Original Research Article

SICKLE CELL HEPATOPATHY: PREVALENCE AND PRESENTATION IN CHILDREN WITH SICKLE CELL ANEMIA SEEN IN ENUGU STATE UNIVERSITY TEACHING HOSPITAL, PARKLANE, ENUGU.

ABSTRACT

Background:

Sickle cell hepatopathy (SCH) refers to the range of hepatic pathologies from a variety of hepatic insults in Sickle Cell Disease (SCD) patients. These are related to sickling, multiple transfusions, chronic haemolysis and less commonly hepatic infarcts, abscesses, etc. These conditions present similarly yet have varied prognosis. A high index of suspicion is therefore needed for early and proper diagnosis. Few published literature on the clinical conditions which constitute SCH exist.

Aim:

This study aims to evaluate the clinical and laboratory evidence of SCH in children with sickle cell anemia (SCA) being followed up at the Paediatric SCD clinic of Department of Paediatrics of the Enugu State University Teaching Hospital (ESUT-TH), Enugu, South-East Nigeria.

Methods:

This was a cross-sectional observational study of 100 children with SCA on regular clinic follow-up who were seen over a period of 3 months. History of scleral icterus, abdominal pain, multiple blood transfusions and frequent vaso-occlusive and haemolytic crises were obtained. Patients were examined for sclera icterus as well as hepatomegaly and right upper quadrant tenderness. Complete blood count and blood film, liver function test (LFT), abdominal ultrasonography, Hepatitis virus serology, Haemoglobin quantitation and serum ferritin were requested. All clinical and laboratory data were documented in a short interviewer administered questionnaire. A patient was presumed to have SCH if presenting with icteric or anicteric hepatomegaly with or without right hypo-chondrial pain. A presumptive diagnosis of SCH was made in thirty (30%) of the 100 patients who made up the study population, 15 males and 15 females in a ratio of 1:1. Only 10 out of the 30 (33.3%) patients had complete laboratory results bringing the final sample size from 30 to 10. A definitive diagnosis of SCH (AIHC, AHSS and AHSCC) based on LFT features with or without USS support but with associated sudden decline from steady state haemoglobin and right upper quadrant pain for AHSS. Characteristics of the subjects, comparisons of and relationships between variables were analyzed with appropriate

descriptive and inferential statistics using the Statistical Package for Social Science (SPSS) version 21.

Results:

One (10%) had positive history of frequent blood transfusions. Haemolytic crisis was a frequent finding. All had hepatomegaly with varying degrees of jaundice, while 1/10 (10%) also had right upper quadrant (RUQ) pain. Nine of them (90%) had evidence of haemolysis on blood film with no significant haemoglobin (Hb) drop from steady state levels. Mean Hb concentration was 6.7g/dl. Eighty percent (8 out of 10) had mild-to-moderate derangement of LFT. One patient (10%) had evidence of acute hepatic sequestration syndrome (AHSS). A patient (10%) had LFT suggestive of acute intra-hepatic cholestasis (AIHC) and increased echogenicity on USS. One patient (10%) fulfilled the criteria for acute hepatic sickle cell crisis (AHSCC) There were no evidence of hepatitis B and C infections, iron overload, gallstones and biliary obstruction.

Conclusions: Sickle cell hepatopathy is rare in children but may present as AHSCC, AHSS and AIHC.

Keywords: Hepatic insults, Abnormal Liver Function, Clinical evidence, Sickle cell hepatopathy.

INTRODUCTION

Sickle cell disease (SCD) is a common hemoglobinopathy which can affect multiple organ systems in the body. Within the digestive tract, the hepatobiliary system is most commonly affected in SCD. The manifestations range from benign hyperbilirubinemia to overt liver failure, with the spectrum of acute clinical presentations often referred to as "sickle cell hepatopathy", an umbrella term referring to liver dysfunction and hyperbilirubinemia due to intrahepatic sickling process during crisis leading to ischemia, sequestration and cholestasis[1]. Acute Hepatic Sickle Cell Crisis (AHSCC), Acute and Chronic Intra-Hepatic Cholestasis (AIHC and CIHC) and Acute Hepatic Sequestration Syndrome (AHSS) constitute the liver pathologies arising primarily from the sickling process. Secondly, a range of hepatic diseases arise from multiple transfusions and include Hepatitis B and C infection and Iron overload. These have been described by some authors as 'multi-transfusion hepatopathy'. The hepatic consequences of chronic haemolysis such as gallstone, cholecystitis, choledocholithiasis with chronic bile duct obstruction comprise the other common group of Sickle Cell Hepatopathy.

These clinical conditions present similarly with hepatomegaly, right upper quadrant abdominal pain, jaundice and varying levels of derangement of serum bilirubin and liver enzymes. The definition of acute hepatic crisis is not always precise, and the true incidence may be lower than 10%. A typical hepatic crisis presents with painful hepatomegaly, bilirubin less than 200 μM, and transaminase level of less than 300 IU[2]. The pathophysiology of acute hepatic crisis(AHSCC) and sickle cell intrahepatic cholestasis is probably the same with intrasinusoidal

sickling and subsequent obstruction and hepatocyte ischemia[2] but with different levels of severity. Namely, the benign, isolated, acute intrahepatic cholestasis in which patients also present with extreme hyperbilirubinemia but without failure of synthetic function (AIHC)[3,4]. Sickle cell intrahepatic cholestasis may present as a severe syndrome of acute liver failure with extremely high bilirubin levels (as great as 1,500–2,500 μM) which is associated with a very high mortality (CIHC)[5,6]. Another severe hepato-biliary manifestation of SCA is hepatic sequestration (AHSS). It presents with sudden hepatomegaly, pain, and acute anemia but without cholestasis[5,7]

Thus AHSCC is mild and self -resolving in children, AHSS is a medical emergency while AIHC may progress to CIHC, fulminant hepatic failure and ultimately death[6]. Therefore, the similarity in presentation yet varied prognosis makes it imperative that a high index of suspicion and in-depth laboratory evaluation is needed for proper diagnosis and early, appropriate intervention in these patients. Few literatures have described these clinical conditions in detail[1-6].

METHODS

The study was a cross-sectional observational review of 100 children with sickle cell anaemia (SCA) on regular clinic follow-up. History of scleral icterus, abdominal pain, multiple blood transfusions and frequent vaso-occlusive and haemolytic crises, demographic data such as age and sex, were obtained. Patients were examined for sclera icterus as well as hepatomegaly and right upper quadrant tenderness. Liver function test (LFT) for bilirubin in umol/L total and direct and for enzymes in IU/L: aspartate and alanine transaminases (AST and ALT) and alkaline phosphatase(ALP) Urinalysis for haematuria(urobilinogenuria), complete blood count (CBC) for white blood cell (WBC) x 10^9 and haemoglobin(Hb) in g/dl, abdomino-pelvic ultrasound scan (USS), hepatitis virus serology, quantitation of haemoglobin and serum ferritin of subjects were obtained. A patient was presumed to have SCH if presenting with icteric or anicteric hepatomegaly with or without right hypo-chondrial pain and haematuria (urobilinogenuria). A presumptive diagnosis of SCH was made in thirty (30%) of the 100 patients who made up the study population, 15 males and 15 females in a ratio of 1:1. Only 10 out of the 30 (33.3%) patients had complete laboratory results bringing the final sample size from 30 to 10. The collected data was analyzed using both descriptive and inferential statistics. The descriptive statistics – frequency, percentage, mean, 5% trimmed mean, range and standard deviation were used to summarize the characteristics of the subjects. The inferential statistics – Paired Samples t-test, Independent Samples t-test and Pearson Correlation were used for comparisons and ascertaining relationships at 5% level of significance. Hence, significant difference or

relationship existed if p-value is less than .05, ($p < .05$). These statistics were done with the aid of the Statistical Package for Social Science (SPSS) version 21 and Microsoft Excel 2007.The relationship between the Haemoglobin (Hb), White blood cell (WBC) and LFT was evaluated. A previously obtained steady state[8] Hb and WBC were compared with similar parameters obtained at the time of the study. The LFT, liver sizes, Hb and WBC values of subjects at steady state and at time of the study were compared. Similar comparisons were made between those with SCH diagnosis and those without. Diagnosis of AIHC was made based on marked elevation of ALP, AST ALT, bilirubin total with conjugated > 50% of total[1] . AHSSC was diagnosed based on normal or mildly elevated ALP, moderately elevated AST and ALT, moderately elevated bilirubin total with conjugated < 50% of total[1]. A diagnosis of AHSS was made with moderately elevated ALP, normal ALT, normal or mildly elevated AST, moderately elevated bilirubin total with conjugated < 50% of total and significant drop in steady state haemoglobin accompanying hepatomegaly[1].

RESULTS

Table1: Prevalence of SCH based on Age and Gender n = 10

Characteristics		**SCH**		**Total**
		Positive	Negative	
Age (years)	- 1 – 4	0 (0.0)	2 (100.0)	2
	- 5 – 8	3 (50.0)	3 (50.0)	6
	- 9 – 12	0 (0.0)	2 (100.0)	2
Gender	Male	0 (0.0)	4 (100.0)	4
	Female	3 (50.0)	3 (50.0)	6

Table 2: LFT characteristics (Serum bilirubin and enzyme levels) of the subjects n = 10

	Frequency	Percentage	Range	M±SD	5% Trimmed Mean
Bilirubin Total(mg/dl)8-17			11.3 – 370.2	70.82±107.97	57.49
Normal	1	10.0			
Elevated	9	90.0			
Mild-20 – 100	8	80.0			
Mod-100 – 300	0	0.0			
Marked-300 +	1	10.0			
Bilirubin Direct(mg/dl),n=<8			1.2 – 293.5	39.25±89.51	27.42
Normal	3	30.0			
Elevated	7	70.0			
ALP(IU/L), n=25-92			172.2 – 332.8	242.10±56.84	240.94
Elevated	10	100.0			
Mild-100 – 200	3	30.0			
Mod-200 – 300	5	50.0			
Marked-300 +	2	20.0			
ALT(IU/L),n=3-40			11.4 – 90.2	32.92±24.60	30.93
Normal	4	40.0			
Elevated	6	60.0			
Mild-20 – 50	4	40.0			
Mod-50 – 70	1	10.0			
Marked70 +	1	10.0			

AST(IU/L),n=5-40			32.6 – 106.1	54.94±25.20	53.34
Elevated	10	100.0			
Mild-20 – 50	6	60.0			
Mod-50 – 70	1	10.0			
Marked-70 +	3	30.0			

Table 3: Relationship between CBC(Hb and WBC) and LFT in subjects:

	Hb r (p)	WBC r (p)
Total bilirubin	.063 (.873)	-.061 (.876)
Direct bilirubin	.028 (.944)	.004 (.992)
ALP	-.123 (.753)	.400 (.287)
ALT	-.102 (.794)	.071 (.855)
AST	-.398 (.289)	.066 (.866)

Table 4: Comparison of the LFT of SCH positive and negative

	SCH	M±SD	T	Df	p-value
Total bilirubin	Positive	139.67±200.08	1.386	8	.203
	Negative	41.31±27.49			
Direct bilirubin	Positive	103.97±164.18	1.628	8	.142
	Negative	11.51±6.46			
ALP	Positive	235.83±24.93	-.216	8	.835
	Negative	244.79±67.91			
ALT	Positive	60.70±29.30	3.517	8	.008
	Negative	21.01±8.38			
AST	Positive	88.43±15.87	6.504	8	<.001
	Negative	40.59±8.22			

Table5: Comparison of mean Hb and WBC of SCH positive and negative at steady state and study time.

	SCH	M±SD	T	Df	p-value
Hb(at study), g/dl	Positive	6.33±1.29	-1.790	7	.117
	Negative	7.77±1.06			
WBC(at study) $x10^9$	Positive	18.97±1.48	.778	7	.462
	Negative	17.15±3.80			
Hb(steady state) g/dl	Positive	7.37±0.61	-.706	5	.512
	Negative	7.80±0.91			
WBC(steadystate) $x10^9$	Positive	12.37±2.43	-1.030	5	.350
	Negative	14.71±3.28			

Demographic characteristics of the Subjects: The subjects were evenly stratified into age groups 1-4 years (2), 5-8 years (6), 9-12 years (2). Age range was 2-11years with mean and standard deviation of M±SD 6.40±2.76. Modal age group was 5 – 8 years (60.0%). There were 4 (40%) males and 6 females (60%)

Clinical features of subjects: All 10 patients had hepatomegaly, 5 (50%) had liver size > 4cm while the other 50.0% had hepatomegaly of < 4 cm. Six subjects (60.0%) had jaundice and 1(10.0%) had right upper quadrant pain. All had urobilinoginuria on urinalysis. All 10 subjects were presumed to have SCH.

LFT (Serum bilirubin and liver enzymes):

Table2: Most of the children had an elevated total bilirubin (90.0%), direct bilirubin (70.0%) and ALT (80.0%). All had an elevated ALP (100.0%) and AST (100.0%). Specifically, the range, mean and standard deviation as well as 5% trimmed mean of the total and direct bilirubin, ALP, ALT and AST are depicted.

Prevalence of SCH:

Table1: Overall prevalence of SCH was 30 percent (3/10). These were in females and in the 5-8 years age range. Age prevalence of SCH was 0.0% (1 – 4years), 50.0% (5 – 8 years) and 0.0% (9-12 years). Sex prevalence of SCH was 0.0% for males and 50.0% for females.

CBC:

A comparison of mean Hb and mean WBC at steady state and at the study time showed that mean WBC at study time was significantly higher than at steady state (19.10±1.93; 13.71±2.99) ($p = .004$). For Hb, there was no significant difference between the two values ($p = .293$);

Relationship between CBC and LFT in subjects:

Table3. Although not statistically significant, the relationship between WBC and ALP show a positive trend ($r = .400$, $p = .287$) while that between Hb and AST show a negative trend ($r = -.398$, $p = .289$). This implies that higher WBC level was associated with higher ALP level and vice versa while higher Hb level was associated with lower AST level and vice versa.

Comparison of the liver sizes in SCH positive and negative:

SCH positive subjects had significantly larger liver sizes than the SCH negative (6.00±2.00; 2.93±0.73)($p = .006$).

Comparison of the LFT in SCH positive and negative:

Table4. There was significant difference between the two groups for ALT ($p = .008$) and AST ($p =<.001$). For both SCH positive subjects had higher values [(60.70±29.30;21.01±8.38)(88.43±15.87;40.59±8.22)] ALT and AST respectively. There was no significant difference in the ALP, total bilirubin ($p = .203$) and direct bilirubin ($p = .142$) between the two groups although subjects who were SCH positive seemingly had higher total and direct bilirubin. All SCH negative and two (66.7%) of the SCH positive had direct bilirubin < 50% of total while and 1(33.3%) had direct >50% of total

Comparison of the study time and steady state mean Hb and WBC in SCH positive and negative.

Both Hb values and steady state WBC were lower with higher study time WBC in SCH positive but there was no significant difference between these values in the two groups. All p values = > 0.05.

Hb quantitation of the subjects:
The ranges, mean and standard deviation of HbS, HbF, HbA_2 and HbA_1 were 79.4 – 86.6, 4.5 – 11.0, 3.1 – 5.1, 3.6 – 9.6, M±SD 82.18±3.12, 8.03±3.46, 3.88±0.87 and 5.93±2.61 respectively.
Abdomino-pelvic ultra-sound scan:

Hepatomegaly and nephropathy are common in SCH positive and negative.

DISCUSSION

It has been documented that hyper-bilirubinaemia may punctuate the course of SCA resulting from haemolysis, intercurrent infection, viral hepatitis and intra-hepatic sickling[9]. Similarly, 90% of our subjects had haemolysis evidence of elevated total bilirubin with unconjugated fraction greater than 50% of total in eight out of the nine. Similar to the observation by Johnson *et al*[10] AST was elevated in all, the high AST being associated with low Hb an extra evidence of haemolysis[10]. Thus abnormal LFT are common in patients with SCA even in the absence of liver disease and raised bilirubin predorminantly unconjugated are universal due to chronic hemolysis.[11]

Neutrophillia, a total WBC significantly higher than steady state levels as well as the observed positive trend between mean WBC and serum ALP levels are the observed evidences for inter-current infection in this study. The absence of significant difference between study time and steady state WBC in both SCH positive and negative supports the idea that intercurrent infections are responsible for the observed trend in WBC rather than SCH.

Hepatic sequestration may occur in SCA usually presenting with right upper quadrant pain, increasing hepatomegaly and a falling hematocrit.[12,13] Only 16 probable cases of AHSS has been reported to date[14,15,16] and proved fatal in earlier cases[14]. We report a 10% prevalence of AHSS in our small sample sized study.

Repeated episodes of intra-hepatic sickling (AHSCC) in SCA resulting in fluctuating intra-hepatic cholestasis (AIHC) and presenting with recurrent attacks of abdominal pain and jaundice has been reported[9,14] Our patient with features of AIHC may have had similar symptoms in the past. Similar to our finding, cases of AHSCC have been reported with right upper quadrant pain, hepatomegaly, jaundice, low grade fever and in approximately 10% of children with SCA[9,14]. A significant proportion of our patients presented with hepatomegaly and jaundice while few had right upper quadrant pain. The liver sizes were significantly larger in those with SCH than

others. The female preponderance of SCH noted in addition to the age prevalence among 5-8 year olds hasn't been reported earlier.

Ann *et al*[17] observed that SCH is an uncommon complication in children which collaborates the 30% prevalence observed in this study. They[17] also noted that SCH is characterized by variable hyperbilirubinaemia and either mild or severe hepatic dysfunction. Similarly, the significantly elevated serum transaminases in SCH connote hepatic dysfunction. In contrast, the observed differences in total and differential bilirubin levels though seemingly higher in those with SCH than others were not statistically significant. This difference may be due to the small sample size of this study.

Hatton *et al*[18] had described 2 cases of AHSS with little alteration in the LFT in whom there was a rapid decrease in the haematocrit paralled by a transient dramatic increase in hepatic size. Similarly, 10% of our subjects with moderately elevated ALP, normal ALT, normal or mildly elevated AST, moderately elevated bilirubin total with conjugated < 50% of total and significant drop in steady state haemoglobin accompanying hepatomegaly[1] had diagnosis of AHSS.

In contrast, the documented characteristic finding of AIHC is markedly elevated plasma total bilirubin up to 273mg/dl[7] with conjugated greater than 50% of the total[19] and marked elevation of serum transaminases. These features of AIHC are mirrored in another 10% of our study participants in whom a diagnosis of AIHC was made based on marked elevation of ALP, AST ALT, bilirubin total with conjugated > 50% of total[1].

Diggs[20] noted that 10% of the subjects with AHSCC had mildly elevated plasma total bilirubin with indirect greater than direct in addition to mild to moderate elevation of the transaminases. This has also been reported by some other authors.[9,14,15] This picture mimicks that of another 10% in our study in whom AHSSC was diagnosed based on normal or mildly elevated ALP, moderately elevated AST and ALT, moderately elevated bilirubin total with conjugated < 50% of total[1] . A picture that reflects elevated liver enzymes of AHSCC accompanied by exacerbation of the chronic hemolytic state of SCA.

Serum ferritin levels of subjects were in normal limits. This is expected as there was barely any history of multiple transfusion therapy since serum ferritin levels have been found to correlate with the number of units of blood transfused and increased risk of iron overload[21].

Sheehy[14] and Johnson *et al*[10] found that the clinical course of sickle cell anaemia patients with acute hepatitis could either differ[10] or not differ[14] from control patients without sickle cell anaemia. None of our patients had evidence of hepatitis B or C probably because the risk of this infection is related to the number of units of blood transfused.

Abdominal ultrasound of our subjects showed no evidence of biliary obstruction such as gall stones and bile duct dilatation[22].

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