, outcome of treatment and final diagnosis at discharge or death. In our hospital, children are usually discharged when there is some resolution of the presenting symptoms and signs, intravenous drugs are no longer necessary and carers will be able to continue care for the children at home. Demographic variables extracted included patients' ages, sex and educational levels and occupations of their parents. The families were classified into socioeconomic groups using a combined score derived from the occupation and maximum educational level of both parents (or their substitutes) as described by Oyedeji.[8] Data were entered into a microcomputer and analyzed with SPSS version 20.0. Means, standard deviations, medians and inter quartile range computed for continuous variables. Categorical variables were presented as frequencies.

Results

There were 174 admissions of 161 children during the period of study. Of these, 149 (85.6%) had one admission each, 22(12.6%) had two admissions each and three (1.7%) had three admissions each. Their ages ranged from nine months to 18 years with a mean (±1 standard deviation) of 7.3 (4.0) years. Socio-demographic parameters of the children are shown in Table1.

The haemoglobin phenotype was SS in 148 (91.9%) and SC in 13 (8.1%) of the children studied.

Table 1: Socio-demographic parameters of children

Parameter		Frequency	Per cent
Sex	Male	90	55.9
	Female	71	44.1
	Total	161	100
Age group (years)	0-4	46	28.6
	5-9	66	41.0
	10-14	43	26.7
	≥15	6	3.7
	Total	161	100
Socioeconomic class	I	23	14.3
	II	43	26.7
	III	55	34.1
	IV	38	23.6
	V	2	1.2
	Total	161	100

Different forms of crises were present in 130 (74.7%) the 174 hospital admissions; the most frequent form of associated crisis was the vaso-occlusive type and the least common was the aplastic type (Table 2). Of the 29 children that had hyperhaemolytic crises, 16 also had associated vaso-occlusive crisis. Two patients had each had a combination of painful and splenic sequestration crises. All cases of acute splenic sequestration (ASS) and aplastic crisis were of the Hb SS phenotype. Eight (72.7 percent) of the cases of ASS were aged five years or older. Of the 130 children with different forms of crises, there was associated infection in 97 (74.6%) of them. The commonest infections associated with crises were septicaemia (46), malaria (40), acute osteomyelitis (20), and pneumonia (15). Less common associated infections were urinary tract infection (nine), aseptic arthritis (eight), pharyngitis (four) chronic osteomyelitis (three) and meningitis (one).

Table 2: Frequency and age distribution of sickle cell crisis in 174 admissions

Type of crisis	n (%)	Age (years) Range	Mean (SD)
Vaso-occlusive	107 (61.5)	0.75-18.0	7.1 (4.0)
Hyper haemolytic	29(16.7)	1.4-18.0	8.5 (4.7)
Acute splenic sequestration	11 (6.9)	2-14	8.9 (4.3)
A plastic	1 (0.6)	7	7

SD= standard deviation

Different forms of infections were present in 126 (72.4%) of the 174 admissions with a male: female ratio of 1.4:1. The commonest infections for which the children were treated were septicaemia, malaria, acute osteomyelitis and Pneumonia (Table 3).

Table 3: Frequency of infections in 174 admissions of children with sickle cell disease

Infection*	n	%
Septicaemia	56	32.2
Malaria	49	28.2
Acute osteomyelitis	24	13.8
Pneumonia	23	13.2
Septic arthritis	10	5.7
UTI	12	6.9
Meningitis	3	1.7
Chronic Osteomyelitis	3	1.7
Pharyngotonsillitis	5	2.9

*multiple infections present in some patients

Bacterial isolates

Twenty five (44.6%) of the 56 children with suspected septicaemia had blood cultures done which was positive in 12 as follows: *Staphylococcus aureus* (five), *Klebsiella* species (five), *Escherichia coli* (one) and Coagulase- negative *staphylococcus (*one). Diagnosis of septicaemia in the other children was based on their clinical presentation, negative malaria parasite tests and urine cultures, and presence of toxic granulations in neutrophils. Some patients could not afford the cost of blood culture before commencement of antibiotics. Significant bacteriuria was found in seven of the 12 children treated for urinary tract infection (UTI) and the urinary isolates were *Klebsiella* species in four cases and *Escherichia coli* in three cases. The remaining children treated for UTI were symptomatic and had pyuria.

Multiple bacterial agents were isolated in some patients. *Klebsiella* spp were isolated from the blood and urine of a child with septicaemia, urinary tract infection and radiological features of acute osteomyelitis. Another patient had *Klebsiella* septicaemia and *Escherichia coli* UTI. A third patient had *Staphylococcus aureus* septicaemia and *Klebsiella* UTI.

Non-infectious complications

Among the 174 admissions, non-infective complications of sickle cell disease observed were cerebrovasular accident (CVA) in 16 (9.2%), transient ischaemic attack in 1(0.6), afebrile seizure in 1(0.6%), priapism in 3(1.7%), avascular necrosis of the femoral head in 2 (1.1%) and acute kidney injury in 2(1.1%). Four of the 16 cases of CVA were previously diagnosed cases on chronic blood transfusion programme and 12 were new cases representing 6.9 percent of all admissions. All cases of CVA were of the HbSS phenotype. There was also one case each of Hodgkin lymphoma and non-Hodgkin lymphoma admitted for chemotherapy.

Duration of admission

Duration of admission ranged from 1-131 days with a median of 8 days and inter-quartile range of 5-15 days. There was no significant association between the type of crises and being admitted for more than seven days (Table 4). Analysis of the risk of being admitted for longer than seven days computed for the different infections and complications revealed that patients with septicaemia, acute osteomyelitis, cerebrovascular accidents and avascular necrosis of the femoral head were at increased risk of prolonged admission (Table 5).

Table 4: Relationship between type of crises and duration of admission in 130 children who presented with crises

Type of crises	Admitted for ≤ 7 days (n=63)	Admitted for >7 days (n= 67)	Total (N=130)	Exact Sig (2side)
Pain	42	47	89	0.709
Hyper-haemolytic	8	5	13	0.388
Acute splenic sequestration	4	5	9	1.0
Aplastic crises	1	0	1	0.485
Pain + Hyperhemolytic crises	7	9	16	0.792
Pain + splenic sequestration	1	1	2	1.000
Total	63	67	130	

Table 5: Duration of admission and risk factors for admission longer than seven days

Complications	Median duration of admission (days)	Risk of admission > 7 days	
		Odd ratio	95 % Confidence Interval
Septicaemia	11	4.13	2.06, 8.29*
Malaria	6	0.65	0.33, 1.26
Acute osteomyelitis	14	6.03	1.97, 18.49*
Pneumonia	8	1.32	0.54, 3.19
Septic arthritis	18	4.2	0.87, 20.38
Urinary Tract Infection	14	2.05	0.59, 7.08
Meningitis	51	1.98	0.18, 22.21
Chronic osteomyelitis	5	0.48	0.04, 5.42
Pharyngotonsillitis	7	0.64	0.105, 3.95
Cerebrovascular accidents	18	5.39	1.14, 25.35*
Avascular necrosis of the femoral head	82	2.0	1.7, 2.3*

*significant

Anaemia and Blood Transfusions

Haematocrit levels during admission ranged from 7-36 percent with a mean (SD) 20.7 (6.4) percent. There was severe anaemia i.e. a haematocrit of less than 15 percent in 36 (20.7%) episodes of admissions. Blood transfusion was administered in 68 (39.1%) of admissions. The numbers of blood transfusions received was one in each of 51 (29.3%) admissions, two in each of 12 (6.9%) admissions, 3 in each of 4 (2.3%) admissions and five in 1(0.6%) admission.

Mortality

There were three deaths yielding a case fatality rate of 1.9 percent of the 161 children. The causes of death were cerebrovascular accident in one child and adverse reaction to blood transfusion in a child on chronic blood transfusion programme for secondary stroke prevention in another. The third child was on chemotherapy for Hodgkin lymphoma and died from meningitis with cerebral oedema and pulmonary haemorrhage confirmed at autopsy.

Discussion

The present study has shown that Sickle cell disease is a common cause of hospital admission in Ibadan with male preponderance similar to observations in Enugu; Eastern Nigeria.[2] The pattern of hospital admission of children with sickle cell disease (SCD) varies in different parts of the world. Whilst vaso-occlusive crises account for majority of admissions in some parts of the world particularly in developed countries[9,10] infections account for most admissions in others, particularly developing countries.[2,11] Given, the reduction in invasive pneumococcal disease associated with penicillin prophylaxis, it is possible that the predominance of vaso-occlusive crises and under representation of infections in developed countries may be related to use of pneumococcal prophylaxis in prevention of infections.[9,12]

Our study showed that infections and various forms of crises made almost equal contributions to admissions with infections having a slight lead. In Nigeria like many sub-Saharan African countries, penicillin prophylaxis and pneumococcal immunization in children with SCD is not routine. This is attributed to purported lack of evidence in support of the role of *Streptococcus pneumoniae* in causing infections in SCD in tropical Africa.[13] Although the proportion of patients who had blood cultures in our study was small due to financial constraints faced by parents, the paucity of *Pneumococcus* as an aetiological agent in bacteraemia observed is similar to findings from other studies in equatorial Africa.[5,13] Rather, *Staphylococus aureus* and Gram negative organisms seem to be prominent in our study, in keeping with findings in a previous Nigerian study.[6] The rarity of Pneumococcal isolates in Nigeria has been attributed to prior use of over-the-counter antibiotics and decreased susceptibility to *Streptococcus pneumoniae* as a result of splenomegaly which persists due to malaria.[6,14] There is a need for large scale studies across equatorial Africa to firmly establish the role of *Streptococcus pneumoniae* in causing infections in children with SCD and to evaluate the role, if any, of pneumococcal vaccines in preventing infections and reducing mortality. The low yield of microbial aetiological agents for infections in this retrospective study due to inability of carers to pay for cultures prior to commencement of antibiotics represents a challenge to appropriate management. There is need for prospective studies aimed at identifying aetiological agents and antimicrobial sensitivity patterns for infections in children with sickle cell disorders to guide antimicrobial choices in their treatment.

Early diagnosis of infections in SCD and timely institution of appropriate treatment is paramount in reducing morbidity and mortality. The present study showed the co-existence of multiple infections in the same patient, sometimes by different aetiological agents. This has previously been reported in children with sickle children with SCD.[15] A high index of suspicion of the possibility of multiple infections is therefore necessary in evaluating this subset of children to guide complete treatment. However, a potential obstacle to this process is the out of pocket expenditure for laboratory investigations which many parents are unable to afford as typified in the present study. This may be addressed by strengthening of the Nation's Health Insurance Scheme.

The prominence of vaso-occlusive crises above other forms of sickle cell crises observed in the present study is well known.[9,10] Most cases of Acute Splenic Sequestration (ASS) are in children with Hb SS and are known to occur below three years of age.[16] The occurrence of splenic sequestration crisis up to the age of 14 with majority occurring at five years of age or more in our study contradicts the previously known facts in the United States. [16]. Possible explanations of this different pattern in the present study may be death of younger children from ASS before presenting in hospital. Another possibility may be persistence of enlarged spleens in children with SCD in the tropics beyond the age when autosplenectomy should have set in, attributable to malaria. [14] This might leave room for ASS to occur.

The burden of anaemia and blood transfusion in the present study contrast with those in a previous study in Enugu, south-eastern Nigeria.[2] In the present study, severe anaemia was present in 20.7 percent of children, blood transfusion given in 39.1 percent of admissions and multiple blood transfusions in less than 10 per cent of admissions; the corresponding figures in Enugu were 39.4 percent, 73.2 percent and 40.8 percent respectively.[2] Possible explanations for these marked differences could be variations in compliance of patients with routine haematinics and malaria prophylaxis as well as variations in blood transfusion guidelines in the two hospitals. Blood transfusion is usually life saving but may also be associated with risks as typified by one

death in the present study attributed to blood transfusion reaction. It is therefore necessary to counsel and support parents and patients on prompt health seeking habits that minimize the risk of severe anaemia and subsequent blood transfusion.

Hospitalization of children with SCD constitutes a significant burden on the caregivers. The median duration of hospitalization in the present study is similar to findings reported in the United Kingdom.[9] In addition, the findings of the present study indicate that individuals with septicaemia, acute osteomyelitis, cerebrovascular accident and avascular necrosis of the femoral head were at increased risk of prolonged admission. In an attempt to lighten the burden of admissions, some hospitals instituted carrying out elective blood transfusions in day care settings without overnight admissions. [17] Considering the finding that almost 40 percent of our study patients required blood transfusion, provision and utilization of daycare settings may go a long way in reducing the frequency of hospital admissions particularly in children in whom no major infection or complication needing prolonged admission is found.

The case fatality observed in this study was lower than 6.61 percent observed in admitted children with sickle cell anaemia in Zambia[18] and 8.5 per cent in Enugu Nigeria.[2] Although the small number of deaths in our study makes it difficult to make strong conclusions on the pattern of mortality, the fact that two out of the three deaths were related to cerebrovascular accidents calls for the need to strengthen measures towards primary stroke prevention. This need is further heightened by the relatively high contribution of stroke to admissions. Routine screening of children with SCD by Transcranial Doppler ultrasonography to detect high risk cases and institution of appropriate preventive measures is recommended.[19] Blood transfusion greatly reduces the risk of a first stroke in children with sickle cell anaemia who have abnormal results on transcranial Doppler ultrasonography.[19]

Conclusion

Hospital admission of children with sickle cell disease in Ibadan, Nigeria results from a wide variety of clinical conditions but mainly infections and various forms of crises. There is a need to clearly establish the aetiologic agents of infections in these children to guide appropriate antimicrobial therapy. The use of prophylaxis against pneumococcal infections if supported by evidence, has a great potential of reducing morbidity and mortality as has been shown in the United States of America.[11] There is also need for establishment of comprehensive programmes for sickle cell disease in Nigeria to improve the quality of life of affected children. This should include neonatal diagnosis and early institution of health promoting measures and regular screening tests for possible complications such as risks for stroke.
Unhindered access to health care is also paramount in relieving the financial burden borne by caregivers and therefore giving the children a better chance of survival.

Conflict of interest: None
Funding: None

Acknowledgment

The role of resident, consultant and laboratory staff in the management of children with SCD in the department is acknowledged. The resident doctors were also of assistance in data collection.

Limitation

The low yield of bacterial isolates among patients treated for sepsis partly due to inability of the parents to pay for microbial cultures make the results on aetiological organisms of limited value for generalization.

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