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Hepatobiliary abnormalities in pediatric patients with sickle cell disease

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Summary

Objetive: *to describe clinical, laboratory and ultrasonographic abnormalities in the hepatobiliary system of pediatric patients with sickle cell disease in the city of Salvador, Brazil.* ***Material and Methods:*** *pediatric patients with sickle cell disease were clinically evaluated, their charts were reviewed and findings of supplementary tests were examined to identify hepatobiliary abnormalities.* ***Results:*** *a total of 134 patients were evaluated, 65 of whom (48.9%) presented hepatomegalia. Elevated transaminases were present in 42.2% and 11.4% presented cholelithiasis. There was a statistically significant association between the presence of hepatomegalia and SS homozygotes and between cholelithiasis and patients over 10 years of age (p=0.01 and p=0.00, respectively).* ***Conclusion:*** *hepatobiliary abnormalities in patients with sickle cell disease were common, particularly in patients with hemoglobin SS and in adolescent patients.*

Key words: *sickle cell disease, pediatric patients, liver abnormalities.*

Alteraciones hepatobiliares en pacientes pediátricos con la enfermedad de células falciformes

Resumen

Objetivo: *describir las anormalidades clínicas, analíticas y ecográficas de los pacientes pediátricos con enfermedad de células falciformes en la ciudad de Salvador, Brasil.* ***Material y métodos:*** *los pacientes pediátricos con enfermedad de células falciformes fueron evaluados clínicamente. Se revisaron sus historias clínicas y se examinaron los hallazgos de las pruebas complementarias para identificar las anormalidades hepatobiliares.* ***Resultados:*** *se evaluó un total de 134 pacientes, 65 (48.9%) de los cuales presentaron hepatomegalia. La elevación de las transaminasas estuvo presente en el 42.2% de los casos y el 11.4% presentaron colelitiasis. Hubo una asociación estadísticamente significativa entre la presencia de hepatomegalia y la homocigosis SS, y entre la colelitiasis y los pacientes mayores de 10 años de edad (p=0.001 y p=0.00, respectivamente).* ***Conclusión:*** *fueron frecuentes las anormalidades hepatobiliares en los pacientes con enfermedad de células falciformes, particularmente en los portadores de hemoglobina SS y los adolescentes.*

Palabras claves: *enfermedad de células falciformes, pacientes pediátricos, anormalidades hepáticas.*

Sickle cell anemia (HbSS) is caused by a point mutation (GAG → GTG) in the ß-globin gene, which defines the substitution of glutamic acid by valine in position 6 of the ß chain of amino-acids, resulting in abnormal hemoglobin, hemoglobin S (HbS). This hemoglobin presents physical and chemical abnormalities and a tendency to polymerization under certain circumstances. The presence of HbS associated with other hereditary variants of hemoglobin such as hemoglobin C, D and S/ß thalassemia, among others, characterizes sickle cell disease.[1-3] It is considered the most common monogenic disease in Brazil. Around 3,500 children are estimated to be born with this disease annually and anot-

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her 200,000 with the sickle cell trait.[4] Reflecting the ethnic characteristics of this region, the data from the Bahia State Program for Neonatal Screening indicate a prevalence rate for this disease of 1:650 liveborn infants, which makes sickle cell disease a significant public health issue in this region.[5,6]

Sickle cell disease is a multisystemic disease with a great variability of clinical manifestations modulated by genetic and environmental factors. Liver involvement is common in patients with sickle cell disease, principally in homozygotic patients, and occurs as a result of multiple transfusions, of the superimposition of hepatitis by hepatotropic or non-hepatotropic viruses, by other infections, cholelithiasis or as a result of vascular phenomena related to the primary disease itself. Liver dysfunction may vary from a self-limiting cholestasis to cases of cirrhosis and liver failure; however, severe liver disease rarely occurs in these patients unless other concomitant pathologies, such as infection with hepatitis C virus (HCV) or human immunodeficiency virus (HIV) are present.[7-9]

Although sickle cell disease has been studied intensely, there is a scarcity of data in the literature on the liver abnormalities associated with this pathology, particularly in the pediatric age-group. The objective of the present study was to describe clinical, laboratory and ultrasonographic abnormalities in the hepatobiliary system of pediatric patients with sickle cell disease in the city of Salvador.[7-14]

Patients and Methods

The present descriptive, cross-sectional study was carried out in the pediatric outpatient hematology clinics of the Bahia Hematology Foundation and the *Professor Edgard Santos* Teaching Hospital of the Federal University of Bahia between July 2002 and October 2003, with the objective of evaluating children and adolescents attending these clinics who had been diagnosed with sickle cell disease.

All patients of 0-18 years of age with sickle cell disease who attended the clinic for consultation during this period were invited to participate in the study. If they agreed to participate, the patients and/or their guardians signed an informed consent form. Then, an interview and a physical examination were performed by one of the investigators and clinical and laboratory results, biopsy findings and results of ultrasonography scans of the liver and biliary tracts were recorded.

The patients in the study were then divided into two groups: HbSS patients and non-HbSS patients. Student's t-test was used to compare the mean values of laboratory tests, and the chi-square test was used for comparisons between proportions, corrections being made using Fisher's exact test. p-values <0.05 were considered significant.

Prior to initiation, the project had been submitted to and approved by the Internal Review Board of the Professor Edgard Santos Teaching Hospital, Federal University of Bahia.

Results

During the study period, 134 patients with sickle cell disease were evaluated. The mean age of patients was 7.09 ± 4.36 years (range 0.38 – 18.39 years). The following phenotypes were found: SS in 100 patients (74.6%); SC in 29 (21.6%) and Sβ-thalassemia in 5 (3.8%). The mean age of the children at the time of diagnosis was around two years. Table 1 describes the signs and symptoms that led to the diagnostic investigation of sickle cell disease. Notably, skin or mucosal pallor were reported in 41 patients (22.4%), neonatal screening test in 18 (9.84%), fever in 17 (9.29%), joint swelling in 15 (8.2%), painful crises in 10 (5.46%) and pain in limbs in 10 (5.46%).

The principal findings of the physical and supplementary examinations are described in Table 1. Hepatomegaly was often noted, being found in 65 patients (48,9%), and jaundice in 81 (60,4%).

With respect to the laboratory tests, aspartate aminotransferase (AST) was above the normal range in 64 patients (47.8%), while alanine aminotransferase (ALT) was high in 19 (14.2%). Results of bilirubin had been recorded in 101 patients. Indirect bilirubin was elevated in 60 (59.4%) and direct bilirubin in 65 (64.4%).

Results of serum ferritin levels had been recorded in 73 patients. They were found elevated in 40 (54.8%), with a mean value of 256.2 ± 278.2 ng/ml. In these patients, the mean number of transfusions reported was 5.59, while it was 2.5 in the group of patients with normal ferritin ($p=0.022$).

Of the interviewed children, 80 (59.7%) had undergone a blood transfusion at some time, with a mean of 4.11 ± 4.57 transfusions per patient, ranging from none to 22 transfusions in one case. Mean hemoglobin level was 8.49 ± 3.45 mg/dL.

Tabla 1. *Characteristics of pediatric patients with sickle cell disease.*

Clinical and laboratory characteristics	n	(%)	χ^2	P
Clinical characteristics				
Mean age (years)	7.09 ± 4.36			
Mean number of transfusions per patient	5.59			
Mean hemoglobin level	8.49 ± 3.45mg/dl			
Reported blood transfusions	80	(59.7)		
Vaccinated against hepatitis B	105	(94.6)		
Vaccinated against hepatitis A	0	(0)		
Signs and symptoms				
Skin or mucosal pallor	41	(22.45)		
Neonatal screening test	18	(9.8)		
Fever	17	(9.2)		
Joint swelling	15	(8.2)		
Painful crisis	10	(5.4)		
Pain in limbs	10	(5.4)		
Abdominal pain	9	(4.9)		
Jaundice	9	(4.9)		
Clinical findings				
Skin or mucosal pallor	108	(80.6)		
Jaundice	81	(60.4)		
Hepatomegaly	65	(48.9)		
Splenomegaly	30	(22.4)		
Muscular atrophy	30	(22.4)		
Systolic murmur	23	(17.2)		
Finger clubbing	17	(12.9)		
Palmar erythema	12	(9.1)		
Laboratory findings				
Elevated AST	64	(47.8)		
Elevated ALT	19	(14.2)		
Elevated serum ferritin	40	(54.8)		
Elevated indirect bilirubin	60	(59.4)		
Elevated direct bilirubin	65	(64.4)		
Anti-HAV IgG-positive	14	(47.8)		
Anti-HCV antibodies-positive	3	(2.7)		
Anti-HBsAg-positive	0	(0)		
Ultrasonography findings				
Hepatomegaly	24	(30.4)		
Lithiasis	9	(11.4)		
Splenomegaly	17	(21.5)		
Thick bile	1	(1.3)		
Correlations				
Lithiasis in patients 0-10 years	1	(11.1)		
Lithiasis in patients 11-18 years	8	(88.9)		
Lithiasis vs. age			21.84	0.000
Hepatomegaly in HbSS patients	22	(38.6)		
Hepatomegaly in non-HbSS patients	2	(9.1)		
Hepatomegaly vs. type of hemoglobinopathy			6.534	0.011

Abdominal ultrasonography was carried out in 79 patients (59%) and revealed hepatomegaly in 24 patients (30.4%), lithiasis in 9 (11.4%), splenomegaly in 17 (21.5%), and thick bile in 1 (1.3%). Cholelithiasis was found in 14% of patients from the HbSS group and in 4.5% from the non-HbSS group.). The mean age of the patients with lithiasis was 13 years, the youngest being 5 years old. The difference in age between the patients with and without lithiasis was statistically significant (p=0.000).

None of the patients evaluated tested positive for hepatitis B virus (HBV) surface antigen (HBsAg). Anti-hepatitis A virus (HAV) IgG was positive in 14 patients (47.8%) and anti-hepatitis C virus (HCV) antibodies in 3 of 110 tested patients (2.7%). Only one of the three patients with HCV was able to provide information on the number of transfusions received: 10 units. The other two patients, who were unable to provide this information, were the oldest patients in the study population, at 16 and 17 years of age. One hundred and five patients (94.6%) had been vaccinated against hepatitis B (a mean of 2.7 ± 0.6 doses per patient). None of the children had been vaccinated against hepatitis A.

Only two patients had been submitted to a liver biopsy, one of whom had positive serology for hepatitis C. In both cases, sinusoidal dilatation and perisinusoidal fibrosis were present. Only the patient with HCV infection had lymphocyte infiltration and a diagnosis suggestive of hepatitis.

Data were summarized in table 1. Statistically significant correlations were found between lithiasis and age and between hepatomegaly and type of hemoglobinopathy. When the patients who were submitted to ultrasonography were divided according to age-group into patients of 0-10 years of age and patients of 11-18 years of age, only one individual with lithiasis was found in the younger age-group (11.1%), whereas the 8 remaining patients (88.9%) all belonged to the older age-group (χ^2 = 21.84; p=0.000). When hepatomegaly was compared with the types of hemoglobinopathies, it was found in 22 patients (38.6%) of the HbSS group and in only 2 (9.1%) in the non-HbSS group (χ^2 = 6.534; p=0.011).

Discussion

The hepatobiliary tract of patients with hemoglobinopathies may be affected in various ways, with signs such as hepatomegaly, increases in serum bilirubin and transaminase levels, and occasionally increases in the levels of other markers indicative of disorders of the liver and bile canaliculus. Cholelithiasis is also a particularly common finding in these patients. More severe forms of hepatobiliary involvement are reflected in acute hepatic sickling crises and by sickle cell intrahepatic cholestasis.[14,15] Exacerbated hemolysis and the veno-occlusive phenomena triggered by the abnormal structure of the red blood cells are classically considered to be the principal mechanisms leading to hepatic lesions in sickle cell disease. However, the transfusions to which carriers of hemoglobinopathies are submitted throughout their lives -in addition to exposing them to the risk of infection by hepatotropic viruses, such as HBV and HCV, and other infectious agents, such as cytomegalovirus, Epstein-Barr virus, HTLV and HIV- also act as determining factors of hepatobiliary lesions.[3,7,8,16]

It is estimated that around 10% of sickle cell disease patients may have acute liver involvement through the mechanism of intrasinusoidal sickling of

erythrocytes, resulting in hypoxemia and hepatocyte ischemia, with consequent hepatocyte edema and intracanalicular cholestasis, possibly evolving to fulminant hepatic failure and to death in around 64% of cases.[11,14,17,18]

In the present study, the mean age at diagnosis was two years, suggesting that late diagnosis of sickle cell disease remains frequent in this geographical region. Although the principal fact that motivated the investigation leading to diagnosis of hemoglobinopathy was the identification of skin or mucosal pallor by the physician (22.4% of cases), a positive neonatal screening test in 9.84% of cases played a significant role from an epidemiological and social point of view. Early diagnosis permitted clinical follow-up and allowed to provide information to the families of affected children, successfully preventing complications resulting from sickle cell diseases. This screening test was carried out in 52 children (38.8%) and 21 of these patients (52.5%) tested positive. After August 2000, the sensitivity of the screening test in the study population achieved 100%, coinciding with the systematic implementation of the investigation of hemoglobinopathies in this test.

Jaundice and hepatosplenomegaly are common findings in patients with sickle cell disease. Hepatomegaly was detected at physical examination in 48.9% of the patients, compared to an incidence of 30.4% of this finding at ultrasonography. These figures were below those found in the literature. The number of patients with hepatomegaly was greater among the HbSS patients. This difference was statistically significant (p=0.0011) and is in agreement with the data found in the literature.[7-9,14,17] Other clinical characteristics suggestive of liver failure, such as flapping tremor, spider nevi, evidence of cutaneous hemorrhages and involvement of the nervous system, were investigated. However, the findings were not statistically significant, suggesting that, from a clinical point of view, liver involvement is not extremely severe, at least in the age-group studied.

The majority of patients had elevated AST, indirect bilirubin, LDH, ferritin, serum hemoglobin and mean corpuscular volume (MCV). AST values were high in more than 50% of the children, with a mean level of 56.3 UI/l, whereas mean ALT was 31.5 UI/l. It is important to emphasize that in patients with sickle cell disease, liver function tests may be abnormal but may not necessarily reflect liver disease, since increased levels of aspartate aminotransferase (AST) and indirect bilirubin are also related to chronic hemolysis. Previous studies suggest that in patients with sickle cell disease, serum ALT level may be a better marker of liver involvement.[13-15,19] The correlations of tests with each other, with clinical findings and with the complications of the disease were not statistically significant.

Various studies have suggested that persistently high ferritin levels, although they may also be elevated in inflammatory processes and some chronic diseases, may correlate with the number of transfusions and hepatic iron deposits. In these cases, hepatic iron deposits should always be measured and if iron overload is confirmed, iron chelation therapy should be implemented.[12,20-22] In the present study, the mean number of transfusions in the group of patients with elevated ferritin levels was significantly higher compared to the group of patients with normal ferritin.

Cholelithiasis is more frequent in patients with HbSS and S/ß thalassemia electrophoretic patterns, who have higher indirect bilirubin levels, and is less common in HbSC patients, in whom hemolysis and consequently indirect hyperbilirubinemia are less severe. Cholelithiasis occurs in around 20-30% of HbSS patients up to 20 years of age and in around 12% of HbSC patients.[23,24] In the present study, cholelithiasis was more frequent in the HbSS group than in the non-HbSS group and a larger sample, with greater uniformity between homozygotes and heterozygotes, may confirm this tendency.

Studies suggest that the onset of cholelithiasis in patients with sickle cell disease occurs at two to four years of age and its prevalence increases progressively with age.[23] In the present sample, the mean age of patients with lithiasis was significantly higher. These results suggest that annual screening with ultrasonography after 5 years of age may bring benefits to these patients, collaborating to an early diagnosis of cholelithiasis. Currently, elective laparoscopic cholecystectomy in asymptomatic patients with sickle cell disease has been recommended to prevent recurrent symptoms and complications such as cholecystitis and choledocholithiasis.[25]

The clinical expression of viral hepatitis in patients with sickle cell disease appears to be similar to that found in the general population except for the higher bilirubin levels resulting from the chronic hemolysis that is characteristic of the disease. Nevertheless, in a study carried out by Yohannan *et*

al.[26] in children with sickle cell disease who suffered fulminant hepatic failure, the principal cause for this event was found to be hepatitis A (72% of cases), showing that sickle cell disease is a risk factor for fulminant hepatitis A. These investigators suggested a greater predisposition of patients with sickle cell disease to this complication due to a change in the response of the immune system to the hepatotropic viruses. None of the patients investigated tested positive for HBV infection. Although the present study is unable to supply any definitive data on the true incidence of HBV infection in patients with sickle cell disease, data suggest that the current vaccination policy has been effective in preventing this infection in populations with high rates of blood transfusion.[20,27]

The risk of HCV contamination is directly related to the number of transfusions and increases in those patients who have received more than 10 transfused units. This problem has been decreasing since implementation of the screening of blood derivatives using more sophisticated serological tests for the hepatitis C virus. In the present study, the prevalence of HCV infection (2.7%) was lower than the rates found in the literature, ranging from 8.7% to 30.3% and depending on the screening protocols used in blood banks and the mean number of transfusions.[20,27-29] Patients with HCV had received a large number of transfusions or were the oldest in the study population, thereby corroborating the data in the literature.

The indications for liver biopsy in patients with sickle cell disease are: consistently high transaminases, presence of positive viral markers over a period of more than 6 months and clinical or laboratory abnormalities indicating chronic liver involvement.[30] The most common abnormalities found in liver biopsies in these patients are sinusoidal dilatation and Kupffer cell hyperplasia with erythrophagocytosis. Portal inflammation and chronic hepatitis or cirrhosis, associated with hemosiderosis and hepatitis B or C, are frequent findings. In the current study, only two patients were submitted to liver biopsy. In both, the results revealed perisinusoidal fibrosis and dilatation. The small number of biopsies analyzed does not allow comparison of these results with findings in the literature, since the data were insufficient to provide an actual view regarding histological findings. However, in the case of sinusoidal dilatation, our data are in agreement with those commonly reported.[19,31,32]

In conclusion, liver abnormalities in pediatric patients with sickle cell disease were frequent findings, particularly in HbSS patients and in adolescents. Although liver involvement may be related to the primary disease itself, it should be differentiated from hepatic lesions of other causes so that treatment may be implemented quickly, avoiding complications in the natural course of the disease.

Declaration of interest: *The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.*

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