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Sonographic Diagnosis and Clinical Correlates of Gallbladder Stones in Patients with Sickle Cell Disease in Calabar, Nigeria

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Abstract

BACKGROUND: Sickle Cell Disease (SCD) causes chronic haemolysis which is a risk factor for cholelithiasis.

AIM: To determine the prevalence and clinical correlates of cholelithiasis in SCD patients in steady state treated at the University of Calabar Teaching Hospital.

METHODS: This was a prospective study that took place at the Haematology and sickle cell disease clinics, University of Calabar Teaching Hospital, Calabar, Nigeria between January and June 2018. The study population were aged between 1.5-5.5 years and confirmed to have SCD through haemoglobin electrophoresis. A brief history was obtained, and all the patients had a physical examination. Ultrasound examination was performed using a B-mode mind-ray ultrasound machine using a 3.5-5.0 MHz probe after an overnight fast. A Calculus is diagnosed when a highly echogenic structure casting a concrete shadow is detected in the lumen of the gallbladder.

RESULTS: One hundred and twenty confirmed SCD patients aged between 1.5-55 years were recruited in the study, 69 (57.5%) were males, while 51 (42.5%) were females. The overall prevalence of cholelithiasis was 10%, and it increased with age. The youngest patient with cholelithiasis was 13 years old. All the patients were asymptomatic at the time of examination. At the multivariate level, age, gender, weight and gallbladder volume were associated with gallbladder stones.

CONCLUSION: The prevalence of cholelithiasis in patients treated at the Sickle Cell Clinic at the University of Calabar Teaching Hospital, Calabar is fairly high. The patients were largely asymptomatic, and cholelithiasis is more common in females than males. This study showed a weak association between blood transfusion and gallbladder stone. It is recommended that routine abdominal ultrasound scan for gallbladder be done for SCD patients from the second decade of life in our environment.

Introduction

Sickle cell disease (SCD) is the commonest haemoglobinopathy in people of African racial origin [1]. Sickle cell haemoglobin (HBS) has its highest prevalence in West Africa where it is reported to have originated and is also present in black Americans of African descent, Indians and those from the eastern Mediterranean region [2] [3] [4]. Nigeria by her population is the most sickle cell disease (SCD) endemic country in the world with over 40 million people (30% of its population) being carriers of the haemoglobin `s` gene while the homozygous SS is found in about 3% of the population [5].

Sickle cell disease (SCD) can occur as a homozygous form (HbSS) or heterozygous form, such as HbSC or HbSD among other variants. However, the homozygous variant HbSS has the severest clinical manifestation [6] [7] [8].

Cholelithiasis is a frequent complication of chronic haemolysis due to sickle disease [9]. It is sometimes revealed by digestive symptoms difficult to distinguish from painful abdominal vaso-occlusive crises (recurrent abdominal pain sometimes similar to biliary colic, nausea, vomiting). However, cholelithiasis is often asymptomatic and can lead to serious complications (cholecystitis, cholangitis, pancreatitis, septicaemia starting in the bile) which can jeopardise patients` lives [10] [11].

Many studies show that the prevalence of cholelithiasis in patients with sickle cell disease increases with age and affects 6% of patients before 15 years of age and more than 50% of young adults [9] [12] [13]. It is thought that the prevalence of cholelithiasis is substantially lower in African patients than Jamaican or north American patients [14]. This difference is attributed to differences in dietary cholesterol and/or fibre, but other factors (genetic or environmental) could have an influence. Gallstones treatment is equivocal, but most studies recommend cholecystectomy in the symptomatic cases and regular ultrasonography in other cases [11] [15].

Although there have been reports of the use of ultrasound in the diagnosis of cholelithiasis, the clinical correlates of cholelithiasis in the people with SCD is under-reported [9] [16]. Unlike most of the modern imaging modalities, ultrasound provides a widely available, non-invasive, inexpensive method for evaluating the gallbladder without the use of ionising radiation [17]. These factors are of particular importance in young patients with chronic diseases who require recurrent follow-up imaging. An ultrasound scan can be performed on routine clinic visits as it provides accurate pre-treatment diagnosis essential to plan appropriate management of this pathology.

This study was designed to sonographically determine the prevalence and clinical correlates of gallbladder stones in patients with sickle cell disease in southern Nigeria.

Subjects and Methods

This was a prospective study carried out to determine the prevalence and clinical correlates of gallbladder stones in patients with homozygous sickle cell disease in southern Nigeria, between January 2018 and April 2018. During the study period 120 patients between the ages of 1.5-55 years attending the sickle cell clinics (both children and adult) at the University of Calabar Teaching Hospital, Calabar, Nigeria were consecutively recruited into the study. A brief history was taken with emphasis on some blood transmissions, number and type of crises, chronic abdominal pain and nature of stools. Weight and height of participants were documented.

All the patients had a physical examination including anthropometry, under conditions of privacy with the following being examined:

General examination for pallor, jaundice and clubbing as well as digestive system examination were carried out with emphasis on organ enlargement (liver and spleen), tenderness and Murphy's sign.

Ultrasound examination was performed on all the SCD patients without a history of cholecystectomy. All patients were examined with a B-mode MINDRAY ultrasound machine using a 3.5-5.0 MHz probe after an overnight fast. The examination was performed in supine and decubitus positions on a couch. Calculi were diagnosed when highly echogenic structures with acoustic shadowing were detected in the lumen of the gallbladder.

Informed consent was obtained from all participants and strict confidentially ensured. Ethical clearance was obtained from the Research Ethics Committee of UCTH Nigeria.

Those excluded from the study were SCD patients who had any other coexisting morbidities like HIV or malignancies, SCD patients with a history of cholecystectomy and SCD patients who did not give consent for the examination.

The data were analysed with the Statistical Package for Social Sciences (SPSS) software version 18 for the window. Simple proportions, percentages and graphs were used to analyse the data. Chi-square test was used to test the difference between categorical variables. Student's t-test was used to compare continuous variables. Odds ratio and multiple regression analysis were used to identify predictors of gallbladder stones, a p-value of < 0.05 was regarded as significant.

Results

One hundred and twenty confirmed sickle cell disease patients were recruited into the study. The age range of the study group was between 1.5 to 55 years with a median age of 14.5 years; IQR 6-25years (Figure 1). There was a slight male preponderance; 69(57.5%) were males, while 51(42.5%) were females (male: female ratio of 1.3:1). The mean age for females was 18.4 ± 12.3 years (95% CI 14.9-21.9 years). The mean age for males was 14.6 ± 11.0 years (95% CI 12.0-17.2 years). The males were slightly younger than the females ($t = 1.8$; $p = 0.03$).

Cholelithiasis was reported in 12 patients giving a general prevalence of gallbladder calculi as 10.0% (95% CI 5.3-16.8%). No individual had developed gallbladder calculi in the first 10 years of life. The youngest SCD patient with gallbladder calculi was 13 years old.

At the univariate level, increasing age was significantly associated with the prevalence of gall bladder stones (OR = 15.17; $p = 0.0001$). Gender had no effect ($x^2 = 0.47$; $p = 0.50$). Weight showed a trend (OR = 2.8; $p = 0.09$; 95% CI 0.99-1.04). Height was significantly associated with gall bladder stone (OR 1.02, $p = 0.04$, 95% CI 1.00-1.05).

The body mass index (BMI) had no association with gallstones (OR = 1.06; p = 0.17; CI = 0.98-1.14).

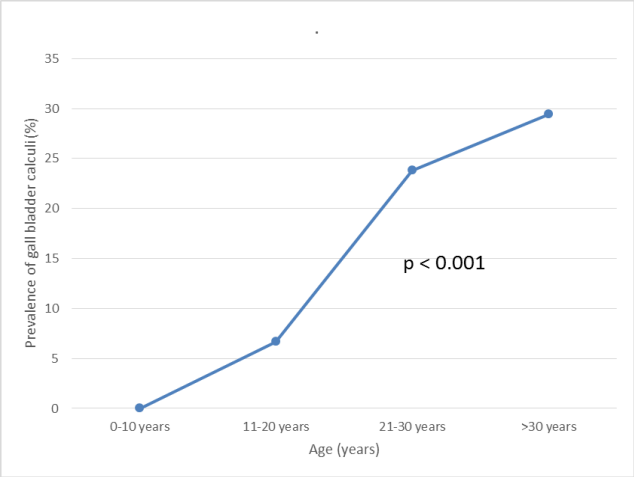

Figure 1: Line graph showing the prevalence of gall Stones with age

At the multivariate level age, gender, weight and gallbladder volume were associated with gallbladder stones (table). Area under the ROC curve was 0.96, indicating a very good model. No subject had positive Murphy's sign.

Table 1: Logistic Regression Model for Predictors of Cholelithiasis in SCD Patients

VARIABLE	UNIVARIATE ANALYSIS ODDS RATIO (95% CI, p-VALUE)	MULTIVARIATE ANALYSIS ODDS RATIO (95% CI, p-VALUE)
Age	1.10 (1.04 – 1.17, 0.001)	1.18(1.05 – 1.33, 0.010)
Gender	1.54(0.44 – 5.42, 0.50)	11.77(1.02 –1.34, 0.05)
Weight	1.02(0.99 – 1.04, 0.09)	0.90(0.82 – 0.99, 0.03)
Height	1.02(1.00 – 1.04, 0.04)	0.99(0.98 – 1.02, 0.97)
Number of blood transfusion	1.40(1.00 – 1.96, 0,05)	1.22(0.76 – 1.98, 0.40)
Gall bladder volume	1.03(1.012 – 1.03, 0.00)	1.04(1.01 – 1.06, 0.00)
Liver span	1.45(1.09 – 1.90, 0.01)	1.50(0.87 – 2.44, 0.15)

Area under ROC curve = 0.9567.

Discussion

Chronic haemolysis with its accelerated bilirubin turnover leads to a high incidence of pigment gallstones, and gallbladder sonography has become the dominant method of examining the gallbladder [18] [19] [20]. This is so because ultrasonography is convenient, safe and does not use ionising radiation. It has 88% sensitivity and 80% specificity for the diagnosis of gallstones [21].

Previous studies on the prevalence of cholelithiasis on SCD patients show a wide variation in the prevalence [12] [22] [23] [24]. The prevalence of cholelithiasis is reported to be substantially lower in African patients than in Jamaican or North American patients.[14]This difference could be attributed to differences in dietary cholesterol and/or fibre, but other factors (genetic or environmental) could have an influence.

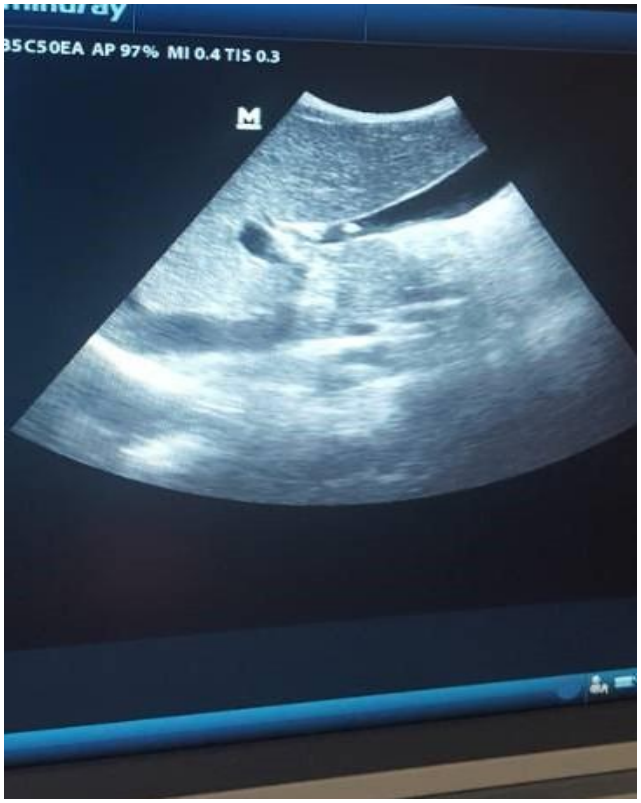

Figure 2: Cholelithiasis in a 32-year-old female SCD patient

In this study, the overall prevalence of gallstones was 10%. The low prevalence of cholelithiasis compared to other studies such as that reported by Agholor CA et al., [16] who reported 16.0% among 150 patients aged between 10 months and 51 years and Durosimi MA et al., [25] who documented 24.2% among 18 to 56 years old Nigerians with SCD could be attributable to dietary factors and access to specialized care. A low prevalence of cholelithiasis of 6% in patients younger than 15 years who were examined by oral cholecystography was reported by Akinyanju and Ladapo in Ibadan, Nigeria [12]. This is similar to the 5% prevalence of cholelithiasis observed byAkamaguna et al., [26] among sickle cell disease patients at the University of Benin Teaching Hospital Nigeria using oral cholecystography and the 50% reported by Odunvbun ME et al., in a study population of 101 aged 1-18years.

The prevalence of gallstones is usually increased with increase in age, and by the age of 18 years, 30% of SCD are expected to have developed gallstones [27] [28]. The youngest SCD patient with gallbladder calculus was 13 years old. This finding was at variance with the study by Akamaguna et al., who reported 5.5-year-old boy as the youngest with gallbladder stones and the study by Odunvbun et al., [29] reported the youngest child with gallstones to be

5 years old. A Ghanaian study reported gallstone in a 2.5-year-old SCD child [22], who was symptomatic. The high age of onset of gallbladder stone in our study may be attributed to dietary and environmental factors. Age, gender, weight and gallbladder volume are predictors in this study. This trend was also reflected in other studies when they were categorised into age groups [24] [30] [31] [32].

This study showed a weak association between blood transfusions and gallbladder stones and no association with chronic abdominal pain, gallbladder wall thickness and change in bowel habit. We studied patients in the steady state and patients with gallstones in this study were asymptomatic. This finding is the same as what has been reported by Barrett-Connor [30], Webb et al., [23] and Attalla et al., [22] where most their patients were asymptomatic. While Sarnaik [28], Cameron et al., [32] Karayalcin [33], and Bond et al., [24] reported that symptoms of typical biliary tract disease were common in patients with gallstones.

With the earliest incidence of gallstones seen in a 13-year-old in this study, routine screening with abdominal ultrasound scan is recommended for people with SCD from the second decade of life for early diagnosis and treatment to prevent complications.

In conclusion, the prevalence of cholelithiasis in patients treated at the sickle cell clinic at the University of Calabar Teaching Hospital, Calabar (1 m 10%). The patients were largely asymptomatic. It increases with increasing age, weight, gallbladder volume, and is more common in females than in males. It is recommended that routine abdominal ultrasound scan for gallbladder be done for sickle cell patient from the second of life in our environment,

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