Original Article

Ultrasound Findings in the Gallbladder of Sickle-Cell Patients: A Cross-Sectional Study in Enugu, Nigeria

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Abstract

Background: Sickle-cell disease (SCD) causes chronic and recurrent hemolysis which is a recognized risk factor for gallbladder (GB) disease. The prevalence of GB disease in SCD is high and increases with age. Cholelithiasis and cholecystitis are relatively common GB diseases in SCD. They are important causes of acute abdominal pain in SCD and also increase morbidity. Ultrasound is a cheap and noninvasive means of evaluating the GB; it has a high degree of accuracy and is widely available. **Aims:** The aim of this study is to sonographically evaluate the GB of SCD patients in steady state at the University of Nigeria Teaching Hospital (UNTH), Ituku-Ozalla, Enugu, and to determine the prevalence of specific GB diseases in SCD patients. **Materials and Methods:** A prospective cross-sectional study of 130 known SCD patients attending sickle-cell clinics at UNTH and 130 controls. Ultrasound of the GB was done after at least 6 h fast, using a Dp2200 mindray mobile ultrasound machine equipped with a 2.5–5 MHz convex probe. The data were analyzed using the SPSS software version 16. **Results:** The GBs of 130 consecutive SCD participants and 130 control group were sonographically evaluated. The prevalence of cholelithiasis in SCD was 10.8%, whereas the prevalence of cholelithiasis in the control group was 3.1%. No other GB diseases were seen. The mean dimensions of the GB for the study group were length (65.78 ± 9.85 mm), width (29.15 ± 6.01 mm), depth (25.58 ± 5.81 mm), wall thickness (1.59 ± 0.74 mm), and volume (26.52 ± 11.18 cm^3). **Conclusion:** The prevalence of cholelithiasis in sickle cell disease in southeast Nigeria is 10.8% while the prevalence of cholelithiasis in the control population is 3.1%.

Keywords: Cholecystitis, cholelithiasis, gallbladder, sickle cell disease, ultrasound

Introduction

Sickle cell disease (SCD) is the most common genetic disease in Africa.[1,2] It has been recognized as a major public health problem by international agencies such as the World Health Organization and the United Nations Educational, Scientific, and Cultural Organization.[3,4] It is a congenital condition of global distribution, and its most common clinical feature is anemia due to chronic hemolysis.[5] Cholelithiasis is a well-documented finding in SCD patients and is one of the most important manifestations of gallbladder (GB) disease in sickle cell.[6] Chronic hemolysis, with its accelerated bilirubin turnover, leads to a high prevalence of pigment gallstones[7-12] The formation of gallstones in SCD is not only from hemolytic causes[6,13] but also from the abnormalities in GB function or bile acid metabolism.[6,14] The prevalence of GB disease in SCD shows a high variation in the different geographical regions of the world[15-17] ranging from 6% to as high as 42%.[15,16] Thickening of the GB wall is an important imaging feature of GB disease; however, it is also a relatively common and nonspecific finding since it is seen in a wide range of GB diseases and extra-cholecystic pathologic conditions.[18] Although several studies on SCD[1,9,19-24] have been conducted, there is a dearth of literature on GB disease and dimensions in SCD from South-east Nigeria where this study was conducted.

The objective of this study was to sonographically evaluate the GB of steady-state SCD patients under routine medical supervision at the University of Nigeria Teaching

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Hospital (UNTH), Ituku-Ozalla, Enugu, and describe the various findings with a view of determining the prevalence of GB pathologies in SCD patients.

Materials and Methods

This was a prospective, cross-sectional study of 130 known SCD participants in steady-state, attending routine clinics at the Hematology and Pediatrics sickle cell clinics of UNTH, Ituku-Ozalla, Enugu, and 130 age and sex-matched control group recruited randomly from staff, students, and patients' relatives. The participants' ages ranged from 10 years to 44 years. All ultrasound scans were performed following at least 6 h fast to allow for bile distension of the GB. Trans-abdominal multiplane scan of the GB was done using a Dp-2200 mindray mobile ultrasound machine equipped with an electronic, convex array transducer with a frequency range of 2.5–5MHz (35C50EB).

Cholelithiasis was seen as a hyperechoic focus inside the GB lumen-casting posterior acoustic shadow[25-27] while stone impacted, and shrunken GB was seen as two curvilinear hyperechoic lines separated by a thin hypoechoic space representing a small amount of bile between the walls of the GB, with acoustic shadowing, distal to the surface of the gallstone (s). This is called the "wall-echo shadow (WES) sign."[19]

Dimensions of the GB were measured and documented. The data analysis was done using the Statistical Software Package for the Social Sciences (SPSS version 16, SPSS Inc. 233 South Wacker Drive, 11th Floor, Chicago, IL 60606-6412, Tel: (312) 651-3000, Fax: (312) 651-3668). The Student's *t*-test analysis was used to compare the means of continuous variables. Correlation analysis was used to correlate the findings with subjects' age, weight, height, and body mass index.

Sample size determination

The sample size was determined using the following formula:

$N = Z^2 PQ \div D$[28] Where, N = minimum sample size, Z = estimated standard deviation = 1.960, P = prevalence of GBD in sickle cell in Nigeria = 9% =0.09,[19] $Q = 1 - P$, D = Degree of accuracy desired = 5% =0.05.

Therefore, the minimum sample size $N = 126$.

Ethical consideration

The study proposal was reviewed and approved by the UNTH, Health Research Ethics Committee. An Ethical clearance certificate with reference number UNTH/CSA/329/Vol. 5 was issued. Informed consent was obtained from the patients and patients relatives.

Results

The study group comprised 130 SCD subjects; 4 (3.1%) heterozygous (HbSC) form and 126 (96.9%) homozygous (HbSS) form. The age range of participants was 10–44 years, whereas the mean age of the subjects was 20.3 ± 9.4. Out of 130 SCD participants, 55 (42.3%) were female, whereas 75 (57.7%) were male.

Forteen (10.8%) out of the 130 SCD participants had cholelithiasis, giving a GB disease prevalence of 10.8% [Table 3]. 3 (21.4%) out of these had stone impacted and shrunken GB with WES sign, whereas 11 (78.6%) had simple, uncomplicated cholelithiasis. One hundred percent of the heterozygous (HbSC) participants had normal GB findings. The healthy control group had a cholelithiasis frequency of 4 out of 130 participants, giving a prevalence of 3.1%. 1 (25%) out of these had stone impacted and shrunken GB with WES sign while 3 (75%) had simple, uncomplicated cholelithiasis. Three (2.3%) of the 130 SCD subjects had thickened GB wall due to cholelithiasis, whereas 1 (0.8%) of the 130 control group had thickened GB wall due to cholelithiasis. In the study group, 9 (64%) of the 14 cases of cholelithiasis was found in males, and 5 (36%) was found in females, whereas in the control group, 3 (75%) was seen in females and 1 (25%) in males [Table 1 and 2]. The overall sex distribution of cholelithiasis was 10 (55%) cases in males and 8 (45%) cases in females. There was no statistically significant difference in the overall sex distribution of cholelithiasis at $P < 0.05$ [Table 4].

Discussion

In this study, the GBs of 130 SCD participants were sonographically evaluated, and the findings documented. Most

Table 1: Demographic characteristics of the participants

Variables	Number of sampled, *n* (%)
Age groups (years)	
10-14	49 (37.7)
15-19	31 (23.8)
20-24	10 (7.7)
25-29	6 (4.6)
≥30	34 (26.2)
Total	130 (100)
Age, mean±SD	20.3±9.4
Male	75 (57.7)
Female	55 (42.3)

SD: Standard deviation

Table 2: Summary of findings in the gallbladder of sickle cell disease

Findings	Number of cases (*n*=130), *n* (%)
GB sludge	0
Uncomplicated gallstone	11 (8.5)
Stone impacted, shrunken GB with WES sign	3 (2.3)
GB mass	0
Adenomyomatosis	0
Phrygian cap	3 (2.3)
Septated GB	3 (2.3)
Normal GB	110 (84.6)
Total	130 (100)

WES: Wall echo shadow, GB: Gallbladder

Table 3: Prevalence of cholelithiasis in sickle cell disease

	Cholelithiasis, *n* (%)		Total
	Yes	No	
HbSS	14 (10.8)	112 (86.2)	126
HbSC	0	4 (3.1)	4
Total			130

HbSS: Homozygous, HbSC: Heterozygous

Table 4: Association between cholelithiasis and age in sickle cell disease

Variable	Gall bladder disease		χ^2	*P*
	Yes, *n* (%)	No, *n* (%)		
Gender				
Male	9 (12)	66 (88)	0.279	0.597
Female	5 (9.1)	50 (90.9)		
Age group (years)				
10-19	4 (4.8)	79 (95.2)	8.458	0.004*
≥20	10 (14.9)	37 (85.1)		

*There is a statistically significant association between the presence of cholelithiasis and age groups in SCD participants (P<0.05). SCD: Sickle cell disease

of the disease conditions seen in the GB of participants were due to cholelithiasis. The prevalence of cholelithiasis in this group of participants was 10.8%. No other diseases of the GB were seen. This suggests that other GB diseases such as GB carcinoma, GB polyps, and adenomyomatosis of the GB are indeed rare in this environment. Several authors[20,25,29] have shown that cholelithiasis is common in SCD due to accelerated hemolysis associated with the disease. The prevalence of cholelithiasis in this study varies slightly with the findings of Akinyanju and Ladapo[20] who reported a marginally lower prevalence of 9% in a 1979 study carried out at the Lagos University Teaching Hospital using oral cholecystography. This slight variation, though not significant, could be due to the use of ultrasound in the present study, which is a more sensitive modality when compared to oral cholecystography. The prevalence of cholelithiasis in the present study is higher than that of Akinola *et al*.[21] who reported a prevalence of 6% in SCD patients who presented with abdominal pain at Ile Ife. This variation is due to the fact that Akinola *et al*.[21] studied only symptomatic patients. Nzeh *et al*.[29] in a study of 161 children with SCD in Ilorin reported a cholelithiasis prevalence of 4.2%, which is much lower than the report of the present study. The lower prevalence recorded in their study could be due to the pediatrics age group they evaluated when compared with the present study which evaluated adolescents and adult age groups. In another study at Ilorin, Ajayi *et al*.[12] reported a gallstone prevalence of 28%, which is much higher than the 10.8% reported in the index study. The report appears to be the highest cholelithiasis prevalence reported in Nigeria, as every other author reviewed, reported lower prevalence. The reason for this variation could be the predominantly adult age group which they studied. It could also be due to dietary or ethnic factors. Agholor *et al*.[23] in a recent study of 150 confirmed SCD participants in Benin reported a prevalence of 16%, which is also higher than the report of the index study. The difference between the report of Agholor *et al*.[23] and the present study could be due to dietary or ethnic factor as the age group studied by Agholor *et al*.[23] were predominantly pediatrics and adolescent age groups.

The prevalence of cholelithiasis in SCD shows a high variation in different geographical regions of the world.[15-17] There is relatively lower prevalence reported in African studies compared to all the studies done in America and Europe. This wide variation is thought to be due to dietary and environmental factors; the different age groups studied; selection of distinct populations; inclusion of symptomatic patients and imaging modalities used in the various studies.[20,22,25]

Although the prevalence of cholelithiasis in males tended to be higher than that of females in the present study, there was no significant difference between them. This is in keeping with the reports of Agholor *et al*.[23] On the contrary, Darko *et al*.[13] in Ghana reported a significantly higher prevalence of cholelithiasis in males compared with that of females (male-to-female ratio of 12:1). The reason for this male preponderance of cholelithiasis in SCD is yet to be clearly elucidated, though Darko *et al*.[13] suggested a higher frequency of hemolytic crisis in males.

The majority of authors agree in reporting that cholelithiasis increases with age. In the present study, there was the increased number of cases of cholelithiasis in the older age group compared to the younger age group; 4.8% seen in the age group 10–19 years, and 14.9% seen in 20 years and above.

The present study did not find cholelithiasis among heterozygous (HbSC) SCD subjects. This is in keeping with the findings of Akinola *et al*.,[21] who did not report cholelithiasis among HbSC participants in their study. It also compares closely in pattern with the findings of Darko *et al*.[13] who noted a relatively lower prevalence of cholelithiasis among HbSC compared with HbSS participants. This pattern of having a higher prevalence in homozygous SCD participants compared with the heterozygous group is consistent with the report of this study. However, it is at variance with the report of Durosinmi *et al*.,[20] who reported a prevalence of 22.6% in HbSS and 33.3% in HbSC.

In the present study, 21.4% of the 10.8% cases of cholelithiasis in SCD had stone impacted and shrunken GB with WES sign. The sign suggests either a large gallstone or multiple small gallstones filling the lumen of a contracted or incompletely visualized GB.[19,30] The GBs of these participants were not visualized apart from the WES sign, which was seen in the GB bed. None of the reviewed authors documented the WES sign in SCD. However, Nzeh *et al*.[29] reported a 1.2% prevalence of nonvisualized GB in 1989. They did not elucidate if those cases of nonvisualized GBs were as a result of cholelithiasis, shrunken GB, or congenital GB malformation. Recognizing

the WES sign helps to avoid misinterpretation of a stone-filled GB as a loop of bowel. This sign is diagnostic of cholelithiasis, but it is also suggestive of acute or chronic cholecystitis.[19,28] However, this must be correlated with clinical history to make a confident diagnosis of acute or chronic cholecystitis. Sometimes, instead of detecting two parallel curvilinear echogenic lines with distal shadow, one may see only a single echogenic line casting a shadow. In some patients, this is due to calcification within the GB wall (i.e. porcelain GB); in others, it may relate to poor axial resolution of the transducer.[19,28]

This study did not document GB sludge in the participants. On the contrary, Nzeh *et al*.[29] and Ma'aji *et al*.[26] reported GB sludge prevalence of 7.5% and 2.8%, respectively. This difference could be due to the fact that all the participants in this study were in a steady-state. GB sludge is commonly associated with prolonged fasting, total parenteral nutrition, pregnancy, SCD, sepsis, and treatment with ceftriaxone.[24] The natural history of GB sludge is variable; it may resolve spontaneously or may progress to gallstone development.[24]

Conclusion

1. The prevalence of cholelithiasis in SCD in South-east Nigeria is 10.8%, whereas the prevalence of cholelithiasis in the control population is 3.1%
2. Cholelithiasis is more likely to occur in SCDs than in the healthy control group.

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Conflicts of interest
There are no conflicts of interest.

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