Original Article

Evaluation of Sociodemographic, Clinical, and Laboratory Markers of Sickle Leg Ulcers among Young Nigerians at a Tertiary Health Institution

OS Olatunya[1,2], DM Albuquerque[1], AD Adekile[3], FF Costa[1]

[1]Hematology and Hemotherapy Center, University of Campinas, São Paulo, Brazil, [2]Department of Paediatrics, College of Medicine, Ekiti State University, Ekiti State, Nigeria, [3]Department of Pediatrics, Faculty of Medicine, Kuwait University, Safat, Kuwait

Abstract

Background: Sickle leg ulcer (SLU) is a chronic and debilitating complication of sickle cell disease (SCD) associated with huge physical and psychosocial discomfort. The occurrence of SLU has remained steady despite successful preventive strategies and advances in SCD care. Although multifactorial factors have been implicated in SLU, these are not fully understood, and data on how these relate to young Nigerian SCD patients are scanty. **Aims:** This study aims to evaluate the sociodemographic, clinical, and laboratory markers of SLU in a young Nigerian SCD cohort. **Patients and Methods:** This study involved 109 young SCD patients and 67 healthy peers. The sociodemographic and laboratory parameters of the participants were examined in addition to the evaluation of the SCD cohort for SLU. **Results:** Only the HbSS patients had SLU. This was found in six of them giving a prevalence of 5.9% (6/101). Their median age was 17, range 14–21 years. There was a preceding history of trauma in 4 (66.7%), and this included a case of traditional scarifications for local therapeutic purposes. Two of the three (66.7%) males with SLU also had priapism ($P = 0.0132$). Patients with SLU were older, had less frequent bone pain crises, and significantly belonged to the low socioeconomic class ($P < 0.05$). Although patients with SLU had relatively higher lactate dehydrogenase, platelet count, aspartate transaminase, bilirubin, white blood cell, and lower Hb concentration and HbF, these did not attain statistical significance ($P > 0.05$). **Conclusion:** This study confirms that SLU is common among young SCD patients with HbSS genotype, low socioeconomic background, and older age. It also suggests that SLU could be more related to hemolysis-associated SCD phenotypes among the patients.

Keywords: *Children, laboratory and clinical parameters, Nigeria, sickle leg ulcer, sociodemographic status*

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Introduction

Sickle cell disease (SCD) is an inherited hemoglobin defect that is very common among Africans.[1] The disease results from mutation in the β-globin gene. This mutation produces an abnormal hemoglobin known as HbS which is characterized by the ($\beta^{6GLU-\rightarrow VAL}$) substitution occuring in compound combinations with other hemoglobin variants such as the Hb C, Hb D and interactions with thalassemia.[1] Patients with SCD present with variable disease severity, but the most severe form is the sickle cell anemia (SCA), which is the homozygous state for the abnormal HbS.[1] Globally, about 312,000 neonates are born with the SCA annually and more than two-thirds (75%) of these occur in Africa.[2] Nigeria is the country with the highest burden of SCA in the world.[3]

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Address for correspondence: Dr. OS Olatunya, Hematology and Hemotherapy Center, University of Campinas, Rua Carlos Chagas, 480, Barão Geraldo, Campinas 13083-970, São Paulo, Brazil.
E-mail: ladeletunya@yahoo.com

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The structural abnormality in SCD leads to sickling of the red blood cells (RBCs) at low oxygen tension. This results in clogging at microvascular level and subsequent vaso-occlusion, hypoxia, and other downstream clinicopathologic manifestations of the disease.[1] Different aspects of the disease have been described based on these clinicopathologic manifestations.[1,4]

Leg ulcer complicating SCD, otherwise known as sickle leg ulcer (SLU), is a chronic and debilitating condition associated with both physical and emotional disturbances.[5-8] The prevalence of SLU varies among patients with SCD. It is low in the Arabian Peninsula, before the first decade of life, and rare in SCD genotypes other than HbSS.[6,8] Despite the fact that SLU was among the complications found in the first documented SCD patient,[9] advances in understanding its pathophysiology and management have been slow.[6,8] SLU is believed to have multifactorial etiology and is more common in SCA patients.[6,8] Hemolysis intensity and deposition of hemolysis products, depletion of nitric oxide, and endothelial function impairments have been implicated in its pathophysiology.[4-8,10] In addition, SLU is believed to be rare in some parts of the world where prevailing genetic factors such as the presence of alpha thalassemia and high fetal hemoglobin levels are thought to ameliorate its occurrence, thus highlighting possible roles for environmental and geographical factors.[6,8,11] Although some studies have been dedicated to the description of SLU,[4-8,10,12] very few studies have solely described SLU among the young SCD population.[11,12]

In Nigeria, there is scanty information on SLU among young SCD patients. Most of the previous studies were conducted among mixed populations of adults and children.[7,13,14] This leaves information on SLU among young SCD patients in the country largely unknown. This study was carried out on a cohort of young Nigerians with SCD. We aimed to corroborate or dispute whether SLU is related to some laboratory markers, SCD subphenotype(s), and sociodemographic factors. Findings from this study could help to improve the knowledge on factors influencing the occurrence of SLU phenotype among young Nigerian SCD patients.

Patients and Methods

This was a cross-sectional retrospective study conducted on 109 hydroxyurea-naïve children and adolescents with SCD in steady state and who are regular attendees at the pediatric hematology unit (PHU) of the Ekiti State University Teaching Hospital (EKSUTH), Ado Ekiti, Ekiti State, Southwest Nigeria, between April 2016 and July 2017. Sixty-seven healthy children who accompanied their siblings to the hospital served as controls. To qualify for inclusion, the SCD participants must have been on regular follow-up at the clinic for a minimum of 1 year before recruitment with up-to-date hospital records. Participants with confirmed or suspected to have other chronic health conditions apart from SCD were excluded. Also excluded were the few SCD patients on regular blood transfusion and/or hydroxyurea therapies as well as those whose caregivers declined to participate. SCD was initially diagnosed by hemoglobin electrophoresis and high-performance liquid chromatography (HPLC). Molecular analysis was conducted on DNA extracted from the patients to confirm the diagnosis of SCD by polymerase chain reaction (PCR) and direct sequencing.

Ethical considerations

Written informed consents of parents/caregivers were obtained. Furthermore, assents and consents of patients were obtained as applicable. The study was approved by the hospital's Institutional Ethics and Research Committee.

Data collection

Clinical, sociodemographic, and laboratory data

A tested chart review form was used to extract relevant information from the hospital records of participants regarding their steady state laboratory parameters and clinical events. Average of at least two steady state results of laboratory parameters performed between 3- and 6-month intervals by standard techniques was recorded for each participant. The laboratory parameters examined for both patients and controls included the complete blood count performed by Sysmex KX21N hematology analyzer (Sysmex Corporation, Kobe, Japan). Serum lactate dehydrogenase (LDH), bilirubin, alanine transaminase, and aspartate transaminase (AST) were measured with standard techniques. The quantitative assessment of HbF, HbA, HbA_2, HbS, and HbC was done by high-performance liquid chromatography (HPLC, Bio-Rad Variant D10, USA). Steady state was defined as being free from any acute event(s) for at least 1 month and transfusion free for at least 3 months.[1]

Details of the clinical events among the patients such as the presence of SLU and its evolution, overt osteonecrosis, overt stroke, priapism, and the number of bone pain crises requiring admission and/or administration of opioids within the preceding 1 year were obtained. The definitions of clinical events were as previously described.[15]

Other information retrieved from patients' charts included the biodata, and patients were classified into socioeconomic groups based on the educational level and occupation of the parents/caregiver.[16]

Data analysis

The Graph Pad Prism Program, version 5 for Windows (San Diego, California, USA) was used for the statistical

analysis. The normal distribution of the quantitative variables was verified by the Kolmogorov–Smirnov and Shapiro–Wilk tests. Continuous variables with nonnormal distribution were expressed in median and analyzed by the Mann–Whitney tests for comparison of two independent groups. Chi-square test or Fisher's exact test was used to compare categorical variables as applicable, and level of statistical significance was set at $P < 0.05$.

Results

The patients were made up of 101 HbSS (SCA) and 8HbSC. They consisted of 72 males and 37 females with median age of 9 and of range 2–21 years. The controls consisted of 40 males and 27 females and were made up of 22 sickle cell trait (HbAS) and 45 HbAA, with median age of 9, range 2–18 years. The SCD patients have been on follow-up for a median of 4 years, range 1.5–14 years. There were no differences in the sociobiographic data of patients and controls [Table 1].

Comparison of laboratory parameters between patients and controls

There were significant differences between the patients and controls in all laboratory parameters [Table 1].

Prevalence and description of leg ulcer among patients

In general, only 6 (5.5%; 6/109) patients had SLU (both active and healed), and they were all HbSS patients (three males and females each) with median age of 17, range 14–21 years, thus representing 5.9% of this group. The leg ulcers were completely healed in 3 (50%) after a median duration of 5 months (range 3–6 months), and yet to heal in the remaining three patients, two of whom are having recrudescence of their ulcers. A 21-year-old who was one of the two patients with recrudescence leg ulcers, also had overt stroke three months after her SLU recrudescence and was counselled for hydroxyurea treatment but never took the drug. Two of the three males with SLU also had priapism. The ulcers were located on the ankles in 5 (83.3%) and right big toe in 1 (16.7%). There was a preceding history of trauma in 4 (66.7%) and this included a case of traditional scarifications for local therapeutic purposes.

Comparison of laboratory parameters between sickle cell anemia patients with and without leg ulcer

Although the LDH, bilirubin, AST, platelet, and white blood cell counts of the patients with SLU were relatively higher compared to their peers without leg ulcer, these values did not attain statistical significance ($P > 0.05$). Similarly, the lower values of Hb, RBC, and HbF of the patients with SLU compared to their non-SLU HbSS counterparts did not attain statistical significance [Table 2].

Table 1: Biodemographic and laboratory parameters in patients and control

Parameters	Median (range)		*P*
	SCD patients (*n*=109)	Controls (*n*=67)	
Age (years)	9.0 (2.0-21.0)	9.0 (2.0-18.0)	0.8786[a]
Sex			
Male	72	40	0.3949[b]
Female	37	27	
Social class			
Upper	10	5	0.7050[b]
Middle	49	27	
Lower	50	35	
Laboratory markers			
Hb (g/dl)	7.5 (6.2-11.2)	11.6 (8.0-14.2)	<0.0001[a]
RBC (million cells/uL)	2.8 (1.8-4.8)	4.5 (2.5-6.5)	<0.0001[a]
MCV (fL)	80.9 (55.9-115.0)	79.0 (60.4-102.6)	0.033[a]
HbF (%)	8.4 (0.2-28.5)	0.8 (0-5.8)	<0.0001[a]
WBC ($\times 10^3$/uL)	12.6 (4.1-29.3)	6.6 (4.5-14.4)	<0.0001[a]
Platelet ($\times 10^3$/uL)	343.0 (108.0-832.0)	278.0 (117.0-591.0)	<0.0001[a]
LDH (IU/L)	771.4 (166.0-1860.0)	360.0 (150.0-993.0)	<0.0001[a]
AST (IU/L)	42.0 (12.0-89.0)	20.0 (6.0-75.0)	<0.0001[a]
ALT (IU/L)	20.0 (8.0-77.0)	10.0 (4.0-45.0)	<0.0001[a]
Total bilirubin (mg/dl)	1.8 (0.4-8.1)	0.4 (0.1-2.2)	<0.0001[a]

[a]Mann–Whitney test, [b]Chi-square test. Statistical significant *P* values are in bold fonts. SCD=Sickle cell disease; Hb=Hemoglobin; RBC=Red blood cell; MCV=Mean corpuscular volume; WBC=White blood cell; HbF=Fetal hemoglobin; LDH=Lactate dehydrogenase; AST=Aspartate transaminase; ALT=Alanine transaminase

Table 2: Laboratory parameters in sickle cell anemia patients with and without leg ulcer

Parameters	SCA with leg ulcer (*n*=6)	SCA without leg ulcer (*n*=95)	*P*
Hb (g/dl)	7.1 (6.2-8.1)	7.5 (6.3-10.1)	0.3356[a]
RBC (million cells/uL)	2.5 (2.0-2.8)	2.8 (1.8-4.8)	0.067[a]
HbF (%)	7.1 (3.7-10.7)	9.4 (0.9-28.5)	0.377[a]
WBC ($\times 10^3$/uL)	14.5 (10.0-21.3)	13.2 (6.1-29.3)	0.4421[a]
Platelet ($\times 10^3$/uL)	473.5 (207.0-669.0)	361.0 (108.0-832.0)	0.247[a]
LDH (IU/L)	972.0 (681.7-1682.0)	800.0 (197.0-1860.0)	0.095[a]
AST (IU/L)	40.0 (35.0-56.0)	36.0 (7.0-89.0)	0.1541[a]
Total bilirubin (mg/dl)	2.1 (1.3-4.1)	1.8 (0.4-8.1)	0.570[a]

[a]Mann–Whitney test. Statistical test. SCA=Sickle cell anemia; Hb=Hemoglobin; RBC=Red blood cell; WBC=White blood cell; HbF=Fetal hemoglobin; LDH=Lactate dehydrogenase; AST=Aspartate transaminase

Table 3: Associations between leg ulcer phenotype, clinical events, and biodemographics of sickle cell anemia patients

Parameters	SCA with leg ulcer (*n*=6)	SCA without leg ulcer (*n*=95)	*P*
Age (years)	17.5 (14.0-21.0)	9.0 (2.0-18.0)	0.0002[a]
Sex			
Male	3	64	0.4016[b]
Female	3	31	
Social class			
Lower	6	42	0.0097[b]
Others (upper and middle)	0	53	
Clinical events			
Bone pain crisis (VOC)	0.5 (0-1.0)	2 (0-6.0)	0.0382[a]
Osteonecrosis	1	4	0.2686[b]
Stroke	1	3	0.2203[b]
Priapism (males only total number=67)	2 (*n*=3)	3 (*n*=64)	0.0132[b]

[a]Mann–Whitney test, [b]Fisher's exact test. Statistical significant *P* values are in bold fonts. SCA=Sickle cell anemia; VOC=Vaso-occlusive crises

Associations between leg ulcer phenotype, clinical events, and sociodemographic data of sickle cell anemia patients

The patients with SLU were relatively older compared to their peers: median age, 17.5 years (14–21) versus 9 years (2–18), $P = 0.0002$. They were all from the low socioeconomic class: low class 6 (12.5%) versus others (middle and upper) 0 (0%), $P = 0.0097$. They had less bone pain episodes ($P = 0.038$) and the males among them were more associated with priapism ($P = 0.0132$). However, the occurrence of leg ulcer was not differentiated by the sex of the patients, presence of overt stroke and/or osteonecrosis ($P > 0.05$) [Table 3].

Discussion

Although improved treatment strategies such as vaccinations and prophylaxis against infections, transfusion services, use of hydroxyurea, and other supportive cares have favorably influenced the prognostic outlook of SCD, SLU still remains a worrisome complication of the disease.[7,8,10]

There is scarcity of information on SLU among young Nigerian patients with SCD despite the huge burden of SCD in the country and this makes comparison of data difficult. Although fewer in number than their HbSS counterparts, the finding that none of the patients with HbSC genotype had SLU is in support of earlier reports from other parts of the world that SLU is not common among this group of SCD patients.[6,8,10,12]

Similarly, the finding that most cases of SLU were preceded by trauma as well as the sites/locations of the leg ulcers among patients in this study are in agreements with previous reports.[8,10,17,18]

However, the observation that SLU occurred as a result of local and unorthodox therapeutic scarification in a child in this study is a rare occurrence that may not be unconnected with the strong belief of Africans in some traditional practices that may be inimical to the health of children. In some cases, these may be deleterious to the health of the patient with SCD[18] as found in this case or constitute some forms of child abuse.[19] This raises the need for more education of caregivers to desist from some local and African traditional practices that could be inimical to the health of their wards.

Similar to previous local[17] and international reports,[8,10,12] the occurrence of leg ulcer among our patients is not common within the first decade of life. Furthermore, the 6% prevalence of leg ulcer in this study is very similar to the 5% among the children in the USA[12] and between 5.4% and 7.6% described locally by Akinyanju and Akinsete[17] and Idaewor *et al*.,[14] respectively, in their studies of mixed populations of both children and adults from Western Nigeria.

However, this is higher than the 1.3% found among children from Southeast Nigeria[13] and 2.6% among

the pediatric cohorts of a mixed study comprising both adults and children in Brazil.[20] Nonetheless, it is lower than the prevalences of 27% and 22% found by Madu *et al*.[7] and Bazuaye *et al*.,[18] in their mixed studies of both children and adults from Eastern and Southern Nigeria, respectively. Similarly, it is lower than the 75% described from groups of children and adults in Jamaica.[21] These observations suggest that the occurrence of leg ulcer varies from place to place. The studies by both Belini Junior *et al*.[20] and Serjeant[21] clearly demonstrated that the prevalence of SLU increases with age. However, the apparently lower prevalence of SLU among the Brazilian children[20] could be because of the use of hydroxyurea by some of the children in the study as none of ours was on this drug. Hydroxyurea is known to ameliorate the severity of SCD and reduce the occurrence of leg ulcer through its induction of HbF and lessening of hemolysis in SCD patients.[20] As noted, none of our participants was on treatment with this drug.

In addition, the findings of association of leg ulcer with low socioeconomic condition in this study is in tandem with observations by Minniti and Kato[8] and Cumming *et al*.[10] that poor socioeconomic status is a risk factor for leg ulcer among SCA patients. The exact link between SLU and socioeconomic level has not been described, but it could be speculated that general lack of care and inadequate or poor nutrition with possible worsening anemia that are generally associated with poor socioeconomic status could be contributory. These could lead to increased neglect and decreased wound healing tendencies. The lack of sex predilection for leg ulcer in the current study has been reported among Nigerians[14] and patients in other parts of the world.[5] However, one Nigerian study[17] found a male preponderance.

Several researchers have attempted to classify SLU.[4-7,20] Some authors thought it is associated with very severe phenotype of SCD.[4-6,20] On the contrary, others have argued that SLU is probably not related to very severe SCD phenotype.[7] However, there is a general consensus that SLU is closely associated with hemolysis intensity and some other hemolysis-related phenotypes of SCA such as priapism, stroke, and pulmonary hypertension.[4-6,20-22]

Due to lack of facilities, we could not confirm the diagnosis of pulmonary hypertension among our patients. In addition, only few patients with overt stroke were diagnosed, and there is therefore the possibility of missing cases of silent infarcts. Nonetheless, priapism in the male SCD patients in this study is associated with SLU, thus suggesting the possibility of higher hemolysis in those affected with both leg ulcer and priapism.

Furthermore, although not statistically significant, we observed a trend of higher LDH, AST, and bilirubin among the SLU group while their Hb and HbF were lower, compared to those without SLU. This is suggestive of possible higher hemolysis in the leg ulcer group. That these differences did not attain statistical significance might be due to the sample size of this study given that some larger studies have reported association of hemolysis markers with leg ulcer in SCA patients.[4,6,7,22]

In this study, we found that the SLU patients had less episodes of painful crises (vaso-occlusive crises [VOC]), which is in keeping with findings by previous authors[7,23] and suggests that the two complications (SLU and VOC) are distinct phenotypes. This supports the hypothesis that while VOC is related to blood rheology/viscosity-associated complications,[24,25] the SLU is linked to hemolysis.[4-8,22]

This study, being from a single center, is limited by size. The apparently fewer complications attributable to SCD phenotypes could be due to the fact that the study participants were children who were relatively young and as such yet to develop some of SCD complications. Despite these limitations, this study was able to show that SLU is not uncommon among children with the HbSS genotype, i.e. SCA. In addition, some sociodemographic and clinical associates of SLU were found.

Conclusion

This study showed that SLU occurs among young Nigerian SCD patients with HbSS genotypes, poor socioeconomic background, and in older children. In addition, this study suggests that SLU is not related to the VOC phenotype but rather more related to hemolysis-associated SCD phenotype of priapism thus supporting the previous hypothesis that SLU is a distinct phenotype that is probably not related to blood viscosity/rheology complications of SCD. There is need for more studies on the SLU phenotype among young SCD patients to fully understand how this phenotype affects children with SCD.

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Conflicts of interest

There are no conflicts of interest.

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