ISSN NO. 2320-5407

Journal homepage: http://www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH

RESEARCH ARTICLE

FREQUENCY AND OUTCOME OF HEPATOBILIARY DISORDERS IN ADULT HOMOZYGOUS SICKLE CELL DISEASE PATIENTS

Hany M. Elsadek[1], Ahmad M. Hassaneen[2], Mamdouh M. Radwan[3]

1 Gastroenterology unit, Internal Medicine department, Faculty of Medicine, Zagazig University, Egypt
2 Clinical Pathology department, Faculty of Medicine, Zagazig University, Egypt
3 Pathology department, Royal Commission Medical Center (RCMC), Yanbu, Saudi Arabia

Manuscript Info

Manuscript History:

Received: 19 September 2014
Final Accepted: 29 October 2014
Published Online: November 2014

Key words:

sickle cell disease, hepatobiliary, hepatopathy, iron overload

Corresponding Author

Hany M. Elsadek

Abstract

Background: Sickle cell disease (SCD) may affect the hepatobiliary system at different ages in different ways. The liver may be affected by intrasinusoidal sickling, vaso-occlusion, intrahepatic cholestasis, iron overload and viral hepatitis. The biliary tree could be affected by gallstones, biliary sludge, and obstruction.

Objective: The aim of this study was to identify the frequency and outcome of hepatobiliary disorders in adult patients with homozygous SCD.

Methods: In this prospective screening study we evaluated the demographic, clinical, laboratory, radiologic and histopathologic data concerning hepatic and biliary disorders with emphasis on the related complications and mortality, in 118 adult Saudi patients with homozygous SCD, over three years of follow up, in Yanbu, Saudi Arabia.

Results: The mean age of all participants was 27.9 ± 9.0 (18-46) years and 55.9% were males. Hepatobiliary disorders were discovered in 90.7% of patients, including acute conditions like, hepatic crisis (9.3%), acute calcular cholecystitis (7.6%) and acute sickle cell hepatopathy (5.9%), and chronic conditions like, hepatomegaly (61.9%), asymptomatic cholelithiasis (33.9%), hepatic iron overload (31.4%), as well as viral hepatitis C (16.9%) and B (11.0%). Intrasinusoidal sickling and Kupffer cell hyperplasia were consistently seen in all liver biopsies (n=25), denoting a degree of vascular process. There were 11 cholecystectomies (9.3%), seven cases with hepatic dysfunction (5.9%), one mortality (0.8%) due to acute severe sickle hepatopathy, and un otherwise uncomplicated clinical course in most cases.

Conclusion: Hepatobiliary disorders are common in adult homozygous SCD patients and often have a benign disease course

Introduction

Sickle cell disease (SCD) is an inherited chronic hematological disorder in which there is an abnormality in the amino acid sequence of the β-globin chain responsible for production of hemoglobin S (HbS). It is characterized by chronic hemolytic anemia and vaso-occlusive events that may cause multiple organs infarctions and damage [1].

Patients who are homozygous for this mutation (SS) have the full blown picture of the disease with a wide range of manifestations and complications as pain syndromes, hematological, musculoskeletal, pulmonary, hepatobiliary and other disorders. Whereas, those with heterozygous genotypes tend to have a mild form of the disease [2].

Disorders of the liver and biliary system in SCD patients are common and multifactorial. These may result primarily from chronic hemolysis (e.g. pigmented gallstones and choledocholithiasis) and intrasinusoidal sickling of red blood cells (RBCs) (e.g. hepatic crisis and sickle cell hepatopathy), or they may be secondary to treatment with repeated blood transfusion (e.g. hemosiderosis and viral hepatitis) [3-5]. The spectrum of hepatobiliary disorders in adults with SCD includes in addition, asymptomatic hepatomegaly, asymptomatic elevation of liver enzymes, as well as some rare complications or associations to SCD e.g. hepatic infarction, liver abscess, and biloma, autoimmune hepatitis, Budd-Chiari syndrome and hyperammonemia due to zinc deficiency [2,5-6].

Sickle cell hepatopathy is a relatively uncommon primary complication of homozygous SCD, not explained by hemolysis, hepatic sequestration, extrahepatic obstruction or viral hepatitis, but instead results from intrasinusoidal sickling and vascular stasis with subsequent hypoxic injury to the liver parenchyma and intrahepatic cholestasis [7].

The reported prevalence of homozygous SCD at different areas in Saudi Arabia, ranges from 0.24% to 2.6% [8-11]. However, no estimations of the rates and outcomes of hepatobiliary disorders related to SCD in Saudi adult patients are available, and only a scanty number of limited case series involving other populations are available [3-4,6]. Given the complexity of differential diagnosis of abnormal liver functions in SCD patients and the challenge facing physicians to recognize the life-threatening conditions from the more frequent mild syndromes [4], we conducted this study to identify the spectrum and frequency of hepatobiliary disorders and their related outcomes in Saudi adult homozygous SCD patients in Yanbu, a city in the western province of Saudi Arabia.

METHODS

Selection of Patients:

In this prospective screening study, we evaluated 118 Saudi adult homozygous SCD patients (mean age:27.9±9.0, males:55.9%), who had been diagnosed and managed in Royal Commission Medical Center (RCMC), Yanbu, Saudi Arabia, over a follow up period from June 2011 till June 2014. Demographic features, clinical findings pointing to suspected hepatobiliary disorders and confirmatory tests were recorded. In addition, we reported the outcomes including self limitation and full recovery, hepatic dysfunction, chronicity, recurrence after initial recovery, need for surgery or other interventions like endoscopic retrograde cholangio-pancreatography (ERCP), and mortality. SCD in children was beyond the scope of the study, and otherwise, there were no exclusion criteria. The study was approved from the ethical committee of RCMC, and an informed written consent was obtained from each patient.

Clinical presentations and confirmatory tests of hepatobiliary disorders: according to previously defined criteria [2,5].

- Acute right upper quadrant pain syndromes refer to acute abdominal pain in sickle cell patients associated with symptoms of hepatobiliary diseases. These are differentiated from skeletal pains of SCD by the new onset, localization of pain, accompanying nausea and vomiting as well as more jaundice than usual. These include:
  - Biliary disease: Increasing nausea and vomiting, colicky nature of pain, positive Murphy's sign, total serum bilirubin exceeding 4 mg/dl and elevated alkaline phosphatase point to gallbladder and biliary disease to be confirmed by abdominal ultrasound. Direct hyperbilirubinemia rather than bile duct dilatation is typical for the usually low-grade biliary obstruction caused by the classically small pigment stones.
  - Hepatic crisis: Right upper quadrant fullness with dull pains, tender hepatomegaly and elevation of serum alanine aminotransferase (ALT) similar to or more than serum aspartate aminotransferase (AST) (usually less than 300 IU/liter) point to hepatic crisis, in which, serum bilirubin levels decrease to prior values in about two weeks, as well, elevation of ALT starts to decrease after a few days and return to prior values in about three months [2,12].
  - Acute Sickle cell hepatopathy (intrahepatic cholestasis): It is characterized by marked direct hyperbilirubinemia (usually total bilirubin >13 mg/dL) and nearly normal or mildly elevated liver transaminases. The disease has a mild self limited form with a bilirubin level ≤ 30 mg/dl, and a severe form that represents a life threatening acute liver cell failure (LCF), characterized by severe coagulopathy, encephalopathy and deep jaundice with a bilirubin level ≥ 30 mg/dl and sometimes exceeding 80 mg/dl [7].

  - Hepatic infarction that is diagnosed by abdominal ultrasonography and computerized tomography (CT).
- Other rare acute complications that are either diagnosed by ultrasonography and CT e.g. liver abscess, biloma and Budd-Chiari syndrome, or diagnosed biochemically e.g. hyperammonemia due to zinc deficiency.
- Chronic Sickle cell hepatopathy, results from progression of either mild or severe acute forms, with persistent or recurrent extreme hyperbilirubinemia. Sickle cell hepatopathy is confirmed by histopathologic findings, on examination of liver biopsy, including ischemic cholangiopathy, strictures of intrahepatic biliary radicals, cannalicular dilatation and less specifically sinusoidal dilatation, Kupffer cell hyperplasia, erythrophagocytosis, focal necrosis, portal fibrosis, and micronodular cirrhosis [7,13].
- Other concomitant chronic hepatic diseases that may progress to liver cirrhosis.
  - Viral hepatitis is diagnosed serologically.
  - Hemosiderosis (iron overload) is diagnosed biochemically if serum ferritin level is >1000 ng/ml, with or without histopathologic confirmation.
  - Autoimmune hepatitis is rare and can be diagnosed by detection of specific antibodies.
- Asymptomatic hepatomegaly.
- Asymptomatic persistent elevation of hepatic transaminases.

Methods of Laboratory evaluations

- Sickle cell disease was diagnosed by:
  I – Hemoglobin electrophoresis: Capillary electrophoresis was done using the Minicap instrument (Sebia, USA). The principle of this technique is separation of different hemoglobins in very narrow capillary tubes filled with electrolyte solution in presence of high voltage and tight temperature control which allows fast analysis and excellent resolution. Ethylenediamine-tetraacetic acid (EDTA) blood was centrifuged at 5000 rpm for 5 minutes, the overlying plasma was removed and the packed RBCs were vortexed for 5 seconds. After the sample (packed RBCs) was loaded into the Minicap instrument, electrophoresis was performed in alkaline buffer (pH 9.4) and separation was done by solution pH and endosmosis. The hemoglobins were measured by the instrument at 415 nm wavelength. Electrophoretograms were recorded with the location of specific hemoglobins in specific zones [14].
  II – Sickling test: One drop of EDTA blood was added to 5 drops of freshly prepared reducing agent formed of 2 volumes of sodium dithionate and 3 volumes of disodium hydrogen phosphate on a slide with a cover glass then examined microscopically. In case of SCD, sickling of RBCs occurs almost immediately.
- Other laboratory tests:
  Liver function tests [bilirubin, albumin, ALT, AST & alkaline phosphatase (ALP)] were assessed using Cobas Integra 400 chemistry autoanalyzer (Roche Diagnostics). Prothrombin time was estimated using BFT II Analyzer (Siemens) and results were expressed as international normalized ratio (INR). Serum ferritin was estimated using the VIDAS system (bioMérieux, France) by enzyme linked fluorescent assay (ELFA) technique. The principle of the assay is one-step enzyme immunoassay sandwich method with a final fluorescent detection. Complete blood count (CBC) was performed using automated blood counter (Sysmex N21), and reticulocytic count was done using brilliant cresyl blue reagent. Hepatitis B surface antigen (HBs Ag) and Hepatitis C antibodies (HCV Ab) were detected by Cobas e 411 immunoassay analyzer (Roche Diagnostics), the principle is electro-chemiluminescence immunoassay (ECLIA). Polymerase chain reaction (PCR) was applied to patients with positive results. Antinuclear antibody (ANA), Anti–smooth muscle antibody (ASMA) and Anti–liver-kidney microsomal antibody - type 1 (anti–LKM-1) were detected by Indirect Immunofluorescence, for diagnosis of autoimmune hepatitis.

Histopathologic examination of liver biopsies

Liver biopsies were obtained from 25 patients with one or more of: unexplained hepatomegaly and persistently elevated liver enzymes, positive HCV serology, abdominal surgery (cholecystectomy, or splenectomy) during the study period. Biopsies were taken either intraoperative (15 cases) or as percutaneous technique (10 cases), after getting informed consent. Biopsy specimens were fixed in 10% formaldehyde solution, embedded in paraffin, and read by the same single pathologist. Histopathological sections were stained with Hematoxylin-eosin, van Gieson, Gomori's trichrome, periodic acid-Schiff, Prussian blue and Gomori's silver stains. Degree of hemosiderosis was evaluated according to the deposition of hemosiderin in the Kupffer cells and hepatocytes and reported as mild, moderate or severe. Chronic hepatitis was evaluated by the modified histological activity index [15].

Statistical analysis

Statistical analysis was done by using SPSS (Statistical Package for Social Science) version 19. The data were presented in the form of means and standard deviation, or in the form of numbers and percentages. Data were tested using the proper tests, including student's t-test, one way ANOVA and Chi-Square. Statistical significance was set at $p< 0.05$.

RESULTS

The demographic and clinical criteria of all participating adult homozygous SCD patients (n=118) were shown in table (1). The mean age was 27.9±9.0 years and 55.9% were males. Mean number of transfused units of blood / year was 10.9±5.4. Table (2) shows the percentages of cases with abnormal liver function tests and positive markers for viral and autoimmune hepatitis. In addition, table (2) showed the mean values of hemoglobin concentration (8.73 ± 2.48 g/dl), reticulocytic count (6.48 ± 3.59 %) and serum ferritin (391.7± 304.5 ng/ml).

As shown in table (3), abdominal ultrasound revealed hepatomegaly and features suggestive of liver cirrhosis (irregular surface, coarse echo texture ± small size) in 61.9% and 7.6% of patients, respectively. Gall bladder was surgically removed in 9.3% of patients. Gallstones were detected in 41.5% of the study population, with signs of inflammation in nine patients and choledocholithiasis in four patients.

Table 1. Demographic and Clinical criteria of all patients

Criteria	No. (%) or mean±SD (range)
Sex	
Male	66 (55.9%)
Female	52 (44.1%)
Age (mean±SD, range) years	27.9 ± 9.0 (18-46)
BMI (mean±SD, range)	18.9 ± 2.6 (16-24)
Jaundice	58 (49.2%)
Encephalopathy	4 (3.4%)
Units of blood transfusion (no./year)	**10.9±5.4**
< 10	54 (45.8%)
10-19	56 (47.5%)
≥ 20	8 (6.8%)
Comorbidities	
Diabetes mellitus (DM)	3 (2.5)

Table 2. Laboratory values of all patients

Criteria	No. (%) or mean±SD (range)
Abnormal liver function tests	
↑ALT (≥2 folds)	36 (30.5%)
↑AST (≥2 folds)	53 (44.92%)
↑ALP (≥2 folds)	50 (42.73%)
↑Total bilirubin (>2 mg/dl)	68 (57.6%)
↑Direct bilirubin (>50% of total)	31 (26.3%)
↑INR (>1)	7 (5.9%)
↓Albumin (< 3 g/dl)	1 (0.8%)
Hemoglobin (mean±SD, range) g/dl	8.73 ± 2.48 (6-11)
Reticulocyte % (mean±SD, range)	6.48 ± 3.59 (2.5-12)
Serum ferritin (mean= 391.7± 304.5 ng/ml)	**↑ in 70 (59.3%)**
Normal: <300 ng/ml in male, <150 ng/ml in females	48 (40.7%)
Above normal: up to 1000 ng/ml	33 (28.0%)
High: > 1000 ng/ml	37 (31.4%)
HBs Ag: positive	13 (11.0%)
HCV Ab: positive	20 (16.9%)
ANA: positive	1 (0.8%)
ASMA: positive	1 (0.8%)
Anti–LKM-1: positive	1 (0.8%)

Table 3. Ultrasonographic criteria of all patients.

Criteria	No. (%)
Hepatomegaly	73 (61.9%)
Cirrhotic pattern	9 (7.6%)
Cholelithiasis	49 (41.5%)
Choledocholithiasis	4 (3.4%)
Gallbladder sludge	15 (12.7%)
Cholecystectomy	11 (9.3%)

The principal histopathologic findings in all liver biopsies (n=25) were shown in table (4). Vascular lesions were found in all biopsied cases. A degree of liver siderosis was found in 80% (20/25) of patients. Seven cases showed fibrosis; one had chronic viral hepatitis B & C, one had autoimmune hepatitis, one had chronic hepatopathy and all had iron overload). Cirrhosis was seen in four cases.

Table 4. Liver histopathology of all biopsied cases.

	Vascular lesions	Hepatopathy	Hepatitis B	Hepatitis C	Liver siderosis	Autoimmune hepatitis
1	Kupffer cell hyperplasia, erythrophagocytosis ± sinusoidal dilatation.	–	–	–	Severe disease	–
2		–	–	–	–	–
3		–	–	Inactive disease	–	–
4		–	–	–	Mild disease	–
5		–	–	–	Severe disease with fibrosis	–
6		–	–	–	Mild disease	–
7		–	–	–	Moderate disease	–
8		Mild disease	–	–	Severe disease	–
9		–	Inactive disease	–	–	–
10		–	–	–	Mild disease	–
11		–	–	Inactive disease	–	–
12		Severe disease with fibrosis & cirrhosis	–	–	Moderate disease	–
13		–	Inactive disease	–	Mild disease	–
14		–	–	–	Moderate disease	–
15		Mild disease	–	–	–	–
16		–	–	–	Mild disease	–
17		–	Active disease with fibrosis & cirrhosis	Active disease with fibrosis & cirrhosis	Severe disease with fibrosis & cirrhosis	–
18		–	–	–	Severe disease with fibrosis	–
19		–	–	–	Moderate disease	Active disease with fibrosis & cirrhosis
20		–	–	–	Mild disease	–
21		–	–	–	Mild disease	–
22		–	–	Inactive disease	Mild disease	–
23		–	–	–	Severe disease with fibrosis & cirrhosis	–
24		–	Inactive disease	–	Mild disease	–
25		–	–	Active disease	Moderate disease	–

Overall, hepatobiliary disorders were recorded in 107 of our SCD patients. Despite the great overlap of clinical and laboratory criteria, we could classify them into acute and chronic disorders, with detailed recording of their frequencies and outcomes, as described in table (5). The commonest acute condition was hepatic crisis (9.3%), followed by acute calcular cholecystitis (7.6%). The commonest chronic condition was hepatomegaly (61.9%),

followed by asymptomatic cholelithiasis (33.9%). In three cases (2.5%), hepatic dysfunction occurred acutely, that was treated conservatively and recovered in two of them and ended fatally in a third patient with an acute severe sickle hepatopathy who constituted the only case of mortality (0.8%) in the study population. Chronic hepatic dysfunction with ascites, recurrent encephalopathy and coagulopathy developed in four patients (3.4%).

Table 5. clinical spectrum, frequency and outcome of hepatobiliary disorders in our patients.

Spectrum	Frequency (n= 118)	Age	Male Sex (n=66)	Diagnostic criteria	Outcome					
					Self limited	Hepatic dysfunction	Chronicity	Recurrence	Surgery or ERCP	Death
	No, %	mean±SD (years)	No, %		No, %	No, %	No, %	No, %	No, %	No, %
ACUTE CONDITIONS	32, 27.1	28.7±9.0	17,53.1		11, 34.4	3, 9.4	7, 21.9	4,12.5	11, 34.4	1, 3.1
Hepatic crisis	11, 9.3	19.8±1.2	6, 5.5	Mean ALT: 238 IU/L	7, 63.6	1, 9.1	0, 0.0	3,27.3	0, 0.0	0, 0.0
Hepatopathy	7, 5.9	31.1±6.9	4, 5.7	Total bilirubin: 31.5 mg/dl ± Histopathologic stigmata	2, 28.6	1, 14.3 (died)	3, 42.9	1,14.3	0, 0.0	1,14.3
Hepatic infarct	3, 2.5	29.3±9.3	2, 66.7	Abdominal Ultrasound	2, 66.7	1, 33.3 (abscess)	0, 0.0	0, 0.0	0, 0.0	0, 0.0
Liver abscess	1, 0.8	25	0, 0.0	Abdominal CT	0, 0.0	1, 100	0, 0.0	0, 0.0	0, 0.0	0, 0.0
Calcular cholecystitis	9, 7.6	35.2±8.3	4, 44.4	Abdominal Ultrasound	0, 0.0	0, 0.0	4, 44.4	0, 0.0	7, 77.8	0, 0.0
Choledocho-lithiasis	4, 3.4	38.8±3.3	2, 50.0	Abdominal Ultrasound + ERCP	1, 25.0	0, 0.0	0, 0.0	1,25.0	4, 100.0 (ERCP+ surgery)	0, 0.0
CHRONIC CONDITIONS	82, 69.5	28.5±9.3	47,57.3		5, 6.1	4, 4.9	82,100.0	9,11.0	2, 2.4	0, 0.0
Hepatomegaly	73, 61.9	28.3±9.2	39,53.4	Abdominal Ultrasound	0, 0.0	0, 0.0	73,100.0	0, 0.0	0, 0.0	0, 0.0
Persistently ↑ ALT ≥ 2 folds	36, 30.5	25.7±8.9	21, 58.3	Mean ALT: 109.4±28.1 IU/L	5, 13.9	0, 0.0	22, 61.1	9,25.0	0, 0.0	0, 0.0
Chronic hepatopathy	3, 2.5	40.0±4.4	2, 66.7	Mean total bilirubin: 58.7 mg/dl (mainly direct) ± Histopathologic stigmata	0, 0.0	1, 33.3	3, 100.0	0, 0.0	0, 0.0	0, 0.0
Viral hepatitis B	13, 11.0	28.8±9.3	10, 50.0	Positive HBsAg & PCR ± Histopathologic stigmata	0, 0.0	0, 0.0	13,100.0	0, 0.0	0, 0.0	0, 0.0
Viral hepatitis C	20, 16.9	29.8±8.0	7, 53.8	Positive HCV Ab & PCR ± Histopathologic stigmata	0, 0.0	1, 5.0	20,100.0	0, 0.0	0, 0.0	0, 0.0
Hemosiderosis	37, 31.4	29.5±9.5	24, 64.9	Serum ferritin > 300 in males and > 150 in female ± Histopathologic stigmata	0, 0.0	2, 2.9	37,100.0	0, 0.0	0, 0.0	0, 0.0
Autoimmune hepatitis	1, 0.8	34	0, 0.0	Positive ANA, ASMA and Anti–LKM-1 + Histopathology	0, 0.0	0, 0.0	1, 100.0	0, 0.0	0, 0.0	0, 0.0
Asymptomatic cholelithiasis	40, 33.9	30.9±9.2	18, 45.0	Abdominal Ultrasound (2 cases had Choledocholithiasis in addition)	0, 0.0	0, 0.0	40,100.0	0, 0.0	0, 0.0	0, 0.0
GB sludge	15, 12.7	30.7±9.3	7, 46.7	Abdominal Ultrasound	0, 0.0	0, 0.0	15,100.0	0, 0.0	0, 0.0	0, 0.0
OVERALL	107,90.7	28.6±9.1	59, 55.1		16,13.6	7, 5.9	86, 72.9	13,11.0	11, 9.3	1, 0.8

Table (6) shows a significant positive relationship between the number of transfused blood units and each of elevated serum ferritin ($p<0.001$) and positive serology for chronic hepatitis B ($p=0.039$) and C ($p=0.028$). Nevertheless, no significant relationship was found between the number of transfusions and occurrence of sickle cell hepatopathy.

Table 6: Relation between number of transfused units of blood and chronic hepatobiliary disorders.

	Transfused units of blood (maximum number per year)	P
Serum ferritin		<0.001
Normal (n=48)	6.8±2.0	
High (n=33)	10.3±1.7	
Very high (n=37)	16.8±5.5	
Viral hepatitis B serology		0.039
Positive (n=13)	13.8±5.2	
Negative (n=105)	10.5±5.4	
Viral hepatitis C serology		0.028
Positive (n=20)	13.3±3.6	
Negative (n=98)	10.4±5.6	
Sickle cell hepatopathy		0.957
Present (n=7)	10.9±5.5	
Absent (n=101)	11.0±4.7	

DISCUSSION

Various hepatobiliary disorders are frequently encountered in SCD patients [5]. The incidence of liver disease in these patients is difficult to ascertain because of its multifactorial nature, the overlap of clinical and laboratory stigmata in different disorders and lack of definite diagnostic criteria [16]. However, no enough data are yet available about the epidemiologic criteria, clinical features or outcome of hepatobiliary disorders in Saudi Arabia or even worldwide.

In this study, out of 118 adult SCD patients, hepatobiliary disorders were found in 107 cases (90.7%) over the study duration (mean age: 28.6±9.1 years, males: 55.1%). Acute conditions were detected in 27.1% (32/118) of SCD cases, and chronic conditions were diagnosed in 69.5% (82/118) of SCD cases. In 70.1% (75/107) of cases with hepatobiliary disorders a secondary cause was found, in the form of iron overload and/or viral hepatitis both resulting from repeated blood transfusion. While in the remaining 29.9% (75/107) of cases, these disorders were primarily attributed to the SCD process itself.

In agreement with our results, a study on 70 Brazilian SCD patients by Traina et al., [4] reported chronic hepatobiliary abnormalities in 67 patients (96%); these included abnormal liver function tests, viral hepatitis, liver ultrasonographic changes and cholelithiasis. The sickling process was the only explanation in 24% of patients. One or more defined reasons, including viral hepatitis, cholelithiasis, clinical hemosiderosis, alcoholism or diabetes, justified the liver abnormalities in 76% of the patients. Nineteen of the 20 liver biopsies presented some degree of vascular lesion. However, the study of Traina et al., [4] was limited by the relatively small number of patients, inclusion of sickle cell trait, inclusion of both children and adults and by being retrospective over short follow up period. Almost similar results were previously obtained from the study of Gürkan et al., [3] performed on 48 Turkish SCD patients, a study that was prospective but otherwise had the same limitations of the Brazilian study.

Acute right upper quadrant pain syndromes characterized by pain and jaundice were not uncommonly described in SCD patients as being produced by acute hepatic sequestration, intrahepatic cholestasis, or cholelithiasis [17]. In this screening, acute sickle hepatic crisis affected 9.3% of patients who had a benign disease course with the exception of a mild self limited hepatic dysfunction in one patient. In addition, three of our patients (2.5%) developed hepatic infarction; two of them had self limited disease, while the third case was complicated with liver abscess and subsequent acute hepatic dysfunction that was later recovered after successful intensive care management. The above rates and outcomes were comparable to those previously reported in both adults and children with SCD [5,18-19].

In the current study, sickle cell hepatopathy, also known as intrahepatic cholestasis, was presented acutely in seven patients (5.9%). Two patients had severe form (mean total bilirubin level: 63.6±3.7 mg/dl) and the remaining five patients had mild form (mean total bilirubin level: 18.7±8.8 mg/dl). The disease was self limited with full recovery in two cases, it showed initial recovery then recurred in one patient, it acquired chronicity in two patients, and it progressed to acute hepatic dysfunction that ended fatally in one patient. The frequency and outcome of sickle cell hepatopathy recorded in this screening study lie close to that reported in several case series and studies [7,20-21].

Moreover the fact that sickle cell hepatopathy primarily originate from the sickling process itself that was reported by several authors [7,20-21], was reinforced in this study by the lack of significant relation to the number of transfusions and the unique histologic findings.

In this screening, hepatomegaly was the commonest among all hepatobiliary disorders in a rate of 61.9%, that was consistent with a range of 40-80% mentioned in multiple studies [3,22]. The current study showed prolonged elevation of serum ALT in 30.5% of our patients, and other hepatic enzymes were more frequently but less specifically elevated. These findings were in agreement with previous reports of elevated liver enzymes in 27-42% of SCD patients [3,6,23].

In accordance with the literature [24-27], the present study showed elevated serum ferritin in 59.3% of SCD patients, and a significantly higher number of transfusions in such patients as compared to those with normal ferritin level ($p<0.001$). Moreover, serum ferritin levels exceeded 1000 ng/ml (suggesting hemosiderosis) in 38.2% of patients. While serum ferritin level is a rough guide to total liver iron, values over 1000 ng/ml indicate liver iron overload, and over many years, fibrosis, cirrhosis and even liver failure may develop, as stated by several authors [2,24-26].

In our study population, chronic viral hepatitis occurred more often than in the general population, as 16.9% of patients had positive hepatitis C serology, and 11.0% had positive hepatitis B serology. Chronic hepatitis B & C cases showed significantly positive relationship with the mean number of transfused blood units ($p= 0.039$ and 0.028, respectively). The above findings came in accordance to other studies [18,28-30].

Going with previously published case reports [31-32], in this study, one female SCD patient, 34 years old had autoimmune hepatitis type-1. Diagnosis was confirmed by histologic examination of liver biopsy which showed chronic active hepatitis with lymphocytic infiltrate, perisinusoidal fibrosis and micronodular cirrhosis. Whether a pathophysiologic link exists between SCD and autoimmune hepatitis still needs to be determined.

In agreement with other studies [3,33], the liver biopsy performed in 25 SCD patients in this study, showed changes due to sickling process in almost all patients, intrahepatic cholestasis in 12% (3/25) of cases and concurrent iron overload, viral hepatitis and autoimmune hepatitis in 80%, 32% and 4% of all biopsies, respectively. Cirrhosis was seen in 16% (4/25) of biopsies.

The rate of liver cirrhosis among SCD patients in the current study was 7.6%, that was related to multiple overlapping factors including hemosiderosis, viral and autoimmune hepatitis and sickle cell hepatopathy. Several authors reported similar etiologic relations in SCD patients, however being with variable rates of cirrhosis from 5% to more than 20% [4,34-36]. The variability among studies including ours may be due to the method used to diagnose cirrhosis, the duration of SCD and the age of the patient.

It is well known that the prevalence of gallstones (mostly pigmented) is high in SCD patients and increases progressively with age, affecting 35-50% of young adults [3,5,37]. In the present study, gallstones were detected in 41.5% of patients. Nine patients presented with abdominal pain, whereas others were asymptomatic. Moreover, gallbladder sludge existed in 12.7% of patients.

Regarding the outcome of hepatobiliary disorders in all participants of this study, hepatic dysfunction occurred in seven cases (5.9%) and cholecystectomy was performed to 11 patients (9.3%) with symptomatic gallstones including four patients (3.4%) who experienced biliary obstruction due to choledocholithiasis and underwent ERCP before surgery. There was only one case of mortality (0.8%), this was a 32 years old male patient, who died from acute severe sickle hepatopathy. Whereas, the remaining majority of SCD patients had benign uncomplicated course of the disease apart from chronicity in many cases and recurrences in others. However scanty, the available data regarding outcome of hepatobiliary disorders in SCD were in agreement to our results [3-4,6].

CONCLUSION

Hepatobiliary disorders commonly affect adult homozygous SCD patients (>90%), with a wide clinical spectrum ranging from mild asymptomatic hepatomegaly or liver function tests abnormalities, to significant hepatic dysfunction. However the overall rates of morbidity and mortality associated with these disorders are low.

Conflicts of interest: none

REFERENCES

1. Odièvre MH, Verger E, Silva-Pinto AC, Elion J. Pathophysiological insights in sickle cell disease. Indian J Med Res 2011 Oct;134:532-7.
2. Ballas SK, Kesen MR, Goldberg MF, Lutty GA, Dampier C, Osunkwo I, Wang WC, Hoppe C, Hagar W, Darbari DS, Malik P. Beyond the definitions of the phenotypic complications of sickle cell disease: an update on management. Scientific World Journal 2012;2012:949535.
3. Gürkan E, Ergun Y, Zorludemir S, Baslamisli F, Kocak R: Liver involvement in sickle cell disease. Turk J Gastroenterol 2005;16:194–8.
4. Traina F, Jorge SG, Yamanaka A, de Meirelles LR, Costa FF, Saad ST. Chronic liver abnormalities in sickle cell disease: a clinicopathological study in 70 living patients. Acta Haematol 2007;118(3):129-35.
5. Ebert EC, Nagar M, Hagspiel KD. Gastrointestinal and hepatic complications of sickle cell disease. Clin Gastroenterol Hepatol 2010;8(6):483-9
6. Almeida RP, Ferreira CD, Conceição J, Franca R, Lyra I, Silva LR. Hepatobiliary abnormalities in pediatric patients with sickle cell disease. Acta Gastroenterol Latinoam 2009;39(2):112-7.
7. Ahn H, Li CS, Wang W. Sickle cell hepatopathy: clinical presentation, treatment, and outcome in pediatric and adult patients. Pediatr Blood Cancer 2005 Aug;45(2):184-90.
8. Al-Hamdan NA, AlMazrou YY, AlSwaidi FM, Choudhry AJ. Premarital screening for thalassemia and sickle cell disease in Saudi Arabia. Genet Med 2007;9:372–7.
9. Al-Qurashi MM, El-Mouzan MI, Al-Herbish AS, Al-Salloum AA, Al-Omar AA. The prevalence of sickle cell disease in Saudi children and adolescents. A community-based survey. Saudi Med J 2008;29:1480–3.
10. Jastaniah W. Epidemiology of sickle cell disease in Saudi Arabia. Ann Saudi Med 2011;31(3):289-93.
11. Memish ZA, Saeedi MY. Six-year outcome of the national premarital screening and genetic counseling program for sickle cell disease and β-thalassemia in Saudi Arabia. Ann Saudi Med 2011;31(3):229–35.
12. Norris WE. Acute hepatic sequestration in sickle cell disease. Journal of the National Medical Association 2004;96(9):1235–9.
13. Issa H, Al-Haddad A, Al-Salem A. Sickle cell cholangiopathy: an endoscopic retrograde cholangiopancreatography evaluation. World J Gastroenterol 2009;15(42):5316–20.
14. David F. Keren, MD, Deborah Hedstrom, MT(ASCP), Ronald Gulbranson, MT(ASCP), Ching-Nan Ou, PhD, and Richard Bak, PhD. Comparison of Sebia Capillarys Capillary Electrophoresis With the Primus High-Pressure Liquid Chromatography in the Evaluation of Hemoglobinopathies. Am J Clin Pathol 2008 ;130:824-831.
15. Ishak K, Baptista A, Bianchi L, Callea F, De Groote J, Gudat F, Denk H, et al. Histological grading and stagingof chronic hepatitis. J Hepatol 1995;22(6):696-9.
16. Kotila T, Adedapo K, Adedapo A, Oluwasola O, Fakunle E, Brown B. Liver dysfunction in steady state sickle cell disease. Ann Hepatol 2005;4(4):261-3.
17. Banerjee S, Owen C, Chopra S. Sickle cell hepatopathy. Hepatology 2001 May;33(5):1021-8.
18. Johnson CS, Omata M, Tong MJ, Simmons JF, Jr., Weiner J, Tatter D. Liver involvement in sickle cell disease. Medicine (Baltimore) 1985;64(5):349-56.
19. Ojuawo A, Adedoyin MA, Fagbule D. Hepatic function tests in children with sickle cell anemia during vaso-occlusive crisis. Cent Afr J Med 1994;40:342-3.
20. Irizarry K, Rossbach HC, Ignacio JR. Sickle cell intrahepatic cholestasis with cholelithiasis. Pediatric Hematology and Oncology. 2006;23(2):95–102.
21. Brunetta DM, Silva-Pinto AC, Bassi SC, Piccolo Feliciano JV, Ribeiro FB. Intrahepatic cholestasis in sickle cell disease: a case report. Anemia 2011;2011:975731.

22. Olaniyi JA, Abjah UM. Frequency of hepatomegaly and splenomegaly in Nigerian patients with sickle cell disease. West Afr J Med 2007;26(4):274-7.
23. Schubert TT. Hepatobiliary system in sickle cell disease. Gastroenterology 1986;90(6):2013-21.
24. Pippard MJ. Iron overload and iron chelation therapy in thalassaemia and sickle cell haemoglobinopathies. Acta Haematologica 1987;78(2-3):206–11.
25. Vichinsky E, Butensky E, Fung E, et al. Comparison of organ dysfunction in transfused patients with SCD or β thalassemia. Am Journal Hematol 2005;80(1):70–4.
26. Fung EB, Harmatz P, Milet M. Morbidity and mortality in chronically transfused subjects with Thalassemia and Sickle Cell Disease: a report from the multi-center study of iron overload. Am J of Hematol 2007;82(4):255–65.
27. Ghugre NR, Wood JC. Relaxivity-iron calibration in hepatic iron overload: probing underlying biophysical mechanisms using a Monte Carlo model. Magnetic Resonance in Medicine 2011;65(3):837–47.
28. DeVault KR, Friedman LS, Westerberg S, Martin P, Hosein B, Ballas SK. Hepatitis C in sickle cell anemia. J Clin Gastroenterol 1994;18(3):206-9.
29. Hasan MF, Marsh F, Posner G. Chronic hepatitis C in patients with sickle cell disease. Am J Gastroenterol 1996;91(6):1204–6.
30. Richard S, Billett HH. Liver function tests in sickle cell disease. Clin Lab Hematol 2002;24(1):21-27.
31. el Younis CM, Min AD, Fiel MI, Klion FM, Thung SN, Faire B, Miller CM, et al. Autoimmune hepatitis in a patient with sickle cell disease. Am J Gastroenterol 1996;91(5):1016-8.
32. Chuang E, Ruchelli E, Mulberg AE. Autoimmune liver disease and sickle cell anemia in children: a report of three cases. J Pediatr Hematol Oncol 1997;19(2):159-62.
33. Aken'ova YA, Olasode BJ, Ogunbiyi JO, Thomas JO. Hepatobiliary changes in Nigerians with sickle cell anaemia. Ann Trop Med Parasitol 1993;87:603–6.
34. Darbari DS, Kple-Faget P, Kwagyan J, et al. Circumstances of death in adult sickle cell disease patients. Am J Hematol 2006;81:858–63.
35. Savafi NA, Akbulut S, Köseoglu T, Albayrak L. Chronic liver disease in a patient with sickle cell anemia. Turk J Gastroenterol 2006 Jun;17(2):123-5.
36. Berry PA, Cross TJ, Thein SL, et al. Hepatic dysfunction in sickle cell disease: a new system of classification based on global assessment. Clin Gastroenterol Hepatol 2007;5:1469–76.
37. Gumiero AP, Bellomo-Brandão MA, Costa-Pinto EA Gallstones in children with sickle cell disease followed up at a Brazilian hematology center. Arq Gastroenterol 2008;45(4):313-8.