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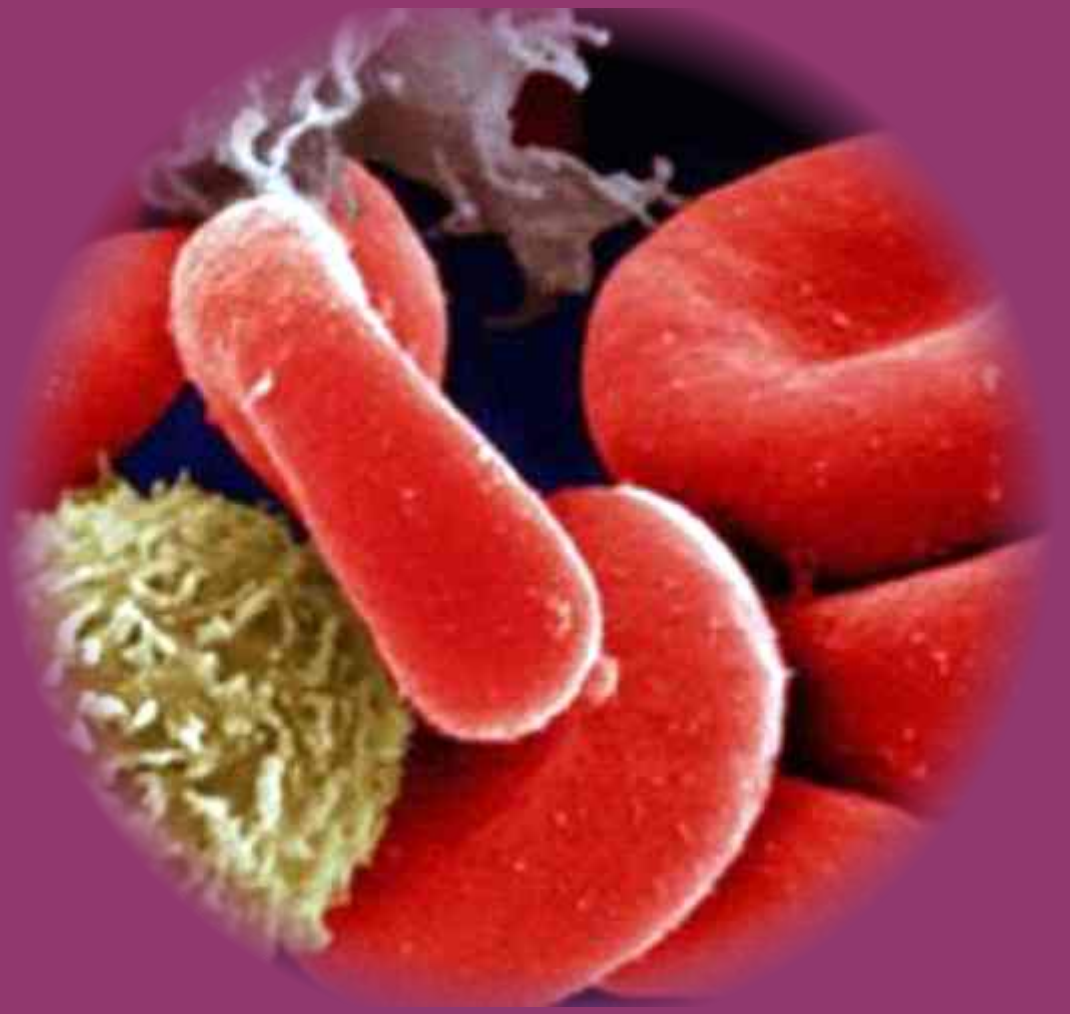

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Cholelithiasis and Hepatic Derangement in a Cohort of Homozygous Sickle Cell Disease Patients in Nigeria

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ABSTRACT

Background:
Cholelithiasis is a chronic complication of SCA and many liver enzymes have been associated with severity.

Aims and Objectives:
To assess frequency and predictive clinical and laboratory associations of cholelithiasis and liver dysfunction among steady state SCA patients.

Method:
Steady state clinical and laboratory data were obtained from the case notes of 248 sickle cell anaemia (SCA) patients. Information assessed included; age, haemoglobin (Hb) concentration, white cell count (WBC), platelet count, serum bilirubin, alkaline phosphatase (ALP), aspartate transaminase (AST), alanine transaminase (ALT) levels and frequency of crisis per annum.

Results:
Two hundred and forty eight SCA patients who were in steady state aged 6 to 55 years (median = 24 year, 95% CI = 23-25) were assessed. The prevalence of cholelithiasis was found to be 4.4%. Deranged levels of alkaline phosphatase, aspartate transaminase and alanine transaminase were found in 23.5%, 51.5% and 26.5% of the patients respectively. Serum ALT had a significant inverse relationship (P = 0.026) with the Hb, while ALP had a direct relationship (P = 0.023) with WBC. There was no association between the occurrence of cholelithiasis and the usual markers of disease severity in SCA, such as Hb, WBC, frequency of crisis per annum, age and platelet count.

Conclusion:
The prevalence of gall stones in SCA was found to be 4.4%. Cholelithiasis in homozygous sickle cell does not have a greater prevalence in people with severe disease. Elevation of serum ALT and ALP are associated with a low Hb and a high WBC, respectively.

Keywords: cholelithiasis, gallstones, sickle cell, hepatic impairment

INTRODUCTION

Sickle cell anemia (SCA) refers to the most common form of sickle cell disease (SCD), with a homozygous mutation in the ^{S}allele (Hb SS), affecting 60% to 70% of people with SCD. [1, 2] Approximately 24% of Nigerians are carriers of the sickle cell trait while another 150,000 children are born annually with SCA. [3] Although this presents a significant public health problem, improved management has resulted in increased life expectancy for patients with SCD. [4] Hepatic impairment in sickle cell disease is usually classified as acute or chronic. The acute painful episodes involving the right hypochondrion is sometimes due to infarction of the hepatic parenchyma as a result of vaso-occlusion. Other more sinister scenarios include; cholestasis, hepatic impairment and hepatitis. The chronic complications tend to occur more frequently with increased longevity and usually due to cholestasis secondary to bilirubin gall stones, iron overload from multiple transfusions and viral hepatitis. The incidences of these

complications have been found to vary widely in previous studies ranging from 26 to 58% for gall stones and up to 72% for elevated liver enzymes.[5, 6]

Elevation of the serum level of Lactate dehydrogenase (LDH), aspartate transaminase (AST) and Indirect bilirubin is usually observed in about 72% of SCD patients. [7] These changes can be attributed to shortened red cell life span, consequent on the increased rate of red cell lysis. Transitory elevated serum levels of transaminases are indicative of liver parenchymal damage. However, sustained high steady state values are indicative of a baseline hepatic dysfunction. Cholelithiasis, diagnosed by ultrasonography has been observed in 26%-58% of SCD patients. It has also been found to occur more in homozygous S patients than in HbSC individuals. [5] Other chronic hepatic complications such as iron overload due to transfusion, has not been observed in significant proportion of African SCD patients and this is further supported by low incidence of liver cirrhosis in these patients. [8]

Hepatic vaso-occclusion despite the dual blood supply to the liver has been proposed to be the reason for hepatic infarction observed in 34% of autopsies in SCD. [5, 9] Marked haemolysis in severe SCD, leads to low haemoglobin concentration and elevated bilirubin and LDH levels. Vaso-occlusion has also been linked to increased white cell levels, as had been noted in previous studies. [10, 11] A combination of these factors obviously predisposes to an increased tendency to develop chronic liver dysfunction and gall stone formation. Increases in these factors have also been observed in people with severe SCD with a consequently reduced life expectancy. [12, 13]

This study focuses on gall stones as well as distortions in the liver enzymes, as these are the more frequent observations. It seeks to document the burden of cholelithiasis as well as other hepatic dysfunctions among the sickle cell anemia patients in steady states. The study was also aimed at assessing the predictive capabilities of the known clinical and laboratory features of disease severity with respect to these chronic hepatic complications. It is expected that the findings of this study will promote further research interests aimed at comprehensive care and better quality of life for people living SCA.

MATERIALS AND METHODS

The study is a retrospective cross-sectional study of SCA patients see in the out-patient department of the University of Nigeria Teaching Hospital. The case notes of 248 homozygous sickle cell anaemia patients were assessed for information on the steady state laboratory parameters, which included their haemoglobin concentration, white cell and platelet counts, serum direct and indirect bilirubin levels, serum alkaline phosphatase and transaminases. Other clinical data obtained included; age, sex and frequency of crisis per annum. The term elevated liver enzymes or hepatic impairment was assumed for all patients whose liver enzymes levels were above the reference range for the population. [10] The diagnosis of cholelithiasis was assumed for those who had positive findings on ultrasonography. Data were collected from outpatients seen at the sickle cell clinic over a ten-year period, between April 2006 and May 2016.

Data Analysis: The data were analyzed using SPSS version 19 (IBM Corporation, Armonk, NY, USA). Pearson or Spearman correlation as well as multi-variate analysis, general linear model was used to test for significant association between the occurrence of elevated liver enzymes and other indicators of disease severity in sickle cell disease. A P-value of less than 0.05 was regarded as significant and 95% confidence intervals were reported where indicated.

Ethical Approval: Ethical approval was obtained from Health Research and Ethical Committee of the University of Nigeria Teaching Hospital, Ituku/Ozalla, Enugu.

RESULTS

A total of 248 patients were assessed, aged 6 to 55 years, with a median age of 24 years (95% CI = 23-25), the age was not documented for 7 patients. Males were 157 (63.6%), females 90

(36.4%), while the gender was not documented for one (1) patient (the information was not available on the electronic data records). Eleven (4.4%) had gallbladder stones (GBS) out of which, seven (63.6%) were males and four (36.4%) were females. The prevalence of GBS in both sexes as well as the combined prevalence was 4.4%. Cholelithiasis was observed as the sole chronic complication in three (30%) patients, while it occurred with sickle leg ulcers in four (40%), priapism in three (30%) and nephropathy in three (30%) patients.

Hepatic impairment:

In terms of the hepatic enzymes; 32 (23.5%) out of 136 patients had elevated alkaline phosphatase level, 70 (51.5%) out of 136 had elevated aspartate transaminase (AST) while 36 (26.5%) out of 136 patients had elevated alanine transaminase level. Only 7 of the patients had all their bilirubin and liver enzymes levels within the reference range for the population. Direct hyper-bilirubinaemia was observed in 67.6% (92/136), while the elevation of the indirect portion was seen in 57.4% (78/136) of them. The mean and median values of the serum direct bilirubin as well as the liver enzymes are expressed in Table 1. The pictorial relationship between the serum bilirubin and the occurrence of chronic complications of SCA is shown on Figure 1b, and this seems to be associated with pulmonary hypertension. There was a significant inverse relationship between Alanine transaminase (ALT) and Hb -0.143 (P = 0.026), and while an increasing Alkaline phosphatase (ALP) was significantly associated with an increasing WBC 0.134 (P =0. 023). Also observed were significant associations between the; AST and direct bilirubin 0.160 (P = 0.008), ALT and ALP 0.130 (P = 0.032), ALP and frequency of crises per annum 0.151 (P = 0.05). There were no other associations between the serum levels of the other liver enzymes and the age, sex, Hb, WBC, frequency of crises per annum or platelet count. Viral hepatitis B infection had been diagnosed in two of the patients in the study. The serum direct bilirubin levels in the patients with the chronic complications of sickle cell are shown in Figure 1a.

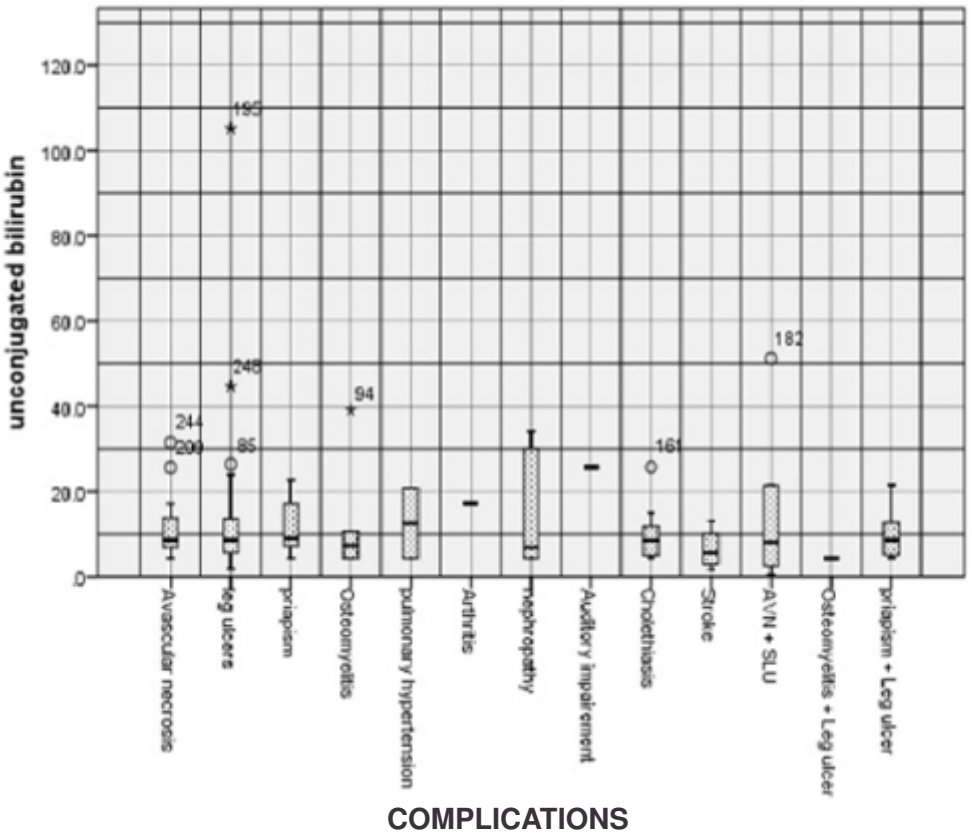

Figure 1a: Serum direct bilirubin in the patients with the various chronic complications of sickle cell

Cholelithiasis:

The occurrence of gall bladder stones did not show any significant relationship with any of the clinical or laboratory parameters assessed. There was no significant association between the frequency of crisis per annum and the occurrence of Cholelithiasis (P = 0.205). Other important indicators of disease severity also did not show significant relationship with the occurrence of cholelithiasis, p values obtained were; age- 0.288, Hb - 0.356, WBC – 0.334, platelet count – 0.336. The Independent T-test and Kendaull tau_b correlation coefficient, for assessing relationship are shown in Table 1. The occurrence of other chronic complications of sickle cell together with Cholelithiasis also revealed that three patients had cholelithiasis without any other detectable complications. However cholelithiasis was found to occur with priapism, leg ulcers and chronic kidney disease though no significant association was found.

Multi-variate analysis revealed no association between the occurrence of GBS and other features of severe sickle cell disease. Values obtained were; age (P = 0.532), leucocyte count (P = 0.645), AST (P = 0.7), frequency of crisis (P = 0.339), Hb (P = 0.328) and platelet count (P = 0.386).

DISCUSSION

The patients in this study group were mainly young, median age 24 years and the prevalence of gall bladder stones was lower than had been observed in previous studies. [14, 15] However, the majority of the sickle cell anaemia patients had derangement in one or more of their liver enzymes. This may be explained by the repeated necrosis of the hepatic parenchymal cells following episodes of vaso-occlusion. Elevation of ALT has been noted in previous studies to be associated with occurrence of pulmonary hypertension [16] and priapism, [17] this was not supported by in this work . It is established that the pathogenesis of these complications of SCA have not been fully delineated and may not directly involve this enzyme. Neither direct nor indirect hyperbilirubinaemia were associated with increased disease severity or occurrence of gall stones.

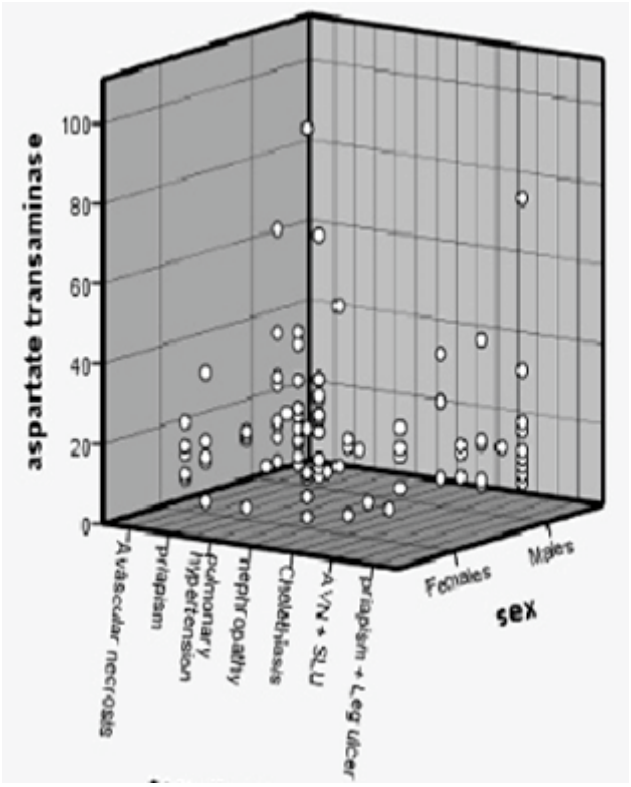

Figure 1b: The serum aspartate transaminase levels across males and females with chronic complications of sickle cell

Table 1. Clinical and laboratory features in sickle cell disease patients

Clinical & Laboratory Steady state Values	N	Mean (SD)	Median (95% CI)	Independent T-test (P value)	Correlation coefficient (significance)
Age (years)					
All Patients	241	25.4 (7.7)	24 (23-25)		
Cholelithiasis	10	29.1 (10.7)	25.5	0.224	-0.058 (0.288)
No Cholelithiasis	227	25.3 (7.3)	24		
Frequency of Crisis per annum					
	152	3.7 (4.8)	2 (2-3)		
All Patients	24	3 (3.2)	3	0.737	0.104 (0.205)
Cholelithiasis	144	3.8 (4.9)	2		
No Cholelithiasis					
White cell count (x 10^9/L)					
All Patients	228	12.4 (6.8)	11.1(10.4-11.7)		
Cholelithiasis	10	10.1 (4.1)	9.9	0.567	0.053 (0.334)
No Cholelithiasis	215	12.6 (6.9)	11.2		
Platelet count (x 10^9/L)					
All Patients	208	346 (166)	329 (310-350)	0.249	-0.027 (0.336)
Cholelithiasis	10	379 (206)	388		
No Cholelithiasis	195	344 (165)	329		
Haemoglobin concentration (g/dL)					
All Patients	198	7.8 (2.0)	7.8 (7.5-8.1)		
Cholelithiasis	10	7.2(1.6)	7.4	0.598	0.055 (0.356)
No Cholelithiasis	185	7.8 (2.0)	7.8		
Indirect bilirubin (mmol/L)	140	16.3 (23.7)	8.6 (7.3-9.6)		
All Patients	7	13.2 (8,1)	12.8	0.351	-0.032 (0.658)
Cholelithiasis	131	16.6 (24.5)	8.6		
No Cholelithiasis					
Direct bilirubin (mmol/L)					
All Patients	140	22.0 (28.3)	12.5 (9.0-17.1)		
Cholelithiasis	7	33.1 (35.9)	9.5	0.154	0.048 (0.499)
No Cholelithiasis	131	21.6 (28.0)	12.6		
Serum Aspartate transaminase (U/L)					
All Patients	137	20.9 (18.5)	16.0 (14-18)		
Cholelithiasis	7	20.3 (18.0)	10.7	0.455	-0.054 (0.456)
No Cholelithiasis	129	20.9 (18.9)	16.0		
Serum Alanine Transaminase (U/L)	136	11.9 (11.2)	9.0 (7-10)		
All Patients	7	15.6 (9.0)	15.9	0.178	-0.039 (0.597)
Cholelithiasis	128	11.7 (11.1)	9.0		
No Cholelithiasis					
Serum Alkaline phosphatase (U/L)	136	74.7 (54.0)	61.5 (56-68)		
All Patients	7	68.1 (67.0)	25.4	0.221	-0.029 (0.680)
Cholelithiasis	128	75.3 (55.3)	60.5		
No Cholelithiasis					

Sickle cell anaemia with its attendant high rate of haemolysis leads to raised bilirubin levels which occur with increased concentration in bile. This produces a predisposition to high viscosity of the biliary secretions and consequent stone formation, hence the raised incidence of bilirubin gall stones in SCA patients. Increased severity in SCA has been noted to be associated with increased rates of haemolysis and thus lower haemoglobin levels. [8, 18] It can therefore be inferred that that this should lead to high bilirubin levels and consequently a higher incidence of gall bladder stones. The findings of this study did not detect any significant relationship between the commonly observed features of disease severity and the occurrence of gall stones. This is rather surprising as GBS in SCA is thought to consist mainly of bilirubin and biliary sludge. [5, 12, 19] However, this is not found in this group and may suggest that some other initiating factors such as infection and poor hydration may play important environmental role in its etiology. This also raises the question as to whether other dietary and genetic factors are responsible for this observed incongruence. A third of the patients who had cholelithiasis, had this as a sole complication. This further buttresses the fact that the process of gall stone formation in SCA may be affected to a large extent by other factors different from those that are known to cause the other chronic complications of the disease.

CONCLUSIONS

The prevalence of gall stones in patients with homozygous sickle cell anaemia is not higher in individuals with severe disease. An increase in the serum bilirubin level as well as frequency of bone pain crisis is also not associated with the occurrence of gall stones. This suggests that other factors like diet, genetic predisposition and state of hydration may play a role in the aetiology of this complication. Elevated liver enzymes ALT and ALP are associated with an increasing WBC and decreasing Hb, both known indicators of severe disease. Further investigations using a larger patient cohort is needed to discern the factors leading to the formation of gall stones in homozygous sickle cell disease.

Limitations:

The study being a retrospective study has several patients with incomplete data and this also made it impossible to standardize the diagnostic modality for the detection of gall stones. A cross-sectional prospective study is currently being undertaken by the group to assess these findings as well as investigate other genetic predisposition to gall stone formation.

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Authors' Contributions:

AJ, AU, KAM and AOU designed the study and did the literature review. AU, MU and KAM collected and analyzed the data. AJ, MU and AOU wrote up the discussion.

Conflict of interest:

The authors declare that they have no competing interests.

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