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RESEARCH ARTICLE

Determinants of splenic preservation among patients with sickle cell disease in North-Eastern Nigeria

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Abstract

Objective: In patients with sickle cell disease (SCD), the spleen commonly enlarges during early childhood, but undergoes reduction in size and fibrosis from repeated episodes of vaso-occlusion and infarction. The rate of progression of this process varies markedly among these patients. The aim of current study was to explore clinical and laboratory factors associated with the preservation of the spleen among these patients.

Methods: Two hundred four patients with SCD (103 females; age 1–45 years) underwent abdominal ultrasonography at the University of Maiduguri Teaching Hospital, Nigeria between October 2020 and November 2021 to assess for splenic visualisation and echotexture. Steady-state clinical parameters and blood samples for full blood count, serum chemistry, high-performance liquid chromatography and malaria parasitemia were obtained from all the patients.

Results: The spleen was visualised in 107 (52.4%; 95% confidence interval [CI], 46%–59%) patients with SCD on ultrasonography. While the spleen was visualised in all children less than 5 years of age, it was visualised in only 23.5% of those aged 15 years and older. Visualisation of the spleen was significantly associated with low mean corpuscular haemoglobin concentration and high haemoglobin F (HbF) in those younger than 10 years. The odds of visualisation of the spleen on ultrasonography increased by a factor of 1.17% for every 1% increase in HbF level. Only 32 (15%) patients were on regular hydroxyurea therapy. The HbF level was significantly higher among patients on hydroxyurea (median 12.7 vs. 7.4; $p < 0.0001$).

Conclusion: In patients with SCD, failure to visualise the spleen was not found in children less than 5 years old. Patients with visualised spleens had a higher level of HbF than those with non-visualised spleens. HbF was significantly associated with visualisation of the spleen before 10 years of age. Since early administration of hydroxyurea will increase HbF level, we expect that it would help to preserve the spleen.

KEYWORDS
haemoglobin F, hydroxyurea, sickle cell disease, spleen, ultrasonography

INTRODUCTION

Sickle cell disease (SCD) is an inherited condition characterised by recurrent haemolytic and vaso-occlusive episodes leading to acute and chronic tissue ischaemia, infarction and chronic organ damage [1]. The spleen is one of the organs affected by SCD early in life with evidence of hyposplenism present in the first 12 months of life [2–4]. The spleen acts as a filter in the bloodstream by removing old or damaged red cells, foreign bodies and microorganisms that have gained access to blood. In SCD, the high number of damaged red cells may clog up this filter, causing an initial enlargement and later progressive splenic fibrosis. A detailed description of this process was first published by Diggs [5]. During early childhood, the spleen is

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enlarged because of congestion of the reticular space with large numbers of sickled red cells and dilation of the capillaries in the white pulp. By late childhood, repeated episodes of vascular occlusion and infarction result in the progressive destruction and contraction of the spleen, which eventually becomes a small, wrinkled mass of fibrous tissue [5]. Furthermore, splenic function is usually lost early in life even in the presence of an enlarged spleen (functional asplenia) [4]; the loss of splenic function puts the patients at increased risk of infection with encapsulated bacteria, which can be prevented by penicillin prophylaxis and immunisation [6, 7].

In the majority of patients, vaso-occlusive events in the spleen are clinically silent and the rate of progression of this process varies markedly among individuals with the disease [8]. Also, the sequence of events may be modified in different geographic areas by the frequency of other genetic factors, *HBB* haplotypes, and environmental factors [9]. In a large Jamaican cohort followed from birth, 64% of children aged 9–17 years had visualised spleens on ultrasonography [10]. The higher level of haemoglobin F (HbF), greater frequency of alpha thalassemia and Asian haplotype in some Arab and Indian populations with SCD results in persistence of the spleen into adulthood [11–13]. Malaria endemicity may promote the persistence of the spleen; the spleen was palpably enlarged up to adulthood among 15%–35% of patients with SCD in studies from Southern Nigeria [14, 15]. Also, within a particular region, the spectrum of events may differ from one locality to another; for instance, in Nigeria, the spleen size varies among patients with SCD in the North compared to those in the Southern part [16].

In the current study, we determined the frequency of patients with SCD with spleens present or absent based on ultrasonography across various age groups. We assessed factors that could potentially influence the persistence of the spleen and may be useful to improve their management including haematological parameters, HbF, hydroxyurea therapy, and malaria parasitaemia. We also investigated whether clinical makers associated with disease severity were associated with the persistence of the spleen.

MATERIALS AND METHODS

Study design and participants

The cross-sectional study was conducted between October 2020 and November 2021. Participants with SCD attending outpatient clinics of the paediatric and adult haematology departments of the University of Maiduguri Teaching Hospital (UMTH), Nigeria, considered to be in steady state were invited to participate [17]. The patients were divided into four age groups 1: 1–4 years; 2: 5–9 years; 3: 10–14 years and group 4: 15 years and older. Patients were excluded if they have any current illness, a known inflammatory disease or have received blood transfusion in the last 3–4 months.

Routine clinical data and laboratory analysis

At enrolment, a case report form was used to obtain demographic characteristics and self-reported medical history from the patients (or their carers) including frequency of hospitalisation, febrile episodes and painful crises over the preceding year and history of current hydroxyurea therapy. Whole peripheral blood was collected from all the patients into plain tubes and ethylenediamine tetra-acetic acid-containing tubes. Haemoglobin phenotype was performed by ion-exchange high-performance liquid chromatography on an automatic analyser (Bio-Rad). Full blood counts were performed with the use of an automated analyser (Siemens). Reticulocytes were counted using the standard method with new methylene blue staining [18]. Biochemical tests were performed using a chemical analyser (Hitachi Cobas C311, Roche Instrument Centre). Malaria parasitemia was confirmed using Giemsa-stained thick and thin films following standard methods [19].

Sonographic evaluation

A board-certified radiologist with more than 15 years' experience in abdominal sonography performed all the examinations using Logic P5 Premium BT11 ultrasound scanner (GE Medical Systems) equipped with a low frequency (3–5 MHz) curvilinear transducer. The patients were asked to lie down in a supine position or right lateral position when optimal images were not achieved in the supine position. The oblique intercostal approach was adopted for all patients because this view provides an optimal window for good visualisation of the spleen in most patients. The radiologist assessed the presence or absence of the spleen and the parenchyma for homogeneity and focal abnormalities.

Ethical considerations

The study was carried out according to the Declaration of Helsinki. The study protocol was approved by the University of Maiduguri Teaching Hospital (UMTH/REC/20/606) and Liverpool School of Tropical Medicine (LSTM; REC reference number: 20-010) Ethics Review Boards. A signed, written informed consent was obtained from the adults and parents/guardians of the paediatric participants upon recruitment.

Statistical analysis

The data were analysed using Statistical Package for the Social Sciences (SPSS) (version 25; SPSS). Categorical data were summarised using frequency and proportions, and continuous data using descriptive statistics. Comparison between gender group was performed using Mann–Whitney test, and between age and Hb phenotype groups using the Kruskal–Wallis tests. Factors associated with visualisation of

the spleen were determined using logistic regression. The goal of the analysis was to identify independent clinical and laboratory factors associated with visualisation or non-visualisation of the spleen on ultrasonography. Univariate regression analysis was performed on all variables of interest to obtain the candidate variables and their significance, which were included in the full model. The model effect was determined using the Robust estimator which allows for reliable estimates under a wider range of conditions. The Beta coefficient (logarithmic odds ratios [ORs]) generated was transformed to normal ORs, so that reported ORs and 95% CIs were more clinically meaningful. The level of significance was set at the two-tailed p value < 0.05.

RESULTS

Demography and clinical characteristics of the study population

A total of 214 patients with SCD were enrolled in the study; however, only 204 of these participants presented for the ultrasonography (95.3%), while 10 patients failed to turn up. The general characteristics and baseline laboratory data of the patients are summarised in Table 1. The median age was 12.5 years (25th–75th percentile: 7–22 years). The Hb phenotypes consisted of homozygous sickle cell disease (HbSS) ($n = 196/204$; 96.1%), sickle-haemoglobin C disease (HbSC) ($n = 5/204$; 2.4%) and sickle cell β-thalassaemia (Hb Sβ) thalassemia ($n = 3/204$; 1.5%). In the year preceding the start of the study, the majority of the patients had more than one episode of fever (90.2%) or painful crises (58%), and 32.7% of patients had been hospitalised. Thirty-two (15%) patients had been taken hydroxyurea regularly over the preceding 12 months, whereas 10 patients previously on treatment with hydroxyurea stopped using it for various reasons including side effects and financial constraints; the remaining patients had never heard of the drug ($n = 162$). The majority of the study participants showed a high compliance for the use of bed nets (84.8%) and were on regular antimalaria chemoprophylaxis (78.9%) with proguanil. History of completion of routine immunisation obtained from parents or guardians of the younger patients showed a high compliance, whereas most of the older patients were unsure of their immunisation history during childhood.

Frequency of splenic visualisation on ultrasonography based on age, gender and genotype

The spleen was visualised in 107 (52.4%; 95% confidence interval [CI], 46%–59%) patients with SCD. The frequency of non-visualised spleens increased with age from 0% in all the children less than 5 years to 76.5% in those aged ≥15 (Figure 1). There was no difference in visualisation of the spleen by gender ($p = 0.091$) or Hb phenotype ($p = 0.691$).

TABLE 1 Characteristics of the studied population ($n = 204$).

Variable	Median (25th–75th percentile) or %	Min–max	Observation (n)
Gender (male/female), n	101/103		204
Age (years)	12.5 (7–22)	1.1–45	204
Hb phenotype	196 (96.1)		
HbSS, n (%)	5 (2.4)		204
HbSC, n (%)	3 (1.5)		
HbSB thal, n (%)			
Age group			
Less than 5 years, n (%)	42 (20.6)		204
5–9 years, n (%)	35 (17.1)		
10–14 years, n (%)	42 (20.6)		
15 years and older, n (%)	85 (41.7)		
Clinical parameters			
Hospitalisation over last 12 months	0 (0–1)	0–5	204
Febrile episodes over last 12 months	2.0 (1–3)	0–12	204
Painful crisis over last 12 months	2.0 (1–3)	0–12	204
Proportion of patients on regular Hydroxyurea, n (%)	32 (15.7)		204
Proportion of patients on regular antimalaria prophylaxis	161 (78.9)		204
Proportion of patients using bed net	173 (84.8)		204
Routine immunisation completed			
Yes	94 (46.1)		
No	21 (10.3)		
Not sure	89 (43.6)		204
Proportion of patients on penicillin prophylaxis[a]	2 (4.8)		42
Laboratory parameters			
WBC count ($\times 10^3/\mu L$)	13.0 (10.8–16.3)	3.2–34.0	202
Haemoglobin (g/dL)	7.3 (6.4–8.3)	3.2–14.2	203
Platelets ($\times 10^6/\mu L$)	377 (274–514)	53.0–854.0	203
Reticulocytes (%)	15.0 (8–25)	0.0–40.0	179
MCV (fL)	83.2 (77–89)	55.0–118.0	202
MCH (pg)	28.9 (27–31)	18.3–39.0	203
MCHC (g/day)	35 (33–36)	30.0–39.0	203
Bilirubin (total) (μmol/L)	30 (19–46)	7.0–151.0	176
ASAT (μmol/L)	15 (10–28)	3.0–89.0	176
HbF (%)	8.7 (4.8–13.7)	0.8–33.3	182
HbA_2 (%)	3.3 (2.7–3.8)	2.7–3.8	143
Malaria parasite positive, n (%)	49 (31)		158

Note: Continuous variables are presented as median, interquartile range, while categorical variables are presented as absolute (n) and relative (%) frequency.
Abbreviations: ASAT, aspartate amino transferase; Hb, haemoglobin; MCH, mean corpuscular haemoglobin; MCHC, mean corpuscular haemoglobin concentration; MCV, mean corpuscular volume; WBC, white blood cell.
[a]Data obtained among the less than five years only.

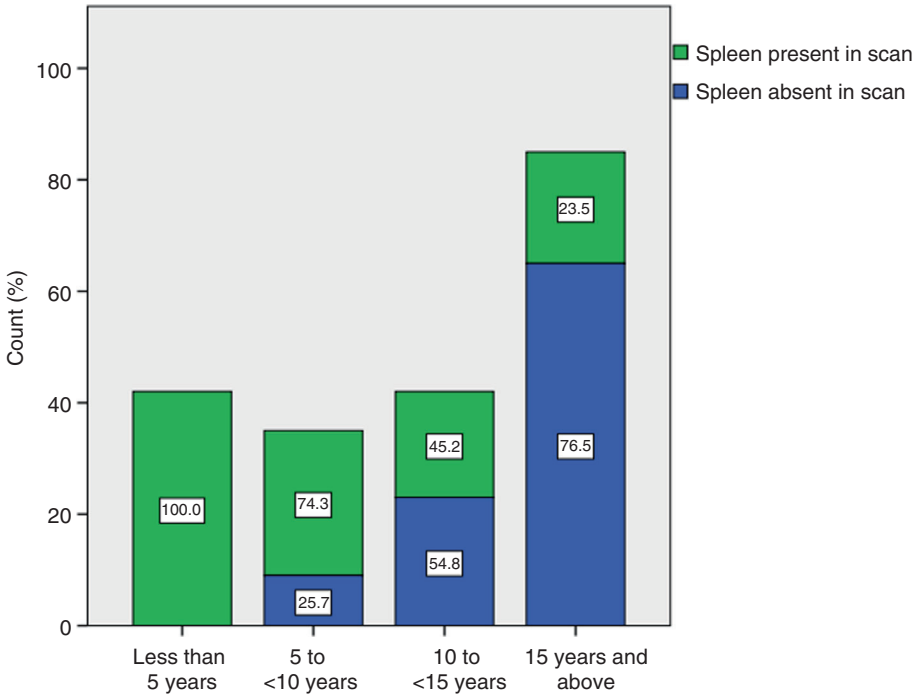

FIGURE 1 Prevalence of visualised or non-visualised spleens on ultrasonography. Stacked chart showing frequency of visualised or non-visualised spleens across age groups among patients with SCD ($n = 204$). The frequency of non-visualised spleen increased with increasing age. SCD, sickle cell disease.

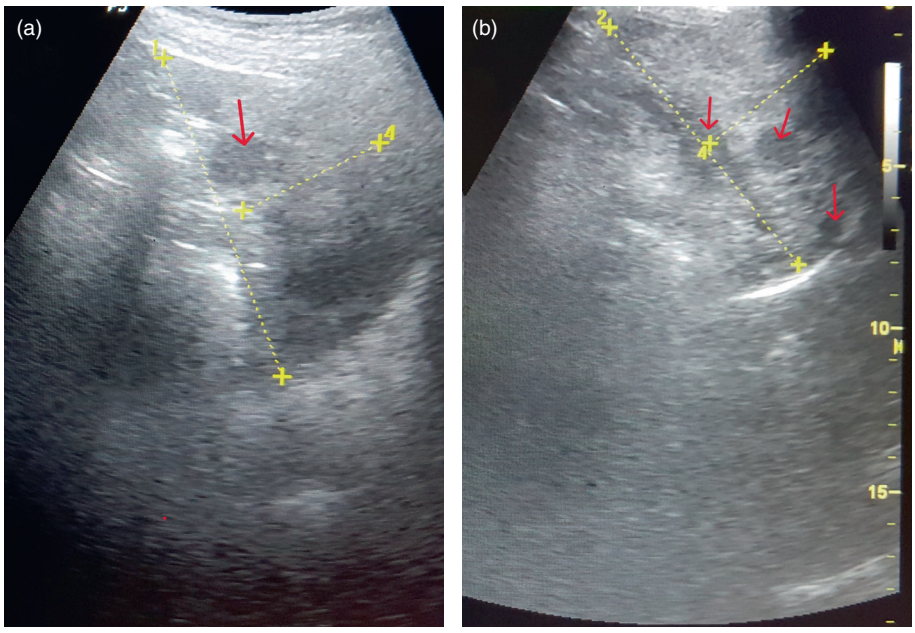

FIGURE 2 Abdominal ultrasonography showing splenic nodules among patients with SCD. (a) (left) Solitary intrasplenic nodule in a 14-year-old male with HbSS. Longitudinal view of the spleen on ultrasonography shows a round hypoechoic nodule close to the hilum (red arrow) and measures up to 2 cm. (b) (right) Transverse view of the spleen showing multiple hypoechoic nodules (red arrows) in a 24-year-old female with HbSS. SCD, sickle cell disease.

Spleen parenchymal echotexture on ultrasonography

The spleen echotexture was normal in 93 (86.9%) patients and increased in 8 (7.5%), while 6 patients (5.6%) had heterogeneous and coarse-appearing spleens with nodules of varying sizes and numbers (Figure 2a,b). Individuals from the age groups 5–9 and 10–14 years had more heterogeneous-appearing spleens and a higher frequency of splenic nodules than patients with SCD younger than 5 years or older than 15 years.

TABLE 2 Unadjusted odd ratios for associations with spleen visualisation or non-visualisation on ultrasonography.

Variables	Spleen not visualised. ($n = 97$)	Spleen visualised ($n = 107$)	OR (95% CI)	p Value
Male, n/n (%)	42/97 (43.3)	59/107 (55.1)	0.62 (0.36–1.08)	0.092
Laboratory parameters				
WBC count, $\times 10^3/\mu L$, mean (SD)	13.4 (3.5)	13.8 (5.2)	1.02 (0.96–1.09)	0.454
Hb, g/dL, mean (SD)	7.0 (1.6)	7.8 (1.7)	1.38 (1.14–1.66)	0.001*
MCV, fL, mean (SD)	84.1 (8.5)	81.9 (9.7)	0.97 (0.94–1.00)	0.115
MCH, pg, mean (SD)	29.5 (3.5)	27.9 (3.6)	0.88 (0.80–0.96)	0.006*
MCHC, g/dL, mean (SD)	35.1 (1.7)	34.1 (1.7)	0.70 (0.58–0.85)	0.0001*
Platelets, $\times 10^6/\mu L$, mean (SD)	445.5 (163.3)	348.8 (161.9)	0.99 (0.99–0.99)	0.0001*
Reticulocytes, %, mean (SD)	8.7 (4.7)	8.0 (5.2)	0.97 (0.92–1.02)	0.364
HbF level, %, mean (SD)	7.5 (5.2)	12.2 (7.4)	1.13 (1.06–1.19)	0.0001*
HbA_2 level, %, mean (SD)	3.6 (1.5)	3.2 (0.8)	0.67 (0.46–0.98)	0.039*
Malaria parasite positive, n/n (%)	14/68 (20.6)	35/90 (38.9)	2.45 (1.19–5.07)	0.015*
Clinical parameters				
Proportion of patients on Hydroxyurea, n/n (%)	9/97 (9.3)	23/107 (21.5)	2.68 (1.17–6.12)	0.020*
Hospitalisation over last 12 months, mean (SD)	0.38 (0.8)	0.63 (0.9)	1.42 (0.99–2.03)	0.057
Febrile episodes, mean (SD)	2.68 (2.3)	2.52 (1.7)	0.96 (0.84–1.01)	0.573
Vaso-occlusive crisis, mean (SD)	2.43 (2.7)	2.52 (2.7)	1.01 (0.91–1.12)	0.811

Note: Continuous variables are presented as mean ± standard deviation (SD), while categorical variables are presented as absolute (n) and relative (%) frequency. OR indicates the odds ratio for patients with spleen visualised or not visualised on scan. Patients with non-visualised spleens were used as the reference category.
Abbreviations: CI, confidence interval; Hb, haemoglobin; HbF, haemoglobin F; MCH, mean corpuscular haemoglobin; MCHC, mean corpuscular haemoglobin concentration; MCV, mean corpuscular volume; SD, standard deviation. WBC white blood cell.
*All p values were less than 0.05.

TABLE 3 Adjusted odd ratios (ORs) for associations with spleen visualisation or non-visualisation on ultrasonography.

Parameter	Co-efficient (standard error)	Adjusted OR (95% CI)	p Value
Hb, g/dL	0.07 (0.2)	1.07 (0.78–1.46)	0.675
MCH, g/dL	−0.16 (0.1)	0.86 (0.72–1.02)	0.077
MCHC, pg	−0.37 (0.2)	0.69 (0.47–0.99)	0.049*
Platelets, $\times 10^6/\mu L$	−0.00 (0.0)	0.99 (0.99–1.00)	0.274
HbF level, %	0.15 (0.1)	1.17 (1.05–1.29)	0.003*
HbA_2 level, %	−0.29 (0.4)	0.75 (0.35–1.58)	0.447
Malaria parasite positive	0.94 (0.9)	2.55 (0.96–6.75)	0.060
Hydroxyurea intake	0.61 (0.7)	1.84 (0.42–7.99)	0.418

Note: OR indicates the odds ratio for patients with spleen visualised or not visualised on scan. Patients with non-visualised spleens were used as the reference category.
Abbreviations: CI, confidence interval; Hb, haemoglobin; HbF, haemoglobin F; MCH, mean corpuscular haemoglobin; MCHC, mean corpuscular haemoglobin concentration.
*All p values were less than 0.05.

Association of clinical and laboratory factors with splenic visualisation on ultrasonography

Factors that were significantly associated with visualisation of the spleen on univariate logistic analysis included increased HbF and haemoglobin, decreased levels of platelets, decreased HbA_2, decreased red cell indices (MCH, MCHC), positive malaria parasitaemia, and history of hydroxyurea therapy (Table 2). On multivariate logistic regression analysis, only HbF (OR, 1.17, 95% CI, 1.05–1.29; $p = 0.003$) and MCHC (OR, 0.69, 95% CI, 0.47–0.99; $p = 0.049$) remained significantly associated with spleen visualisation (Table 3). The odds of visualisation of the spleen on ultrasonography increased by a factor of 1.17% for every 1% increase in HbF level. A subgroup analysis was performed to determine the influence of HbF across the various age groups; as the spleen was visualised in all children less than 5 years, the analysis was confined to the remaining age groups. HbF was significantly associated with visualisation of the spleen among the 5–9 years group (OR, 1.29, 95% CI, 1.03–1.62; $p = 0.028$), but not among the 10–14 years age group (OR, 1.29, 95% CI, 0.93–1.14; $p = 0.591$) or those above 15 years (OR, 1.03, 95% CI, 0.94–1.14; $p = 0.488$). Sex and clinical parameters including frequencies of hospitalisation, painful crises and febrile episodes, had no association with splenic visualisation (Table 2). Only 32 (15%) patients were on regular hydroxyurea; the HbF% level was significantly higher among these patients compared to the patients not on hydroxyurea (median 12.7% vs. 7.4%; respectively; $p < 0.0001$).

DISCUSSION

We have documented the visualisation or non-visualisation of the spleen across various age groups among patients with

SCD using ultrasonography. Factors associated with the preservation of the spleen were also explored. In our study, the spleen was visualised on ultrasonography among all the children under 5 years, but declined in prevalence with successively older age groups, so that only about a quarter of patients had their spleens visualised on ultrasonography after the age of 15 years. A similar pattern was noted recently among a large Jamaican birth cohort of patients with SCD ($n = 2138$); non-visualised spleens increased with age from 34% in those aged 6.0–7.9 years to 72% in those aged 24 years and older [20]. In contrast, a study among SCD children in the United Kingdom ($n = 100$) showed that only 5.6% of children aged 6–10 years and 19.4% of children aged 11–16 years had no visible spleen on ultrasonography [21]. Our current observation that the spleen was visualised in some patients and not in others within each of the age groups indicates the variability in the rate of progression of splenic injury among patients with SCD.

The overall prevalence of patients with non-visualised spleens in our study was 47.2%. This is similar to previous reports from Northern Nigeria (32%–36%) [22, 23] and Sudan (47.8%) [24], but contrasts with the lower rates reported from South-East (23%–33%) [25–27] and South-West Nigeria (0%–11%) [14, 28, 29], and among patients with SCD in the Democratic Republic of Congo (6.7%) [30]. The frequency of non-visualised spleens in our study was also similar to those reported in patients with SCD in Turkey (42.9%) [31] and the United States (35.7%) [32]. Lower frequencies have been found in Asia (11%) [33], the Middle-East (6.1%) [12] and the United States (9%) [21]. The variability of splenic non-visualisation on ultrasonography in the different geographic location may partly be explained by the presence of genetic factors known to inhibit sickling, such as alpha-thalassaemia and HbF [11, 20], improvement in clinical care and outcomes in SCD [21, 32], and also environmental factors that results in the frequent exposure to organisms known to cause spleen enlargement including malaria and bacterial infections [34, 35].

Splenic parenchymal appearances

An abnormal pattern and splenic nodules were more frequent among our patients in the age groups 5–9 and 10–14 years; discreet hypoechoic nodules were seen in 5.6%, and in some cases, the nodules were multiple. Splenic infarcts may appear wedge-shaped or as rounded hypoechoic areas on ultrasonography [36]. None of the patients had symptoms related to the spleen at the time of our examination. A similar age pattern has been observed in children and adolescents with SCD in Nigeria [26] and the United States [32]. An abnormal splenic echotexture may represent the severity and frequency of vaso-occlusion [36]. Similar lesions have been reported at comparable rates among patients with SCD in Sudan (7.8%) [37] and in Turkey (6.0%) [31].

Clinical and laboratory factors associated with splenic visualisation on ultrasonography

HbF was associated with preservation of the spleen among our patients with SCD; however, this association was only significant in patients less than 10 years. HbF was significantly higher among patients whose spleens were visualised compared to those without splenic visualisation. It has been suggested that the high HbF level inhibits HbS polymerisation and consequently reduces the number of irreversibly sickled cells [38]. This slows down the rate of splenic fibrosis. Only a few studies have evaluated the association of preserved spleens on ultrasonography and the level of HbF. One of these studies from South-West Nigeria among children with SCD demonstrated higher levels of HbF in children with visualised spleens compared to those without visible spleens ($p = 0.012$) [39]. Similarly, studies among patients with SCD in Saudi Arabia and Jamaica have demonstrated high HbF levels in patients with visualised spleens compared to those without visible spleens on ultrasonography [12, 20]. Other studies from Africa [40–42] which all used abdominal palpation to detect splenomegaly, found no relationship between the presence of palpable spleens and HbF. Manual palpation is less sensitive than ultrasonography for evaluating the presence or absence of the spleen; this may be because the spleen is not palpable until it is two to three times its normal size [43].

The mean corpuscular haemoglobin concentration (MCHC) showed borderline association with visualisation of the spleen in our study; values were lower in patients with spleens that were visualised on ultrasonography. This is similar to a previous study among SCD in South-West Nigeria [44]. Concurrent alpha thalassemia may be partly responsible for the low MCHC observed in our study population; however, this could not be verified because the study was not designed to assess the co-inheritance of alpha thalassemia. Alpha thalassemia trait is common (36%–54% of the population) in individuals of West and East African origin [45–47]. Furthermore, studies among patients with SCD in Africa have shown a high prevalence of alpha thalassemia trait (37% and 46%) [48–50]. The effect of reduced alpha globin production is manifest by reduced mean corpuscular volume (MCV) and MCHC, both of which are likely to reduce intravascular sickling [51]. The mean MCHC varied considerably among patients with SCD in a Jamaican cohort, with the lowest values occurring in those with homozygous (α−/α–) alpha thalassemia 2 and high values in those without the trait. The low MCHC inhibits HbS polymerisation; consequently, there is lower rate of haemolysis, higher haemoglobin level and persistence of splenomegaly [52]. In another study, patients with homozygous (α−/α–) alpha thalassemia 2 had significantly lower MCHC, MCH, MCV, decreased levels of markers of haemolysis and more had splenomegaly than patients with a normal alpha-globin-gene complement (αα/αα); heterozygotes (α−/αα) for alpha thalassemia had intermediate values [53].

Studies examining the relationship between malaria parasitemia and splenomegaly in patients with SCD have produced contradictory results. In our study, significantly more patients with SCD with visualised spleens had asymptomatic *Plasmodium falciparum* parasitaemia than those whose spleens were not visualised ($p = 0.015$), but this association just failed to reach statistical significance after adjusting for other laboratory parameters ($p = 0.060$). The use of regular anti-malaria chemoprophylaxis and bed nets among our patients with SCD was high and had no effect on the frequency of malaria parasitemia (data not shown). A study among children with SCD from South-East Nigeria found a higher malaria parasite density among patients with splenomegaly and normal spleen sizes compared to those whose spleens were not visualised on ultrasonography [54]. The significant reduction in spleen size following treatment with antimalarial over a 6-month period among children with SCD in South-West Nigeria suggests that malaria may contribute to more frequent and marked splenomegaly ($p = 0.01$) [34]. In contrast, a study among children from South-West Nigeria found no significant relationship between the spleen size on ultrasonography and malaria parasitemia ($p = 0.469$) [39]. Other reports among patients with SCD in Nigeria [41], Kenya [55], and Tanzania [56] found no relationship between spleen size on palpation and malaria parasitemia. In view of the possibility of multiple and interrelated factors that may act as confounders, the exact role of malaria in influencing spleen size still remains to be elucidated in patients with SCD.

No significant difference was observed in the frequency of febrile episodes and vaso-occlusive crises among patients with visualised spleens compared to those with non-visualised spleens in our study. This is unexpected because with fibrosis of the spleen, and associated hyposplenism, there is increased susceptibility to infections which would be likely to increase febrile episodes, painful crisis, hospitalisation and blood transfusion. Rather, we noted more patients with visualised spleens had been admitted to the hospital over the last 12 months compared with patients with non-visualised spleens, although the difference just failed to reach statistical significance ($p = 0.057$). It is possible that frequent infections (including malaria) may cause hyperplasia of the reticulo-endothelial system of the spleen and subsequent splenic enlargement.

Only a few patients were on hydroxyurea (15%) in our study, we noted a higher HbF level among these patients and a trend towards increased visualisation of the spleen compared to the non-hydroxyurea group; however, this did not reach statistical significance, potentially due to a lack of power. Hydroxyurea induces production of HbF and has been used as a disease-modifying agent in SCD over the past three decades [57]. In view of the limited effect of HbF on the presence of the spleen beyond 10 years of age observed in this study, commencing hydroxyurea early may be beneficial for preservation of the spleen. Hydroxyurea is included in the WHO Model Lists of Essential Medicines for the treatment of SCD [58]; however, in a recent cross-sectional study involving physicians, nurses/counsellors, patients and caregivers at 13 different health facilities in Nigeria, the authors demonstrated that the uptake of hydroxyurea was limited by provider prescription practices and patient adherence [59]. The issue of cost and availability also played an important role in the utilisation of the drug; the cost for a pack of 100 tablets of Hydroxyurea (~$40) cannot be afforded by most Nigerians [59]. Therefore, subsidising the cost of hydroxyurea or providing it free of charge may pave the way for wider access and may provide a simple and inexpensive oral medication that can alter the progressive splenic damage associated with SCD and help preserve the spleen.

This study was limited by being a single-center, hospital-based study which may affect the generalisability of our findings as some patients from the rural community may not have been included in the study. Although we have obtained data on the prevalence of patients with persistent spleens among patients with SCD across various age groups, it is difficult to infer factors that are causally related to the preservation of the spleen without longitudinal data. Moreover, there is a difference in splenic parameters between the Northern and Southern parts of Nigeria. This calls for more national and international collaborative studies to investigate the modifying factors.

CONCLUSION

In patients with SCD, failure to visualise the spleen was not found in children younger than 5 years. Patients with visualised spleens had a higher level of HbF than those with non-visualised spleens. HbF was significantly associated with visualisation of the spleen before 10 years of age. Since early administration of hydroxyurea will increase Hb F level, we expect that it would help to preserve the spleen.

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