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Beyond Emergencies: A Five-Year Clinical Profile on the Pattern of Presentation and Seasonal Trend of Out-Patient Visits among Children with Sickle Cell Anaemia.

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ABSTRACT

Background: Sickle cell anaemia (SCA) is a common haemoglobinopathy that disproportionately affects children from resource-challenged nations. **Objectives:** To determine the outcomes of SCA children during outpatient visits and evaluate the impact of the local weather on the incidences of the disease outcomes. **Material and Methods**: A five-year retrospective review of clinical encounters among confirmed SCA children with complaints in an outpatient facility of a tertiary hospital in South-East Nigeria. The main outcome measures included vaso-occlusive crises (VOC), respiratory illnesses, and infectious diseases. Analysis was done by Statistical Package for the Social Sciences software version 21 and R ggplot2 package. **Result:** The clinical details of 516 outpatient visits among 186 children with SCA were collated. The most prevalent complaint was VOC (33.9%) followed by respiratory illnesses (22.7%) and infectious diseases (10.5%). Patients aged 5-10 years had the highest disease burden (39.3%), with the least burden observed among older adolescents (14.7%). The incidence rate of VOC occurred more during the rainy season with twin peaks in March and July, while respiratory illnesses occurred more during February (dry season). Compared to under-five, children aged 5-10 years and 11-15 years had an increased odds of developing VOC (OR 1.746 CI: 1.006-3.031 and OR: 2.095 CI: 1.168-3.758 respectively) while adolescents aged 11-15 years and above 15 years had a decreased odds of presenting with respiratory illnesses (OR 0.233 CI: 0.120-4.52; OR 0.174 CI: 0.072-0.420 respectively). **Conclusion**: VOC constitutes the most prevalent complaint during outpatient visits among children with SCA with predilection in rainy season.

Keywords: Sickle cell anaemia, Sickle cell disease, Outpatients, Children, Crisis, Haemoglobinopathy.

INTRODUCTION

Sickle cell anaemia (SCA) is undeniably one of the most common and oldest genetic disease known to man. This haemoglobinopathy affects millions of people throughout the world and occurs when valine is replaced with glutamic acid in the beta globin chain. Microscopically, SCA is identified by its distinctive

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sickled red cell shape in deoxygenated states and is associated with a glut of complications that affects virtually all organ systems in the body.[1] Survivors of this disease are often times faced with debilitating physical, mental, and psychosocial aftermath of this disease that cumulatively affect their quality of lives.

Over the years, the progressive changes in the comprehensive management of SCA have successfully yielded a relative crisis-free state in an average child.[2] Now, majority of children with SCA, especially in developed countries, grow into adults with reasonably productive lives.[3,4] Notwithstanding this feat, definitive management of SCA which entails a bone marrow transplant, remains largely unpopular due to its astounding cost and life-threatening side effects, which is unacceptably high compared to the relative risks associated with conservative care.[4]

Several studies have consistently demonstrated a significant gap in SCA disease burden between resource-rich nations and their counterparts with meagre resources.[38] Regrettably, in Sub-Saharan Africa, wherein SCA-related mortality can be as high as 50-90%, lack of a robust database, trained specialists, routine drugs and effiective management protocols especially during outpatient visits are some of the key factors that contribute to poor indices emanating from this region.[6] Quite recently, a six-year prospective study conducted in Northern Nigeria demonstrated the adverse impact of seasonal variations on the incidences of SCA co-morbidities among adults, a factor still unexplored in the management of SCA children.[9] Notwithstanding these limitations, there are sparse reports of the health care demands of the average SCA child during outpatient visits. We believe that a comprehensive understanding of their health care needs during outpatient visits and prompt management can help mitigate to a great extent the onset of severe SCA complications. Therefore, in this study, we aim to report the disease outcomes of SCA children during outpatient visits and evaluate the impact of the local weather on these incidences of thesedisease outcomes. We believe that our findings will greatly aid in the design of a comprehensive and cost-effective management protocol that will significantly ease the burden of SCA complications in children from resource-poor nations.

MATERIALS AND METHODS

Study design: A five-year retrospective review of the clinical outcomes and its seasonal trend among children confirmed to have sickle cell anaemia during outpatient visits.

Study location: The outpatient clinic used for this study is located in a tertiary hospital-Nnamdi Azikiwe University Teaching Hospital (NAUTH)-located in Nnewi, Anambra State in South-East Nigeria. Paediatricians specialised in haematology and oncology oversee all the health care needs of children with sickle cell anaemia during the outpatient visits.

Sampling Procedure

Health care records of all children confirmed to have sickle cell anaemia that presented to the outpatient clinic from January 2015 to December 2019 were retrieved and variables of interest collated which include the date of presentation (day, month and year), folder number, age, gender, and clinical outcome. Clinical diagnoses were obtained following a careful clinical assessment and appropriate laboratory investigations

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Inclusion criteria

Clinical encounters of children confirmed to have sickle cell anaemia with at least one complaint

Exclusion criteria

Clinical encounters of children confirmed to have sickle cell anaemia with no compliants.

In effect, out of 1102 outpatient visits among children with sickle cella anaemia that occurred during the five-year study period, 516 (46.8%) encounters by 186 unique SCA patients with at least one clinical complaint were included in this study.

Outcome measures

Clinical outcomes noted include mild painful episodes (Vaso-occlusive crises); upper and mild

lower respiratory tract illnesses, hyperactive airway disease (Respiratory Diseases), malaria, sepsis(Infectious diseases), cerebrovascular accident with paralysis (CNS-Central Nervous Disease); Hodgkin's lymphoma, acute lymphoblastic disease, nephroblastoma (Cancer); Haemolytic and sequestration crisis (Anaemia); acute gastroenteritis, peptic ulcer disease, malnutrition (GIT-Gastrointestinal tract); avascular necrosis of femoral head, osteomyelitis, septic arthritis (Bone); allergic dermatitis, furunculosis, impetigo, leg ulcer (Skin); urinary tract infection, nephropathy, priapism (Renal); dilated cardiomyopathy and arrhythmia (CVS-Cardiovascular disease). The three most prevalent disease outcomes were further categorised across age groups and gender.

Seasonal variations of the study area were extrapolated from a 40-year review of a nearby city's rainfall and water balance in the state where the index clinic is located.[10]

Statistical Analysis

Analysis of data was done using Statistical Package for the Social Sciences (SPSS) software version 21 and R statistical programming for graphical representation of data.[11] Measures for central tendency for continuous variables were depicted as means and standard deviations while categorical variables were described as frequencies and percentages. Bar plot was used to describe the distribution of the clinical outcomes while the seasonal trend of the prevalent clinical outcomes were depicted with line plots. Logistic regression was employed to compare the relationship between the clinical outcomes and variables of interest. Statistical significance was set at $p<0.05$.

Ethical Consideration: Ethical approval was obtained from the Ethical committee of Nnamdi Azikiwe University Teaching Hospital, Nnewi, Anambra State, Nigeria.

RESULTS

Five hundred and sixteen (516) outpatient visits with clinical complaints were documented between the periods of January 2015 to December 2019. 313 (60.7%) of the outpatient visits were male visits with a male visit to female visit of 1.5:1. The mean age of all subjects was 9.3 ± 5.0 years with an age range of 4 months to 20 years. Over a third of the subjects belonged to the 5-10 year age group, with older adolescents as the least age group represented. In all age groups, the male gender constituted more than half of the subjects (Table 2). Other characteristics of the clinical visits are further delineated in Table 1.

Table 1: Baseline Characteristics of SCA Patients in Outpatient Visits

Variables	Frequency (%)
N=516	
Gender	
Male	313 (60.7)
Female	203 (39.3)
Age Category (Years)	
Below 5	103 (20.0)
5-10	203 (39.3)
11-15	134 (26.0)
Above 15	76 (14.7)
Year of Outpatient Visits	
2015	53 (10.3)
2016	68 (13.1)
2017	98 (19.0)
2018	144 (27.9)
2019	153 (29.7)

Pattern of Presentation

The most prevalent complaint was pain depicted as a vaso-occlusive crisis (33.9%). This was followed by respiratory illnesses (22.7%) and other infectious diseases (10.5%). Cardiovascular complications and haemolytic crisis characterised by anaemia were the least prevalent diagnosis reported. (Figure I). Of the three prevalent disease states,

Patients aged 5-10 years had the greatest disease burden, with the least burden observed among children above 15 (Figure II).

Seasonal Pattern of Disease Outcomes

A 40-year review of the rainfall and water balance of the study area indicated two distinct seasons, namely Rainy and Dry seasons. In this review, Rainy season begins from April through November, while Dry season occurs from December to March. In this

study, a bimodal peak for VOC was observed in March and July, as illustrated in Figure III; Respiratory illnesses peaked during the dry season in February, while infectious diseases having no distinct peak occurred more during the rainy season.

Predictors of Predominant Disease Outcomes

Adjusting for gender, age, and seasonal variations, the significant predictor of VOC was observed among SCA children aged 5 to 15 years (Table 3). Although males showed an increased propensity of developing VOC, this was not significant (p=0.755). In respiratory-related illnesses, adolescents were significantly less likely to develop the disease (p =o.0001). Males were observed to have an increased risk of developing other infectious diseases but this was only marginally significant (p=0.056).

Table 2: Stratification of Age Group based on Gender

Age Category	Total (n=516)	Male (n/%)	Female (n/%)
0-5	103	69 (67)	34 (33)
5-10	203	123 (60.6)	80 (39.4)
11-15	134	78 (58.2)	56 (41.8)
Above 15	76	43 (56.6)	33 (43.4)

Chi-square=0.048

Table 3: Predictors of Prevalent Disease Outcomes

			OR	95% CI	*P*-Value
VOC	*Gender*	**Female***			
		Male	1.064	0.720-1.572	0.755
	Age Category	**Below 5***			
		5-10	1.746	1.006-3.031	0.047**
		11-15	2.095	1.168-3.758	0.013**
		Above 15	0.989	0.484-2.022	0.976
	Weather	**Dry***			
		Rainy	1.461	0.994-2.148	0.054
RESPIRATORY DISEASES	*Gender*	**Female**			
		Male	0.716	0.463-1.105	0.131
	Age Category	**Below 5**			
		5-10	0.677	0.407-1.125	0.132
		11-15	0.233	0.120-4.52	0.0001**
		Above 15	0.174	0.072-0.420	0.0001**
	Weather	**Dry**			
		Rainy	0.836	0.537-1.301	0.427
INFECTIONS	*Gender*	**Female***			
		Male	1.870	0.983-3.556	0.056
	Age Category	**Below 5***			
		5-10	1.066	0.493-2.364	0.871
		11-15	1.027	0.443-2.378	0.951
		Above 15	0.612	0.202-1.851	0.384
	Weather	**Dry***			
		Rainy	1.302	0.727-2.33	0.375

*OR: Odds Ratio ; CI: Confidence intervals ; *Reference values; **significant value*

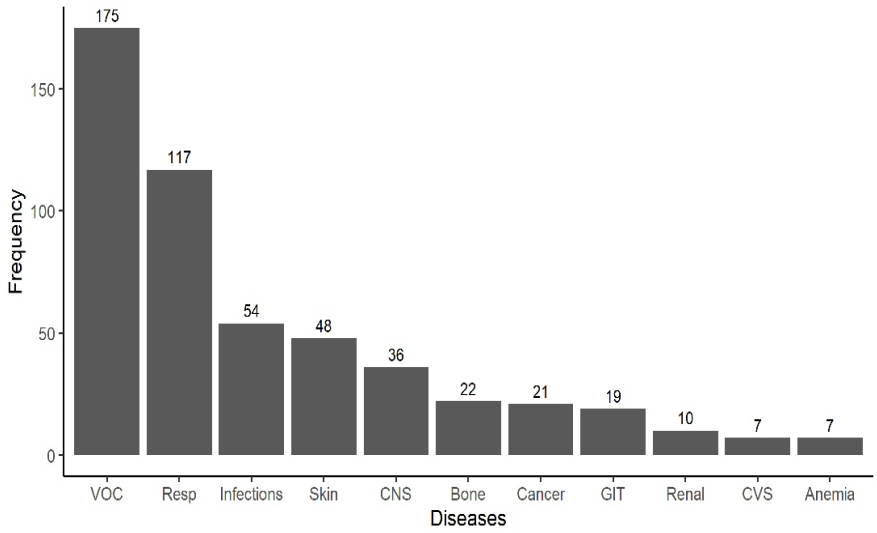

Figure I: Distribution of Disease Outcomes among SCA Patients during Out-Patient Visits

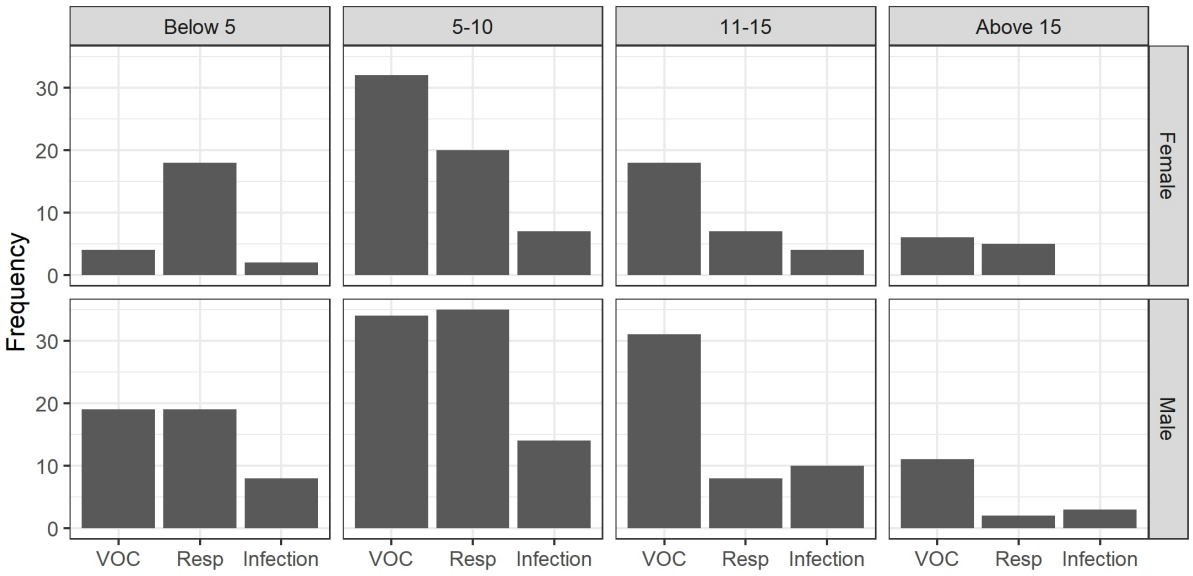

Figure II: Distribution of the Most Prevalent Disease Outcome Stratified by Age Group and Gender among SCA Patients During Out-Patient Visits

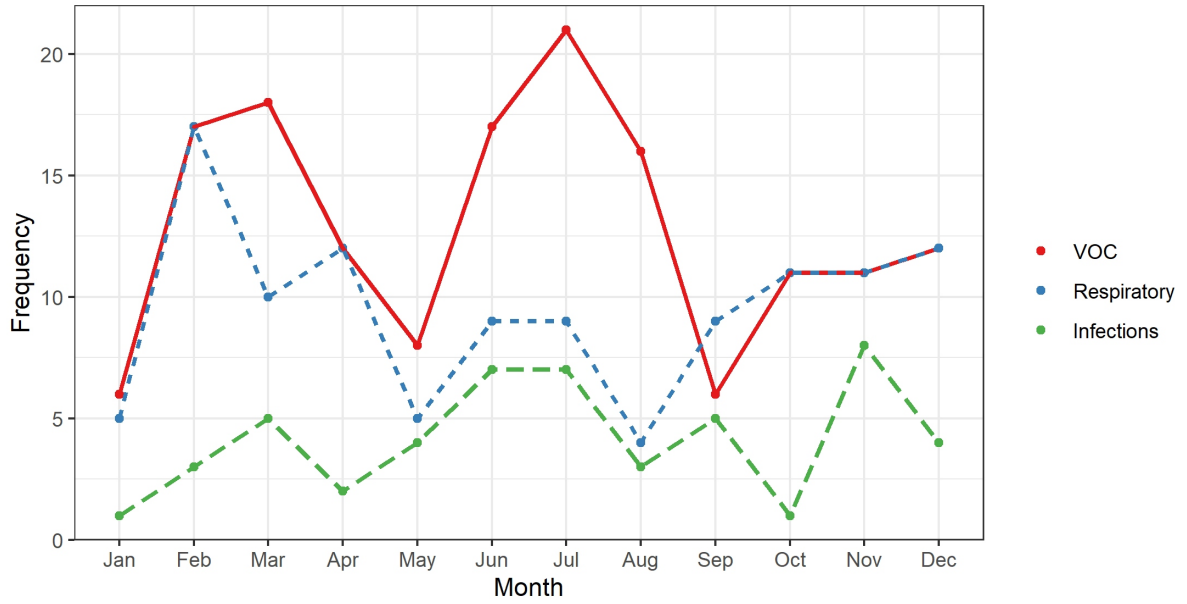

Table III: Seasonal Trend of the Most Prevalent Disease Outcome Among SCA Patients During Out-Patient Visits

DISCUSSION

Addressing the complex needs of children living with sickle cell anaemia logically begins with a comprehensive understanding of their clinical profile in a relatively stable state. Although prior studies on SCA in children focused primarily on expected SCA related crises, in truth, most of these crises are elicited by seemingly indolent or innocuous disease states mainly observed either during follow-up or at home. For example, a mild respiratory infection without proper management can quickly progress to sepsis, severe pneumonia, or acute chest syndrome. Likewise, it can also trigger pain through a complex mechanism that entails the pooling and enhanced stickiness of white blood cells which further promotes sickling and occlusion of the capillary tree.[12,13] This 5-year review provides an inkling of the clinical complaints observed in an outpatient setting among SCA children. Furthermore, it highlights the impact of seasonal variations on the prevalence of these diseases and strives to unveil, albeit crudely, within the boundaries of our limitations, its predictors. It is also important to note that during the period of this review, the routine management care of SCA children entailed the daily administration of folic acid, mutivitamin, penicillin V tablets for children less than five years, and proguanil for anti-malaria prophylaxis. These children were not vaccinated against pneumococcal organisms at five years of age nor was hydroxyurea administered as a routine drug due to its scarcity during the study period. .

Approximately two-thirds of the outpatient SCA visits were males, and this was consistently observed across all age groups. It remains unclear why a staggering proportion of the patients were males. The authors presumed that this wide gender disparity could be the outcome of the male child societal preference, which may have positively influenced caregivers' healthcare-seeking behaviour. While there is no sex predilection in SCA, there are existing reports of gender differences in SCA complications. Notably, males with SCA are more likely to have

VOC, infections and SCA nephropathy.[14] Furthermore, nitric oxide, a compound believed to decelerate the sickling process, is produced more in females, thereby predisposing the male gender to an increased likelihood of SCA complications.[15,16] Interestingly, in this study, male patients demonstrated an increased propensity of developing VOC and infectious diseases, but this was not statistically significant (Table 2).

Patients in the age group 5-10 years comprised over a third of patients (39%) seen in the outpatient clinic, followed closely by age group 11-15 years (26%). Older adolescents above 15 years of age were the least seen in the clinic. Reasons for this pattern of presentation are not far-fetched. Following adjustment for possible confounders, ages 5-15 years that incidentally constituted over half of the patient load, had an increased odds of presenting with vaso-occlusive crises and infectious diseases compared to the under-five age group (Table 2). Conversely, older adolescents above 15 years of age had the least odds of all three prevalent diseases observed. Indeed, this may sufficiently explain the age group presentation pattern derived, as some of these diseases, particularly VOC, can invoke an appropriate health-care seeking behaviour among caregivers caring for the SCA child.

Vaso-occlusive crises was the most prevalent disease outcome observed across all age group and gender. Painful episodes of varying intensity remain the most common and dreaded SCA complication. Notwithstanding that VOC can be managed effectively with several modifying agents, particularly hydroxyurea, none of these agents was part of the routine management protocol at the time of this review due to their scarcity and exorbitant costs.[17,18] Age group of the patients appeared to be a significant predictor of VOC. Compared to the under-fives, children aged 5 to 15 years had an increased odds of developing VOC ($p<0.05$). 70% of children below the age of five have significant foetal haemoglobin, which protects against sickling.[19] Thus, this may sufficiently explain the lower prevalence of VOC in this age group compared to older children with little or none of this haemoglobin variant. Although males appeared to have an increased odds of developing VOC, this was not significant. The prevalence of VOC varied with the seasons, as demonstrated in Figure III. VOC occurs more in rainy season, characterized by extremes of temperature, high humidity and dehydration and these factors can serve as potential triggers of the sickling process.

Respiratory diseases occurred more in children below the age of five. Functional hypo- or asplenism develops from 6 months to 3 years, and together with a complement activation defect, increases the burden of infectious diseases, notably from encapsulated organisms, in this age group. This risk, however, decreases as the child grows. We observed that older children had a decreased odds of developing respiratory illnesses, but this was only significant from ages 11 and above (Table 2). This finding was quite intriguing because in our centre, oral penicillin is routinely administered to SCA children below the age of five to help mitigate the increased susceptibility to infectious diseases.[20] Beyond this age group, however, neither penicillin nor pneumococcal vaccine are administered due to the scarcity of the vaccine and perceived lesser risk of infection in older children. Notwithstanding the decreased odds of respiratory diseases in children aged 5-10 years compared to the under-fives, this was not significant, substantiating the need to continue penicillin prophylaxis in this age group. It is not entirely clear why the prevalence of respiratory illnesses is significantly low in adolescents compared to the under-fives. One may ascribe this finding to the progressive development of both innate and specific immunity in the growing child exposed to environmental pathogens. As expected, respiratory illnesses occurred more during the dry season. A rise in temperature, low humidity and dry winds facilitate the spread of air-borne pathogen infused droplets, promoting the onset of allergies, viral respiratory diseases, and seeding of bacterial infections in an already defective immune state. Other infectious diseases, the chief of which is malaria, were observed to occur more in males but this was marginally significant. The authors believe that males are overly burdened with the primal need to explore their immediate environment, unwittingly exposing them

to vectors that can inadvertently lead to malaria and other infectious diseases. Although infectious diseases were observed more in children aged 5-15 years, it was not significant. We believe that caregivers of children below five years comply better with preventive measures against malaria and other SCA complications than older age groups.[21,22] The decreased odds of infections observed in older adolescents (above 15 years) may portend the adoption of healthier lifestyle choices as the near-adult child becomes increasingly mature and fully aware of the chronicity of SCA and its related complications.

Study limitations: We acknowledge that there are several limitations to this study. The compliance rate of each unique patient and its possible association to the pattern of presentation and clinical outcomes was not explored. Also, we did not assess other important parameters that may be associated some of the clinical outcomes such as the hydration status, exposure to vectors and elements of weather as possible reasons for the impact of seasons on pattern of presentation. Nontheless, we believe that the outcomes of this five-year review study is quite robust to aid in the clinical decision-making and effective management of sickle cell children during out-patient visits with similar climes.

In conclusion, vaso-occlusive crisis remains the most common disease outcome among SCA children during outpatient visits. We advocate the need for increased awareness and the onset of proactive measures against prevalent disease states. These measures include the administration of hydroxyurea, penicillin prophylaxis beyond the age of five years and anticipatory care during the peak seasons such as use of mosquito nets to protect against the vector which breeds maximally during rainy seasons and protection from cold and dehydration during dry seassons. In all, caregivers should be appropriately counselled on proper health-care seeking behaviour and the need for regular follow-up, particularly for male children and adolescents. SCA studies are needed from more resource-challenged nations to identify risk factors and cost-effective measures in the routine management of the SCA child.

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Author contributions: NCA synthesized the concept of the manuscript, UTO reviewed and contributed to the discussion, ODC analyzed the data, OMI contributed to the design of the methodology and discussion, ETS collated the data.

Data availability

The data used to support the findings of this study are available from the site publicly.

Declaration of conflicting interests

The author(s) declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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