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CHARACTERISTICS AND GROWTH AND PUBERTAL PATTERNS AMONG PATIENTS WITH SICKLE CELL DISEASE AT KENYATTA NATIONAL HOSPITAL, NAIROBI
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CHARACTERISTICS AND GROWTH AND PUBERTAL PATTERNS AMONG PATIENTS WITH SICKLE CELL DISEASE AT KENYATTA NATIONAL HOSPITAL, NAIROBI

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ABSTRACT

Background: **Sickle cell disease (SCD) is an autosomal recessive disorder characterized by production of abnormal (sickle) hemoglobin, resulting in anemia, susceptibility to pneumococcal and other infections and multiple organ failure. The aim of this study was to describe the characteristics as well as growth and pubertal patterns among children with sickle cell disease in the Kenyan setting.**

Methods: **This was a cross-sectional descriptive study involving children with confirmed sickle cell disease seen at the Kenyatta National Hospital. Demographic information was obtained using a standard questionnaire and information on prescribed drugs was extracted from medical records. Anthropometric measurements were obtained by measuring weight and height and puberty status was assessed in boys and girls**

Results: **A total of 142 children with sickle cell disease were recruited into the study of whom 86 (60.6%) were males and 56 (39.4%) were females. Their median age was 7.7 years (IQR 5.5, 9.5). Two thirds of the study population (65%) was from the Luo ethnic community With regards to treatment, 86% of the children were on Hydroxyurea, 70% were on Folic acid and only a small proportion were on Paludrine (3.5%) and Penicillin V (2.9%). Among children aged below 5 years 17.1% were underweight (WAZ score <-2SD). Only 9 (27.2%) boys aged > 9 years had testicular size ≥3cc while 4 (17.4%) girls aged >8 years had breast tanner 2.**

Conclusion: **There was low uptake of the recommended antibiotic and antimalarial prophylaxis in our study population. Growth failure and delayed puberty was also observed.**

Key Words: Sickle cell disease, Hydroxyurea, Folic acid, Penicillin V, antimalarial, Growth and Puberty

INTRODUCTION

Sickle Cell Disease (SCD) is a genetic disorder of the haemoglobin molecule, where during low oxygen tensions, sickling of red blood cells (RBCs) occurs, leading to chronic hemolysis, organ damage, vaso-occlusive events, and other potentially life-threatening complications. It is more common among people originating from tropical Africa, the Caribbeans, Mediterranean, Indian and the Middle Eastern regions (1). Children with SCD have significantly lower weight, height and BMI when compared with healthy controls of similar age, sex and ethnicity (2, 3). Growth retardation is the most commonly encountered endocrine disorder in patients with SCD (2).

Studies have revealed that hydroxyurea is an important therapeutic option for patients with SCD as it decreases the frequency of acute vaso-occlusive events, improves hematologic parameters and subsequently prevents or reverses chronic organ damage (4, 5). In people with homozygous SCD, the red blood cell count is lower than normal because the average life span of sickled RBCs is about 17 days. This high cell turnover may deplete the folate stores (6). It is proposed that folate supplementation in the setting of anaemia raises haemoglobin levels and helps provide a healthy reticulocyte response (7).

Younger children with SCD are often more susceptible to infection by encapsulated organisms such as Streptococcus pneumoniae (66%), Haemophilus influenzae, Neisseria meningitidis and Salmonella species (8-10). Before the use of routine penicillin prophylaxis, the case fatality in the United States was as high as 35%, with S. pneumoniae infections often progressing quickly to cause death within 24 hours of onset. Following the introduction of penicillin prophylaxis for SCD patients aged less than 5 years, the rate of S. pneumoniae associated infection has decreased to 1.5 events per 100 patient-years (11).

Malaria is the most common precipitating cause of crises in sickle cell disease in countries where malaria is endemic (12). People with both sickle cell disease and malaria suffer increased morbidity and mortality (13). Fewer deaths and crises have been reported with provision of malaria chemoprophylaxis, while growth, quality of life and resistance to other infections are also thought to improve (12, 14). Many authorities therefore recommend life-long malaria prophylaxis in people with homozygous sickle cell disease.

Sickle cell disease is also associated with delayed onset of puberty by approximately 2 years in both boys and girls (2, 10). A case control study by Soliman et al, found that two-thirds of girls with SCD have delayed breast development (mean age of thelarche at 13.5 years), and the mean age of spontaneous menarche is 15.6 years. Similarly, 25% of boys who have SCD and are above the age of 14 years have absent testicular development (10). Males with SCD and delayed pubertal development have significantly smaller testicular volume and lower testosterone concentrations (3)

Despite availability of data on SCD from numerous studies conducted elsewhere there is limited data on characteristics of patients with SCD in Kenya. The aim of this study was to describe the characteristics as well as the growth and pubertal patterns among children with sickle cell disease seen at a tertiary hospital in Nairobi, Kenya.

METHODOLOGY

Our study was conducted at the Kenyatta National Hospital Paediatric Hematology clinic. Kenyatta National hospital is located in Nairobi and is the largest teaching and referral hospital in East Africa catering for around 500 children with sickle cell disease.

This was a cross-sectional descriptive study involving 142 children with confirmed sickle cell disease. Demographic information on age, gender, ethnicity and socio-economic status was obtained from caregivers using a standard questionnaire. Information on prescribed drugs mainly hydroxyurea, proguanil (antimalarial), folic acid and penicillin V was extracted from children's medical records.

Anthropometric measurements were obtained by measuring length using an infantometer for children aged less than 2 years and a stadiometer for children aged above 2 years. Weight was taken using either an infant or platform digital electronic scale without shoes and with light clothing. Children's heights and weights were plotted on the CDC charts for age and gender. Standardized scores (z scores) was calculated using a computerized program.

Pubertal status in girls was determined by assessing their breast tanner stage as described by Marshall and Tanner while for boys it was assessed by measuring testicular volume using an orchidometer. A complete general examination was performed in all patients. Menarcheal status and age at first menstruation was elicited from girls aged 8 years and older.

RESULTS

Baseline characteristics of the study population: A total of 142 children with sickle cell disease were recruited into the study of whom 86 (60.6%) were males and 56 (39.4%) were females, with a male to female ration of 1.5:1. The median age was 7.7 years (IQR 5.5, 9.5) and majority of the children (47%) were aged 5-9 years. Two thirds of the study population (65%) was from the Luo ethnic community and 25% were from the Luhya community. A small percentage (10%) came from other communities (mainly Kisii, Nubian, Teso, Kamba, Kikuyu and Taita). Majority of the caregivers (43.9%) had secondary level of education and received an average monthly income of Ksh10,000-20,000.

With regards to treatment, 86% of the children were on Hydroxyurea while 70% were on Folic acid. Only a small proportion were on either Iron (9.2%), Paludrine (3.5%) or Penicillin V (2.9%). Table 1 below presents the baseline characteristics of study participants.

Table 1

Sociodemographic characteristics of study participants

Study parameter	**Participants (n=142)**
Age (in years)	
Median (IQR)	7.7 (5.5, 9.5)
Age category (in years)	
0-5 years, n (%)	37 (18.7)
5-9 years, n (%)	54 (47.4)
10-14 years, n (%)	50 (33.1)
15-19 years, n (%)	1 (0.01)
Gender	
Males, *n* (%)	86 (60.6)
Females, *n* (%)	56 (39.4)
Ethnic group	
Luo	92 (65)
Luhya	36 (25)
Others	14 (10)
Caregivers' level of education	

Primary, *n* (%)	37 (26.6)
Secondary, *n* (%)	61 (43.9)
Tertiary, *n* (%)	41 (30.0)
Household level of income (in Ksh)	
<10,000, *n* (%)	5(3.6)
10,000-20,000, *n* (%)	99 (71.7)
20,000-50,000, *n* (%)	34 (24.6)
>50,000, *n* (%)	
Treatment history	
Folic acid, n (%)	100 (70.9)
Pen V, *n* (%)	4 (2.9)
Paludrine	5 (3.5)
Hydroxyurea, *n* (%)	123 (86.6)

Growth characteristics of children: Among children aged 5 years and below, 35.1% were underweight with a WAZ score <-2SD. Only 9.1% of the boys within this age group compared to 30. 8% of the girls were found to be underweight. This difference in proportions was however not statistically significant. Ten percent of our study population was stunted with again no significant difference between boys and girls (Table 2).

Table 2

Anthropometric parameters of children aged ≤ 5 years (n=35)

Anthropometric measurement	**Total**	**By gender**		**p value**
Age ≤ 5 years	**N= 37**	**Males (n= 22)**	**Females (n= 15)**	
Underweight *WAZ <-2SD*	13 (35.1%)	9 (9.1%)	4 (30.8%)	0.2
Stunting HAZ <2SD	4 (10.4%)	2 (9.5%)	2 (14.3%)	1.0

Among children aged 6-19 years (n=61), the mean WAZ score was -0.59 (sd 1.23). Girls had a lower mean WAZ (-0.8) compared to boys (-0.42). The mean HAZ score was 0.05 (sd 2.11) and fewer girls (11.5%) compared to boys (13.5%) were stunted. There was no significant gender difference.

Pubertal characteristics: Majority of the children aged above 9 years (94.6%) had no axillary hair and 91.1% had no pubic hair. Among boys aged> 9 years (n=33), only 9 (27.3%) had testicular size > 3cc and for girls aged > 8 years (n=23) only 4 (17.4%) had breast tanner 2 (Table 3).

Table 3
Pubertal status of children based on tanner staging

Tanner characteristic	Frequency (%)
Axillary hair tanner (n=56)	
Yes	3 (5.4)
No	53 (94.6)
Pubic hair tanner (n=56)	
1	51 (91.1)
2	5 (8.9)
Males (n= 33)	
Testicular size tanner ≤ 3	24 (72.7)
Testicular size tanner >3	9 (27.3)
Females (n= 23)	
Breast size tanner 1	19 (82.6)
2	4 (17.4)

DISCUSSION

The aim of this study was to describe the characteristics as well as the growth and pubertal patterns among children with sickle cell disease in the Kenyan setting.

The demographic characteristics of our study population were similar to those of children with sickle described in previous studies conducted in developing countries. The median age of children in our study was 7.7 years, similar to that of 8.4 years reported by Lukusa in Central Africa and 7.2 years reported by Al-Saqladi in Yemen (14, 15). The age distribution was also similar with majority of the children aged 5-9 years. We however noted that there was a difference in the gender distribution in our study compared to the other 2 studies as we had more males (60.6%) affected compared to females (39.9%).

In terms of ethnicity, 65% of our population was from the Luo community while 25% came from the Luhya community. This distribution is in keeping with findings from another study conducted in Kenya by Aluoch R et al where more than 80% of children with sickle cell disease were from either Luo or Luhya ethnic communities (Luo 58.4%, Luhya 23.9%) (16). These two communities reside on the shores of Lake Victoria in Western Kenya and studies have shown that the sickle cell gene tends to concentrate in hot humid climates where Malaria transmission is endemic (16,17). Prevalence of sickle cell gene among ethnic groups living close to Lake Victoria is reported to exceed 20%.

Hydroxyurea, a myelosuppressive agent, is the only drug proven to be effective in reducing the frequency of painful episodes by raising the level of HbF and haemoglobin level. It has been shown to decrease the incidence of painful episodes by as much as 50%. Based on currently available data, hydroxyurea treatment should be initiated early before the onset of chronic complications and end-organ damage (4). In our study we noted that only 80% of the children were on Hydroxyurea. Potential explanations include inadequate knowledge amongst healthcare on the benefits of hydroxyurea, undue fear of its side effects hence patients and families may not be offered treatment or may decline because of unrealistic fears.

It is hypothesized that due to increased erythropoiesis, people with sickle cell disease are at an increased risk for folate deficiency. For this reason, it is recommended that children and adults with sickle cell disease, particularly those with

sickle cell anaemia, take 5 mg of folic acid orally daily on the premise that this will replace depleted folate stores and reduce the symptoms of anaemia(7). In our study we found that only 70% of the children were on folic acid. The most likely reason again for non-prescription to all children is lack of knowledge by the healthcare providers.

Children with SCD have an increased susceptibility to bacterial infections, especially to those caused by Streptococcus pneumonia (18). Pneumococcal vaccination and daily oral administration of penicillin V have significantly reduced the mortality associated with pneumococcal infection in these children. It is recommended that all children younger than 5 years with SCD take daily prophylactic antibiotics (18). In our study only 2.9% of patients were on Penicillin V way below the recommendation by the Sickle Cell Disease Branch, Division of Blood Diseases, and Resources of the National Heart, Lung, and Blood Institute. Although interventions with daily oral penicillin and vaccination against pneumococcal infections have successfully reduced mortality in developed countries (18), in Africa these interventions have largely not been implemented due to limited evidence of similar effect in the African setting (19,20). A prescription audit done by Olusesan et al among pediatric sickle cell patients in South-West Nigeria revealed that none of the patients was on penicillin prophylaxis, a practice not in keeping with internationally accepted guidelines (19). In yet another study conducted in Nigeria across 18 sickle cell clinics, only eight of them routinely prescribed prophylactic penicillin (20). The low proportion of children on penicillin prophylaxis in our study is comparable to the findings from these studies.

Malaria is the most common precipitating cause of crises in sickle cell disease in countries where malaria is endemic (12, 21). Mortality and morbidity are increased in people with both sickle cell disease and malaria (11,12). Maharajan et al found that malaria parasites were the commonest infecting organism among people with Sickle cell disease requiring hospitalizations (22). Another study by Konotey et al reported malaria as the precipitating cause in 133 of 848 consecutive admissions due to crises in Sickle cell disease in a hospital in Ghana (21).

Fewer deaths and crises have been reported with malaria chemoprophylaxis, while growth, quality of life, as well as resistance to other infections are thought to improve (12, 22). Many studies therefore recommend life-long malaria prophylaxis in people with Sickle cell disease (11,12). Contrary to many studies our study revealed that only 3.5% of children with SCD were on proguanil.

Growth and Puberty

Growth delays among many children with sickle cell disease have previously been demonstrated in various studies. The proportion of underweight children in our study of 35% was lower than what was reported by Lukusa in Central Africa at 47% and Al-Saqladi in Yemen 45% (15, 16). We however noted that the proportion of underweight children did not vary with age similar to what was reported by Lukusa and we also had similar proportions of underweight children for the age categories 0-4 years and 6-19 years. Al-Saqladi had previously reported a positive correlation between age and weight for age status (16). Girls in our study had a lower mean weight for age Z score of -0.5 compared to boys who had a mean score of -0.7 and this was similar to what Zemel found among children with SCD in America (-0.4 and -0.8 respectively) (23). The difference in mean WAZ score comparing boys to girls in our study was however not statistically significant.

The proportion of stunted children in our study population at 10% was also comparable to what was reported in Central

Africa (15). It was however much lower than 54% reported in Yemen by Al-Saqladi. This study in Yemen found significant association between stunting and male gender. Although fewer girls compared to boys were stunted in our study we did not find a similar association between gender and stunting. This lack of association may be explained by the fact that testing for associations was not the primary aim in our study and sample size may have been a limitation in assessing for these associations.

Majority of girls and boys aged 8 and 9 years and above respectively in our study had not initiated puberty. Only 8% had pubic hair tanner stage 2 and only 5% had axillary hair. This finding mirrors reports from the study in America by Rhodes where children with sickle cell disease attained sexual characteristics 1-2 years later than age and sex matched controls. Rhodes attributed this delay to the lower hemoglobin concentration and higher energy expenditure exhibited by children with sickle cell disease (9). In our study only 27% of boys had testicular size >3cc and 17% of the girls had breast size tanner 2. A previous study by Zemel that had assessed breast tanner in girls and testicular volume in boys with SCD reported delayed onset of puberty (23). The median age for breast tanner 2 in girls was 11.4 years while median age for testicular size >3cc was 15.2 years in boys in the study by Zemel. Delays in onset of puberty have been attributed in some studies to defects in secretion of gonadotropin releasing hormone secretion. Abnormalities in testicular structure combined with impaired testosterone response to gonadotropin have also been demonstrated among boys with sickle cell disease (3).

Growth failure in sickle cell disease has generally been associated with multiple factors including nutritionally inadequate diets, high energy expenditure resulting from hyperactivity of the bone marrow and severity of disease (2, 23, 24). Although some studies have reported on endocrine dysfunction as a likely cause with defects in the hypothalamic-pituitary-gonadal axis as the main underlying problem, there has been minimal focus on the role played by growth hormone. The study by Rhodes found no difference in growth hormone levels between children with sickle cell disease and healthy controls. More studies are required in looking at the role of growth hormone deficiency as a contributing factor to the growth delay seen among these children (9).

CONCLUSION

Majority of children seen with sickle cell disease (SCD) at Kenyatta National Hospital (KNH) are from ethnic groups that originate from the western part of Kenya around Lake Victoria where Malaria is endemic.

Although most children with SCD seen at KNH are on hydroxyurea and folic acid, only a small proportion has prescriptions for either prophylactic antibiotics or antimalarials.

Growth failure and delayed puberty affecting both males and females were demonstrated within our study population.

RECOMMENDATION

There is a need to sensitize medical practitioners on the comprehensive approach to the management of SCD through continuous medical education. The observed gaps in the care of patients with SCD raises the need for health care providers be updated on and to adhere to international best practice guidelines and national guidelines.

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