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Original Research Article

The Pattern of Morbidity in Adult Nigerians with Sickle Cell Anaemia: A Tertiary Healthcare Setting Perspective

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ABSTRACT

Background: Sickle Cell Anaemia (SCA) is the commonest genetic disorder affecting the black race globally. Nigeria has the highest SCA burden of any country. Patients with SCA often require frequent hospital care and sometimes die from its complications owing to the peculiar pathologic nature of the disease. Data on the causes of morbidity in adults with SCA in our centre are lacking. Measures geared toward improving the patients' survival and quality of life can only be be useful if information about the causes of illnesses and deaths from SCA are elucidated. This would engender effective preventive strategies and appropriately targeted interventions.
Aim: To determine the pattern of illnesses among adults with Sickle Cell Anaemia, managed at the University of Uyo Teaching Hospital, Uyo.
Methods: All casenotes of adult patients with confirmed SCA managed in the Haematology Department over a two year period, from January 1, 2016 to December 31, 2017, were retrospectively reviewed for pattern of morbidity of SCA.
Results: A total of 64 patients were admitted over the study period for various complications of SCA. The age range was 20-70 years with a median age of 24.9years. Twenty-five (39.1%) were males and thirty-nine (60.9%) were females. There were four deaths during the period. The different morbidities encountered were vaso-occlusive crises (93.8%), Malaria (84.4%), Chronic leg ulcer (15.6%), hyperhaemolytic crises (10.9%), avascular necrosis of the femoral head (10.9%), pentazocine addiction (9.4%), acute chest syndrome (7.8%), septicaemia (7.8%), priapism (7.8%), chronic osteomyelitis (4.7%), nephropathy (4.7%), peptic ulcer disease (4.7%), deep vein thrombosis (4.7%), seizure disorder (4.7%), short stature with kyphoscoliosis (4.7%), stroke (3.1%), hepatopathy (3.1%), urinary tract infection (1.6%), lobar pneumonia (1.6%), pulmonary embolism (1.6%) and congestive cardiac failure (1.6%).
Conclusion: SCA is associated with multiple end-organ dysfunctions and variable clinical outcome. Admissions in our centre were mainly due to vaso-occlusive crises and malaria. Chronic renal failure was the leading cause of death followed by hyperhaemolytic crisis and pulmonary embolism. Early recognition and management of the morbidities seen in SCA are key to the survival of patients with the disease.
Keywords: Sickle cell anaemia, vaso-occlusive crises, hyperhaemolytic crises, pentazocine addiction, Uyo.

INTRODUCTION

Sickle cell anaemia (SCA) is the most common inherited haematological condition that affects mankind. [1] It has a worldwide distribution though its highest prevalence occurs in the Middle East, Mediterranean region, the Caribbean, South East Asia and Africa. [2] Three-quarters of

sickle cell cases are found in Africa particularly sub-Saharan Africa, where 75% of the 300,000 global births of affected children live. [3] Nigeria has the largest cohort of SCA patients worldwide and twenty-five to thirty percent of Nigerians are carriers of the sickle cell gene resulting in the birth of about 150,000 children with sickle cell anaemia annually. [1] The burden of the disease in Africa remains inadmissibly high, with the most vulnerable period being under 5 years old. A World Health Organization (WHO) report estimates that 50-80% of the affected children will die before adulthood. [4] In 2010, there were approximately 29,000 deaths ascribed to sickle cell disease globally. [5]

Furthermore, it is sobering to observe that the vast majority of children who survive into adulthood, consequently, often develop protean multi-systemic damage from the effects of chronic anaemia and haemolysis. [6-8] Platt and colleagues observed that mortality rates increased with the number of pain crises for patients older than age 20. [9] Evidence also suggests that a considerable number of adults with SCA indulge in self-medication practices, as they utilize multiple prescription drugs for management of symptoms related to their disease and may not receive routine hospital care. This accounts for the increased morbidity and early mortality observed in some of them. The ugly trend may be attributed to a number of psychosocial issues widely known to be characteristic of many chronic disease sufferers, notably poor self-image, stigmatization, depression, cognitive impairment, negative thoughts and feelings about the condition. [10-13] Measures aimed at improving the outlook for these patients can only be effective if data on the causes and trends of illnesses and deaths are elucidated, with seamless, holistic and targeted interventions.

Substantial progress has been made in the last few decades to scale up diagnostic services and treatment of SCA, but many patients still have severe complications to contend with. [6-8,14-16] In many sub-Saharan African settings, healthcare facilities are in short supply, government and non-governmental organizations' involvement in healthcare delivery is poor, existing diagnostic infrastructure are weak and access to good health service and drugs is limited to the relatively few persons who can afford fee-soaring private practices. Many affected patients therefore do not receive appropriate and adequate health care. They consequently, suffer a lot of chronic illnesses associated with the disease. [2,5] This adversely affects their quality of life, and thus contributes considerably to morbidity and deaths from the disease. The poor survival of patients with SCA in resource-constrained regions of most African countries further lends credence to the culturally entrenched myths and stigma already associated with the disease. [16-19]

Acknowledging the grim prognosis for patients with SCA in sub-Saharan Africa, some countries in the region have begun to take action by committing ample resources to address the crushing burden of the disease. [6,7,15,16] Unfortunately, management of SCA in Nigeria still poses an enormous medical and public health challenge for many reasons, similar to what is obtainable in most resource-poor countries; and clear, country-specific data are limited. Patterns of morbidity and mortality of the disease particularly in the adult sickle cell population are ill-defined and implementation of preventive care is deficient. However, data on the morbidity and mortality profiles of children with the disease are well documented. [6,18,20-22] Knowledge of the current situation as regards the causes of illnesses and deaths in adults with SCA from different centres would be useful guides in appraising performance and identifying key areas where attention should be focused. Previous reports from various centres identified infectious diseases and the different types of sickle cell crises, as major reasons for hospitalization of SCA patients. [5-8,15,17-22]

There has been no documentation on the patterns of morbidity and mortality in adult patients with SCA from this centre which attends to the healthcare needs of the adult sickle cell population within the state and its environs. Findings from the present study will help identify significant illness trends and aid effective prioritization of intervention efforts to prevent disease progression to chronic end-organ dysfunctions or multi-systemic failures. It would also serve as a template for further studies, and may provide a national framework for relevant policy makers and health care planners to re-evaluate the effects of implementation of existing intervention strategies as regards efficacy, equity, health-system delivery, scale-up, and policy aspects.

MATERIALS AND METHODS

Uyo is the state capital of Akwa Ibom, an oil-producing state in Nigeria. It lies at an altitude of 122 metres above sea level. It is blessed with an abundant rainfall of about 2095mm and has a mean temperature of 27^0C and relative humidity of greater than 60%. It has a population of about 4million people. It is predominantly a Christian city and majorly inhabited by the Ibibios and Annangs though the Igbos, Yorubas, Hausas and other ethnic minorities are also residents. [23]

The study was a retrospective and descriptive review of all adult sickle cell anaemia cases seen in the Department of Haematology, University of Uyo Teaching Hospital, Uyo, from January 1, 2016 to December 31, 2017. The hospital is a 600-bed tertiary health facility that provides specialized healthcare services to inhabitants of the state as well as those of neighbouring states comprising Cross River, Rivers and Abia.

All the SCA patients aged between twenty years and seventy years with confirmed diagnoses of sickle cell anaemia managed in the Haematology Department of the hospital were studied. The following information were obtained from their case notes and documented in a proforma designed for the study: age, gender, definitive diagnoses, duration and outcome of admission. Data obtained were presented in frequency tables.

RESULTS

A total of sixty-four (64) patients were managed for various complications of sickle cell anaemia during the two year study period. The age range of the subjects was 20-70 years with a median age of 24.9years (table 1). There were relatively more females 39(60.9%) than males 25(39.1%) giving a male/female ratio of 0.64:1 (table 1). Vaso-occlusive crisis manifesting as bone pain was the most frequent crisis seen, followed by hyperhaemolytic crisis. Aplastic and acute sequestration crises were not encountered. Table 2 shows the distribution of various morbidities seen in the study population. The causes of morbidity according to age groups were as listed in table 3.

Table 1: Age and gender distribution of study population

	Gender		
Age group (years)	Male (%)	Female (%)	Total (%)
20-29	14(21.9)	28(43.8)	42(65.7)
30-39	7(10.9)	8(12.5)	15(23.4)
40-49	1(1.6)	1(1.6)	2(3.2)
50-59	1(1.6)	1(1.6)	2(3.2)
≥ 60	2(3.1)	1(1.6)	3(4.7)
Total	25(39.1)	39(60.9)	64(100)

Table 2: Distribution and Frequency of various Morbidities Encountered

Morbidity	Frequency n(%)
Vaso-occlusive crises	60(93.8)
Malaria	54(84.4)
Chronic leg ulcer	10(15.6)
Avascular necrosis of the femoral head	7(10.9)
Hyperhaemolytic crises	7(10.9)
Pentazocine addiction	6(9.4)
Acute chest syndrome	5(7.8)
Priapism	5(7.8)
Septicaemia	5(7.8)
Chronic osteomyelitis	3(4.7)
Nephropathy	3(4.7)
Peptic ulcer disease	3(4.7)
Deep vein thrombosis	3(4.7)
Seizure disorder	3(4.7)
Short stature with kyphoscoliosis	3(4.7)
Stroke	2(3.1)
Hepatopathy	2(3.1)
Lobar pneumonia	1(1.6)
Urinary tract infection	1(1.6)
Pulmonary embolism	1(1.60
Congestive cardiac failure	1(1.6)
Most patients had more than one complication	

Common causes of morbidity in all age groups were observed to be vaso-occlusive crises in the form of bone pain followed by malaria. Other causes of morbidity were commoner in patients aged 20-29 years except for venous thromboembolism (deep vein thrombosis and pulmonary embolism) which was more frequent in the middle-aged subjects.

The median duration of hospitalization was 6.0days, with a range of one day to fourteen days. The outcome of most admissions in this study was good, as majority of the patients managed were discharged in good health to be seen in the follow-up clinic. There were four deaths (6.3%) recorded during the study period. Two of the deaths were due to chronic renal failure while the other two deaths were as a result of hyperhaemolytic crisis and pulmonary embolism confirmed at autopsy. Outcome and duration of hospitalization is shown in table 4. One patient left against medical advice and it was on account of gross financial constraints. The frequency of hospitalizations among the patients is shown in table 5. Majority of the patients (62.5%) were admitted once during the study period. The four deaths recorded were during the third episodes of hospitalization.

Table 3: Causes of Morbidity in subjects according to age groups

Morbidity	20-29years	30-39years	40-49years	50-59years	≥60 years
Vaso-occlusive crises	42(100.0%)	15(100.0%)	1(50.0%)	1(50.0%)	1(33.3%)
Malaria	37(88.1%)	12(80.0%)	2(100.0%)	1(50.0%)	2(66.7%)
Chronic leg ulcer	5(11.9%)	3(20.0%)	-	-	-
Hyperhaemolytic crises	4(9.5%)	3(20.0%)	-	-	-
Avascular necrosis of femoral head	3(7.1%)	2(13.3%)	1(50.0%)	1(50.0%)	-
Pentazocine addiction	4(9.5%)	1(6.7%)	1(50.0%)	-	-
Acute chest syndrome	1(2.4%)	3(20.0%)	1(50.0%)	-	-
Priapism	2(4.8%)	2(13.3%)	1(50.0%)	-	-
Septicaemia	2(4.8%)	3(20.0%)	-	-	-
Chronic osteomyelitis	1(2.4%)	1(6.7%)	1(50.0%)	-	-
Nephropathy	2(4.8%)	1(6.7%)	-	-	-
Peptic ulcer disease	2(4.8%)	1(6.7%)	-	-	-
Deep vein thrombosis	-	1(6.7%)	-	2(100.0%)	-
Seizure disorder	3(7.1%)	-	-	-	-
Short stature with kyphoscoliosis	2(4.8%)	1(6.7%)	-	-	-
Stroke	2(4.8%)	-	-	-	-
Hepatopathy	2(4.8%)	-	-	-	-
Lobar Pneumonia	-	1(6.7%)	-	-	-
Urinary tract infection	-	1(6.7%)	-	-	-
Pulmonary embolism	-	-	-	1(50.0%)	-
Congestive cardiac failure	1(2.4%)	-	-	-	-

Table 4: Outcome and duration of care in the patients

Outcome	< 2days	2-7 days	>7days	Total
Discharged	6	34	19	59
Left against medical advice (LAMA)	-	-	-	1
Death	3	1	-	4
Total	9	35	20	64

Table 5: Number of hospital admissions in patients with sickle cell anaemia during the study period

No. of hospital admissions	Frequency n (%)
Once	40(62.5)
Twice	8(12.5)
Thrice	11(17.2)
Four times or greater	5(7.8)
Total	64(100)

DISCUSSION

Focused interventions directed at the prevention of SCA complications and hospitalizations may improve the unsettling morbidity and mortality statistics of the disease in Africa. [24] The results of the present study showed a vast array of systemic complications causing morbidities in these patients with sickle cell anaemia. The clinical features of sickle cell anaemia result from two main pathogenetic processes: haemolysis and vaso-occlusion. Sickle red cells, non-sickle red cells, leucocytes and platelets form heterocellular aggregates, which adhere to the vascular endothecium, causing occlusion of the small blood vessesl, especially the postcapillary

venules. [21,25,26] This microvascular occlusion, leads to acute and chronic tissue ischaemia and infarction, particularly in vascular beds that have intrinsically sluggish venous outflow such as the bone marrow, spleen or inflamed tissues and other organs like the lungs, brain and kidney. It is the underlying pathological basis of the acute painful episodes, crises and many of the chronic vasculopathic complications seen in sickle cell anaemia. [17, 21, 26]

The clinical course of affected patients is characteristically associated with intermittent episodic events, often referred to as crises. These are the hallmarks of the clinical presentation of SCA and are typically marked by exacerbation of the signs and symptoms of the disease. The crises were observed to be an important cause of hospital visits and hospitalizations in this study. This is in keeping with reports from other centres within [18-20] and outside Nigeria. [7,8] Vaso-occlusive crisis in the form of bone pains was the most common cause of hospitalizations of SCA patients in this study. This finding compares favourably with the results reported by Akar and Adekile in Kuwait, [27] Jaiyeimi et al in Oman, [28] Salman et al. in Iraq, [29] Brown et al. in Ibadan, South-West Nigeria, [6] Abhulimhen – Iyoha et al. in Benin City, South-South Nigeria [30] and Ambe et al in Maiduguri, North-East Nigeria. [31] In contrast, studies done by Patel et al [32] and Booth et al [17] showed that severe anaemia requiring blood transfusion and malaria were the commonest causes of hospitalization in SCA patients, respectively. Similarly, an earlier study in hospitalized children with SCA in our centre reported that malaria was the commonest morbidity with 80% prevalence. [22] In our study also, malaria was a major cause of hospital admission (84.4%).

Malaria parasite is a significant pathogen in sickle cell anaemia. It modifies the clinical course of SCA and contributes markedly to increased morbidity and mortality by causing vaso-occlusive and anaemic crises. [21,33,34] Life-long malaria chemoprophylaxis has been shown to reduce the incidence of crises, severe anaemia and hospital admissions, as well as reducing mortality. [16,17,26,35] In most centres in Nigeria, daily proguanil or weekly pyrimethamine are the most frequently prescribed regimens, but the current practice is not effective due to poor compliance and drug resistance. Increased episodes of malaria attacks and other illnesses have been observed in persons with homozygous sickle cell disease who do not take prophylactic antimalarial drugs religiously. The poor adherence is often due to adverse drug effects, for example, hair loss and month ulcers observed in some patients, following prolonged use proguanil. Development of drug resistance usually leads to increased cost of treatment of patients, since newer antimalarials are more expensive. [36] It is therefore important to improve on other preventive measures such as the use of insecticide treated nets, especially in a high malaria transmission locality like ours.

We diagnosed hyperhaemolytic crisis in 10.9% of our patients. It was ranked second to bone pain crisis as a type of crisis accounting for hospitalizations in our SCA patients, but this is in disagreement with the findings of Juwah et al [21] who reported that hyperhaemolytic anaemia was the commonest form of crisis in their cohort of children with SCA. The incidence of 10.9% in our study was lower than the 60.4% and 19.89 reported by George et al [20] and Utuk et al, [22] respectively. This may likely be due to better use of routine antimalarials, improved patients' or caregivers' knowledge of the treatment of malaria using the artemisinin-based combination drugs, better health seeking behaviour, mostly as a result of continuous, community-pervasive public enlightenment campaign and prompt presentation to hospital. Aplastic and acute sequestration crises were not encountered in this study. These have also been reported by other workers to be rare in adult sickle cell patients. [11,12,29]

Morbidities such as infections, chronic leg ulcer (CLU), avascular necrosis of femoral head, priapism and acute chest syndrome, constituted a significant percentage of the total admissions. The complications of injections in sickle cell anaemia have been well documented in the literature. [6,17,27,28,31] Infections remains a major cause of illnesses and deaths in SCA in developing countries and this calls for urgent action among all concerned. SCA patients are susceptible to infections because of hyposplenism, a defect in the alternative pathway of complement activation and reduced ability of neutrophils to kill encapsulated organisms such as streptococcus pneumonia and haemophilus influenza type b. Hyposplenism is due to repeated infarction and subsequent fibrosis of the splenic tissue, resulting in absence of the spleen in most adults. This phenomenon is known as autosplenectomy. The overall susceptibility to infections is of such clinical importance that the frequency and severity of sickle cell crises increase with the degree of the deficiencies; and the risk remains increased throughout life, but is more significantly increased in the first 5 years, when bacteraemia incidence is the highest. [27-32]

Contrary to what we found in the present study, some other authors [6,15,37] have identified infections as the leading cause of hospitalization of patients with SCA in Nigeria. In most advanced economies, vaso-occlusive and other forms of crises are the principal reasons for admission. [38,39] This disparity may be due to the early introduction of penicillin prophylaxis and pneumococcal vaccination in children in most developed countries. Although the current study was carried out in a developing nation, we observed that bone pain crisis was the major cause of admission. Interventions such as the penicillin prophylaxis and pneumococcal vaccinations routinely used in some settings in the last two decades, especially during childhood, patient and caregiver education and public enlightenment campaign on the importance of the vaccinations might have accounted for the reduction in the infection rates in our patients. The benefits of antibiotic prophylaxis and immunizations have been reported by several authors [17,19,33,40,41] Williams et al [40] in Kenya observed that children on daily prophylactic penicillins are at significantly decreased risk of death from sepsis and a vaccine-attributable disease study in the Gambia, [41] demonstrated a 15% reduction in hospitalization and 16% reduction in mortality from infectious complications.

Chronic leg ulcers are common cutaneous manifestations of SCA and a major cause of debility. The ulcers result from vaso-occlusion, poor venous pressure, hypercoagulability and trauma. The prevalence and nature of the ulcers in SCA patients vary from region to region. [42,43] The prevalence of leg ulcers in this study was 15.6% which is higher than rates reported by Hassan et al [42] in Zaria, North-West Nigeria [3.1%], Durosinmi et al [44] in Ibadan, South-West Nigeria [7.5%], Bazuaye et al [45] in Benin city, South-South Nigeria and Knox-Macaulay et al [46] in Sierra Leone (13.2%). The variation in prevalence rates is likely due the differences in sample size, patients' haemoglobin genotype or phenotype and geographical location.

Avascular necrosis (AVN) of femoral head has long been recognized as a chronic, debilitating musculoskeletal complication of SCA. Despite this knowledge, there is a dearth of studies on the prevalence of AVN in Nigeria. The prevalence of AVN in the current study was 10.9%. This was lower than the 15.9%, 39.4% and 22% reported by investigators in Ile-Ife, Nigeria, [47] Salvador-Bahia, Brazil [48] and California, [49] respectively. However, our rate is comparable with rates reported by Milner et al [50] (10%) and Matos et al [51] (11%). Our lower rate may likely be due to decreased awareness of AVN in SCA patients in society, low index of suspicion in most primary and secondary

health facilities and lack of referrals from these settings.

7.8% of our patients presented with priapism. This, however, was much lower than the 21.4% reported by Madu et al, [52] 28% by Mantadakis et al [53] and 37% in the UK group reported by Adeyoju et al. [54] Differences in sample size, geographical location and the presence of other abnormal haemoglobin types could have accounted for the variability in the prevalence rates reported in different series. It must be noted that our study did not exclude other heterozygous variants of sickle cell Disease which may have contributed to the variety of effects.

Among the wide range of SCA complications of extreme complexity, none can become as devastating as acute chest syndrome (ACS). In fact, it has gained notoriety for being the leading cause of death from SCA globally accounting for about 25% of all deaths. [55] Regrettably, there are limited data on the incidence of ACS in Nigeria. An earlier study among children in my centre reported a prevalence rate of 1.9%. [22] The present study showed that ACS accounted for 7.8% of adult SCA patients managed during the period under review. This figure is lower than the 10-20% rate observed by Miller and Gladwin in their study [56] and the 50% reported by Bartolucci et al. [57] The prevalence rate of 7.8% in our study may not be a true reflection of the situation in our population as some unknown SCA patients may have presented with this condition without relevant diagnostic workup and thus missed being captured. It is also possible that due to patients' or caregivers' financial constraints, the only chest X-ray done during hospital admission could have been normal owing to the fact that radiographic features in some case of ACS may progress over time. [58]

Morbidities such as septicaemia (7.8%), pentazocine addiction (9.4%), deep vein thrombosis (4.7%), seizure disorder (4.7%), peptic ulcer disease (4.7%), chronic renal disease (4.7%), chronic osteomyelitic (4.7%), congestive cardiac failure (1.6%), lobar pneumonia (1.6%), urinary tract infection (1.6%) and pulmonary embolism (1.6%), also contributed significantly to the repeated hospital visits and admissions of our patients. This multisystemic distribution of complications in affected patients, further affirms the need for multi-disciplinary collaborations in their care. We believe that successful partnerships with all the relevant specialists will improve the diagnostic and therapeutic landscape, and ultimately lead to improved survival and quality of life for these persons with SCA.

A greater percentage of our SCA patients (62.5%) were hospitalized at least once during the 24-month study period with a few admitted twice or more within the same period. This is similar to the experience of Utuk et al [22] and Brown et al. [6] Most patients were discharged in good health within one week of admission, one patient left against medical advice while four patients died during the period of hospitalization. These findings are in consonance with the findings of Utuk et al. [22] Patients who spent more than seven days on admission would also suffer significant loss of school or working hours, as well as working hours for caregivers. This long hospital stay could cause disruptions to the physical capabilities, social identities and life trajectories of the patients and their families. All of these depict the enormity of burden in the sufferers of the disease, their families as well as their communities.

It will be beneficial to improve preventive measures like community sensitization, genetic counseling to dispel the myths and stigma associated with the disease; and awareness of predisposing factors to common morbidities such as the vaso-occlusive (bone pain) crisis. The use of trained counselors is a cost-effective intervention strategy to use in any country for amelioration of the problems associated with the disease. [19] Also, effective and efficient roll-out of malaria preventive and treatment strategies are required, including early treatment of cases, periodic distribution of insecticide treated bed nets,

reduction of human-vector contact through indoor residual spraying (IRS) or interruption of transmission of the plasmodium parasite from infected humans to naïve mosquitoes by uptake of malaria vaccines. The development and adoption of these measures, bolstered by government and non-government efforts at subsidizing the cost of the vaccine, would engender a wider coverage rate and uptake in many, who cannot afford. This will lead to a reduction in the number of malaria-related illnesses and invariably the frequency of morbidity and hospitalization.

Education of patients and their caregivers about the causes, symptoms and complications of SCA to enable them detect cases promptly and seek medical advice before they become complicated, instituting early preventive care, providing prompt and appropriate treatment for acute illnesses and prophylaxis against infections all contribute considerably to an overall improvement in survival and quality of life. Countries with large cohorts of patients and adequate resources have keyed into these strategies. [16] It is our fervent hope that these would be beneficial in our country.

To foster these laudable intervention modalities, there is a great need to encourage patients to attend clinics regularly, even during the steady-state periods. This helps in close monitoring and treatment of affected patients to prevent occurrence of chronic illnesses which are common in adult SCA patients. [10,46] Reducing the frequency of crises and systemic complications would improve the patients' quality of life and may help to delay the onset of long-term end-organ dysfunctions and failures, eventually extending life expectancy.

This was a single centre perspective and thus, does not represent the true rate of events for adult SCA patients in the general population. We hereby recommend that a large multicentre study including community-based cohort survey be conducted for the purpose of validating our results.

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