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ONLINE BRIEF COMMUNICATION

Hepatobiliary Complications of Sickle Cell Disease among Children Admitted to Al Wahda Teaching Hospital, Aden, Yemen

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المضاعفات الكبدية – الصفراوية عند الأطفال المصابين بمرض فقر الدم المنجلي بمستشفى الوحدة التعليمي في عدن باليمن

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ABSTRACT: ***Objectives:*** This study aimed to describe the pattern of hepatobiliary complications among patients with sickle cell disease (SCD) and to assess their correlation with age, gender and other risk factors. ***Methods:*** This cross-sectional study assessed 106 patients with SCD who were admitted to Al Wahda Teaching Hospital in Aden, Yemen, between January and June 2009. A full history, thorough examination, essential laboratory investigations (including a complete blood count, liver function test and viral markers test) and an abdominal ultrasound were performed on all patients. The clinicopathological characteristics of the hepatobiliary complications were analysed for their correlation to different risk factors such as age and gender. ***Results:*** It was found that 46.2% of the patients with SCD had hepatobiliary complications. Of these, 36.7% had viral hepatitis, 26.0% had cholecystitis and 20% had gallstones. A total of 60.4% of the affected patients were male. The mean levels of alanine aminotransferase (59.4 and 56.0 U/L) and aspartate transaminase (40.1 and 38.3 U/L) were significantly elevated in patients with viral hepatitis and cholecystitis, respectively. Hepatitis B virus surface antigen showed higher positivity (10.4%) than anti-hepatitis A and anti-hepatitis C antibodies. Hepatobiliary complications increased significantly with age and were notably higher among those who were often admitted to hospital and/or underwent frequent blood transfusions. ***Conclusion:*** This study suggests that hepatobiliary complications are common among SCD patients and the likelihood of developing such complications increases as patients age. Thus, regular clinical follow-ups, abdominal ultrasound studies and periodic liver function tests, as well as serological tests for viral hepatitis, are strongly recommended. These can help in the early detection of these complications and allow opportunities for their management and prevention.

Keywords: Sickle Cell Disease; Digestive System; Biliary Tract; Children; Yemen.

الملخص: الهدف: تهدف هذه الدراسة لوصف نمط المضاعفات الكبدية– الصفراوية عند المرضى المصابين بمرض فقر الدم المنجلي، ولتقييم مدى ترابطها مع العمر والجنس وعوامل الاختطار الأخرى. **الطريقة:** تم في هذه الدراسة المقطعية تقييم 106 مريضا بفقر الدم المنجلي أدخلوا لمستشفى الوحدة التعليمي في عدن باليمن بين يناير و يونيو 2009م. وبعد أخذ التاريخ المرضي والفحص الشامل وعمل الفحوص المختبرية الضرورية (والتي شملت صورة الدم الكاملة واختبارات وظائف الكبد ومؤشرات الإصابة بالفيروسات) تم فحص البطن بالموجات فوق الصوتية لكل المرضى. وتم تحليل الخواص السريرية الإمراضية للمضاعفات الكبدية– الصفراوية لتقييم مدى ترابطها بعوامل الاختطار المختلفة كالعمر والجنس. **النتائج:** وجد أن نحو 46.2% من مرضى فقر الدم المنجلي في هذه الدراسة أعراضا دالة على مضاعفات كبدية – صفراوية. وأظهر نحو 36.7% من هؤلاء أعراض مرض الكبد الفيروسي، بينما كان عند نحو 26.0% و20% منهم التهاب مرارة وحصوات صفراوية، على التوالي. وكانت نسبة الذكور بين المرضى المصابين تبلغ 60.4%. وتراوحت متوسطات نشاط انزيمي ناقل أمين الألالين وناقل أمين الاسبيرتات بين 56.0 و 59.4 وحدة دولية و 38.3 و 40.1 وحدة دولية، على التوالي، وكانت نسبها أعلى عند المصابين بالتهاب الكبد الفيروسي و التهاب المرارة. وأظهرت مستضدات السطح في فيروس التهاب الكبد الوبائي ب إيجابية أكثر (10.4%) من أضداد التهاب الكبد الوبائي أ و ج. ووجد أن معدلات المضاعفات الكبدية– الصفراوية تزداد مع العمر، وكانت أكثر حدوثا في المرضى الأكثر دخولا للمستشفى و / أو الذين أجريت لهم عمليات نقل دم بصورة متكررة. **الخلاصة:** وجد أن المضاعفات الكبدية– الصفراوية شائعة عند الأطفال المصابين بمرض فقر الدم المنجلي، وتزداد معدلات حدوثها مع تقدم العمر. ولذا فينصح بمتابعة هؤلاء المرضى سريرا بصورة دورية وعمل دراسات فحص البطن بالموجات فوق الصوتية واختبارات وظائف الكبد والسيرولوجيا للكشف عن التهاب الكبد الفيروسي. وهذا من شأنه المساعدة في الاكتشاف المبكر عن هذه المضاعفات ويوفر فرصا لعلاجها والوقاية منها.

مفتاح الكلمات: مرض فقر الدم المنجلي؛ الجهاز الهضمي؛ السبيل الصفراوي؛ الأطفال؛ اليمن.

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Sickle cell disease (SCD) is an inherited blood disease characterised by chronic haemolytic anaemia. The frequency of the *HbS* gene in Yemen is estimated to be 0.04, with an expected birth incidence of 20/10,000 per year.[1] SCD is a multisystem disease with a variable range and degree of complications. The hepatobiliary system is often involved in SCD complications and can be affected in various ways, ranging from benign liver function abnormalities to dramatic clinical crises marked by acute hepatic failure.[2,3] The liver is frequently affected, with a complex pathophysiology involving interrelated causative factors such as haemolysis, iron overload, transfusion complications, sickling consequences, vaso-occlusion and cholelithiasis.[4] Since the 1950s, it has been theorised that hepatitis may cause liver disease in SCD patients.[5] The global prevalence of viral hepatitis is 30–40%, 2–8% and 1.45% for hepatitis A, B and C strains, respectively.[6] A study by Al-Ghonaim *et al*. found that hepatitis virus A (HAV) is the most common cause of viral hepatitis among children in Saudi Arabia.[7] Gallstones are a common complication of SCD and their development is closely related to the disease's severity and the intensity of haemolysis. Gallstone prevalence often increases in SCD patients over the age of five years.[8]

To the best of the authors' knowledge, no previous studies have been done to characterise hepatobiliary complications among SCD patients in Yemen. The Al Wahda Teaching Hospital, one of the major tertiary hospitals in Yemen, admits many SCD patients with varied complications, including hepatobiliary system diseases. However, treating physicians have at times not recognised these diseases and, consequently, they have been left undiagnosed. The main objectives of this study, therefore, were to highlight the different patterns of hepatobiliary complications in Yemeni patients with SCD and to assess the relationship with age, gender and other risk factors.

Methods

This cross-sectional descriptive study was conducted between 1 January and 30 June 2009 at Al Wahda Teaching Hospital in Aden, Yemen. The inclusion criteria comprised children of both genders between the ages of six months and 14 years with SCD confirmed by haemoglobin (Hb) electrophoresis. Patients who did not have electrophoresis-confirmed SCD, those with combined haemoglobinopathies, those who had not completed the required investigations and those who had abandoned the treatment were excluded from the study.

The parents of the patients were instructed to fill out a predesigned questionnaire, which included questions on demographic characteristics, current medical information, past medical history and previous hospital admissions and blood transfusions. Following this, a thorough physical examination, specifically designed to assess signs of hepatobiliary system disease was carried out for each patient.

All subjects underwent laboratory investigations to assess their Hb levels, white blood cell count, albumin, bilirubin (total and direct), alkaline phosphatase (ALP), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels. The normal ranges for these tests are indicated as follows: total bilirubin = 1.12 mg/dL; direct bilirubin = 0.6 mg/dL; ALT ≤12 U/L; AST ≤14 U/L, and ALP ≥200 U/L. Serological tests for viral hepatitis were performed, using the enzyme-linked immunosorbent assay MAXMAT kit (MAXMAT S.A, Montpellier, France) to detect anti-HAV antibodies, hepatitis B (HBV) surface antigen and anti-hepatitis C (HCV) antibodies.

An abdominal ultrasound was performed on all of the studied patients using a Doppler colour ultrasound machine with a 3.5 megahertz frequency. The patients were instructed to fast overnight and the ultrasound was conducted the following morning. Standard views were obtained in the transverse and sagittal plains with the subjects in supine, right lateral and left lateral *decubitus* positions. The ultrasound results were used to assess the standard features of SCD, such as the surface, edge and size of the liver; the echogenicity of the liver parenchyma; the dilatation of the bile ducts; the status of the pancreas; evidence of gallbladder disease, and other diagnostic features of disease processes, if they were present in the patient. Liver biopsies were not performed on the subjects due to the expense and time required. In suspected cases of salmonella, patients underwent stool and blood culture tests. Other investigations were carried out according to clinical indications.

The data were processed and analysed using the Statistical Package for the Social Sciences (SPSS), Version 16.0 (IBM Corp., New York, USA). The statistical analysis included a quantitative descriptive analysis and summary statistics consisting of the mean, percentages and standard deviations with a confidence interval of 95%. The analysis was based on the Chi-squared test, Fisher's exact test, odds ratio, student-t test and univariate analysis of variance. A P value of <0.05 was considered statistically significant.

This study was approved by the Ethical Committee at the Faculty of Medicine & Health Sciences of Aden University in Aden, Yemen. All of the patients' parents gave permission for their inclusion in the study.

Table 1: Types of hepatobiliary complications by gender and age among patients with sickle cell disease (N = 49)

Variable	Type of hepatobiliary complication n (%)			
	Viral hepatitis n = 18	Cholecystitis n = 13	Gallstones n = 10	Other n = 8
Gender				
Male	8 (44.4)	10 (76.9)	5 (50.0)	4 (50.0)*
Female	10 (55.6)	3 (23.1)	5 (50.0)	4 (50.0)**
Age group				
6 months–2 years	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)†
2.1–5 years	5 (27.8)	1 (7.7)	0 (0.0)	2 (25.0)†
5.1–10 years	8 (44.4)	3 (23.1)	6 (60.0)	2 (25.0)‡
>10 years	5 (27.8)	9 (69.2)	4 (40.0)	3 (37.5)§

**Three patients with biliary sludge and one with periportal fibrosis; **Three patients with biliary sludge and one with liver cirrhosis; †One patient with biliary sludge; ‡One patient with biliary sludge and one with liver cirrhosis; §Two patients with biliary sludge and one with periportal fibrosis.*

Table 2: Frequency of hospital admissions and blood transfusions among sickle cell disease patients with hepatobiliary complications (N = 49)

Variable	Type of hepatobiliary complication n (%)			
	Viral hepatitis n = 18	Cholecystitis n = 13	Gallstone n = 10	Other n = 8
Frequency of previous hospital admissions				
0	1 (5.6)	1 (7.7)	1 (10.0)	1 (12.5)*
1–3	6 (33.3)	5 (38.5)	3 (30.0)	1 (12.5)**
4–9	7 (38.9)	1 (7.7)	2 (20.0)	3 (37.5)†
≥10	4 (22.2)	6 (46.2)	4 (40.0)	3 (37.5)*
Frequency of previous blood transfusions per year				
0	1 (5.6)	2 (15.4)	1 (10.0)	1 (12.5)
1	3 (16.7)	2 (15.4)	1 (10.0)	1 (12.5)
2	4 (22.2)	2 (15.4)	2 (20.0)	1 (12.5)
≥3	10 (55.6)	7 (53.8)	6 (60.0)	5 (62.5)*

**One patient with biliary sludge; **One patient with periportal fibrosis; †Two patients with biliary sludge and one with liver cirrhosis.*

Results

A total of 106 SCD patients were included in the study, of which 49 (46.2%) had hepatobiliary complications. The male to female ratio was 1.5:1 with SCD complications occurring more commonly in male patients (55.1%). The main complications reported were viral hepatitis (36.7%), cholecystitis (26.0%) and gallstones (20.0%). The prevalence of cholecystitis was substantially higher among the male patients, as 76.9% of those affected were male [Table 1].

There was a significant connection between age and the different forms of hepatobiliary complications [Table 1]. Of the patients with cholecystitis, 92.3% were found to be five years of age or older, while 44.4% of the patients with viral hepatitis were 5.1–10 years old.

Of the patients who had previously been admitted to hospital more than 10 times (n = 20), six (30.0%) had cholecystitis, four (20.0%) had gallstones and three (15.0%) had biliary sludge. The frequency of blood transfusions among the patients was related to the varying forms of hepatobiliary complications [Table 2]. Of the patients who had previously had more than three blood transfusions, 62.5% presented with biliary sludge and 60% had gallstones. Hepatobiliary complications increased significantly with age and were notably higher among those who were often admitted to hospital and/or underwent frequent blood transfusions.

The mean Hb levels of the patients with viral hepatitis, cholecystitis and gallstones were 5.3, 6.2 and 6.0 g/L respectively. The mean total bilirubin and indirect bilirubin levels (9.5 and 7.1 mg/dL, respectively) were high in viral hepatitis cases, while the mean ALT (59.4 and 56.0 U/L) and AST (40.1 and 38.3 U/L) levels were significantly higher in those patients with viral hepatitis and cholecystitis, respectively.

Discussion

The hepatobiliary tract of a patient with SCD may be affected by the disease in various ways. Of the 106 patients observed in this study, 49 had hepatobiliary complications. A higher proportion of males were affected in comparison to female patients. Similar studies performed in Yemen by Bamahraz *et al.* and in Saudi Arabia by Mulik *et al.*[9,10] also found a male predominance among their affected subjects. The authors of this study therefore theorise that male patients have a higher prevalence of hepatobiliary complications due to their greater exposure to certain precipitating factors of SCD crises. These factors include frequent infections as well as regular outdoor physical activities that may lead to an elevated metabolic process and increased sweating. This may cause some degree of dehydration, increased blood viscosity and increased oxygen consumption, leaving male patients more susceptible to developing SCD crises.[11]

The results of this study also show that hepatobiliary complications are significantly correlated to a patient's age and the prevalence of such complications significantly increases in patients aged five years and older. In addition, it was observed that a higher proportion of patients with previous histories of hospital admissions and blood transfusions were more commonly affected by hepatobiliary complications, mainly viral hepatitis, cholecystitis and gallstones. This could be explained by the fact that patients who were exposed to a higher frequency of hospital admissions had a greater likelihood of presenting with frequent crises associated with haemolysis. This in turn likely increased their opportunity for further blood transfusions, raising the likelihood of gallstone formation. In addition, it is possible that the blood transfusions predisposed patients to acquiring viral hepatitis from infected blood. Hence, there is a connection between frequent blood transfusions, gallstone formation and viral hepatitis. The current study's findings, with regards to the correlation between hospital admissions, blood transfusions and gallstone formation, were comparable to those reported in a study by Darko *et al*.[12] A high proportion of the patients with hepatitis in the current study had had at least one previous blood transfusion and 5% had had at least three. This result was similar to findings noted by Ocak *et al*.[13]

Cholecystitis is considered one of the most common hepatobiliary complications in patients with SCD, often occurring due to a gallstone obstruction or infections. This complication was observed in approximately one-fifth of those with hepatobiliary complications in the current study, while similar results were found in a comparable study performed in India.[14] It is likely that cholecystitis developed in the affected patients due to an infectious process. However, it may alternatively have been caused by an obstructive gallbladder stone, or as a hepatobiliary crisis due to the sickling process. In the current study, the frequency of developing cholecystitis increased with a patient's age, as a high proportion of cholecystitis patients were over 10 years old. This could be explained by the fact that cholecystitis is largely attributed to gallstone formation, which requires time for development. There was also a higher prevalence of cholecystitis among the male subjects. This result is in contrast to a similar study performed in the Congo that did not see a gender difference in cholecystitis prevalence.[15] These opposing results may be due to the differences in the sample size, time frame and the methods used for cholecystitis detection between the studies.

Biliary sludge is one of the most intriguing complications of SCD.[3] It is a mixture of calcium bilirubinate and cholesterol crystals found within viscous bile, containing a high concentration of mucus and proteins.[16] In the current study, biliary sludge was found in nine patients (18.3%). This was similar to findings from a Saudi Arabian study (16.4%),[10] but exceeded that of studies performed in the Congo (2.1%)[15] and India (8%).[14] These variations may have occurred because the sludge formation and evaporation is a dynamic process caused by frequent intermittent haemolysis, biliary tract infections and fluctuations in the inflammation levels which can differ from one SCD population to another.[8] Patients with biliary sludge need regular follow-up as most are prone to gallstone formation. Therefore, regular examinations are important for the early prevention and proper management of predisposing factors.[17]

The formation of pigmented gallstones in SCD patients is the result of an excessive production of bilirubin due to red cell haemolysis. Its prevalence depends on age, gender and methods of detection, in addition to the patient's geographical location and, in some cases, dietary habits.[18] In this study, only a few patients were found to have gallstones (20.4%). A study performed in Western Orissa, India, had similar results.[14] However, a study from Turkey reported a much higher prevalence,[8] while studies from Yemen[19] and Ghana[12] noted lower prevalences of 4.49% and 4%, respectively. Several factors appear to cause these significant variations in the reported prevalence of gallstones, including the patient's age, type of imaging equipment used and the standard and sophistication of this equipment.[20] The reason for the comparatively low prevalence of gallstones among SCD patients in some areas is not clear. However, it may be related to the general low incidence of gallstones in some populations, such as certain African countries.[12]

In this study, 22.4% of all subjects presented with HBV. This result may reflect the lack of necessary vaccinations available to individuals in Yemen. The authors recommend that Yemeni SCD patients undergo an annual screening for HBV and that patients with an HBV surface antibody titre of <10 should be revaccinated.

The mean Hb values of patients with gallstones were not significantly different from those patients without gallstones; this result is consistent with a study by Sarnaik *et al*.[21] White blood cell counts were high among patients who had gallstones and biliary sludge, which is similar to a study by Longo-Mbenza *et al*.[15] The majority of the current patients had elevated mean total bilirubin, direct bilirubin, AST, ALT and ALP levels, with a significant elevation of AST and ALT in those patients with viral hepatitis and cholecystitis. This is comparable with a study from Brazil.[22]

Based on the results of the current study, the authors recommend that thorough family education and genetic counselling be offered to all those affected by SCD. In addition, the regular and continuous follow-up of patients with SCD should be emphasised. These follow-ups should include routine vaccinations, additional abdominal ultrasounds, periodic liver function tests, serological tests for viral hepatitis and serum ferritin level tests to help in the early diagnosis and management of common SCD complications.

Conclusion

Hepatobiliary complications in SCD patients are common and their prevalence increases as patients age, with the exception of gallstones which can occur from an early age. Among the group of studied patients, the most frequent complications were viral hepatitis, cholecystitis and gallstones. There was a strong correlation between the occurrence of these complications and the frequency of previous blood transfusions and hospital admissions. Based on the findings of this study, genetic counselling and education about the potential complications linked to this condition are recommended for SCD patients and their families. In addition, follow-up appointments and examinations must be prioritised in order to pre-empt the development of SCD complications and to monitor existing symptoms.

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