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Original Article

Cholelithiasis in patients with paediatric sickle cell anaemia in a Saudi hospital

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الملخص

أهداف البحث: يعد فقر الدم المنجلي من أكثر أمراض خضاب الدم المنتشرة في العالم. ومن مضاعفات المرض تكون حصى المرارة وتتفاوت الأعراض المصاحبة لحصى المرارة من كونها صامتة ولا تظهر على المريض أي أعراض، إلى حدوث التهابات المرارة، والقنوات الصفراوية وكذلك البنكرياس. تهدف هذه الدراسة إلى تحديد نسبة حدوث حصوات المرارة لدى الأطفال المصابين بفقر الدم المنجلي في السعودية.

طرق البحث: تمت الدراسة عن طريق مراجعة السجلات الطبية لجميع المرضى الذين تتراوح أعمارهم ما بين عامين إلى ثمانية عشر عاما المصابين بفقر الدم المنجلي. ودراسة عوامل الخطورة المرتبطة بتكوين حصوات المرارة.

النتائج: أظهرت النتائج حدوث حصوات المرارة بنسبة ٢٧٪ لدى المرضى المصابين بفقر الدم المنجلي عند متوسط عمر سبعة سنوات تقريبا. ومن عوامل الخطورة التي ساهمت في زيادة تكون الحصوات بشكل ملحوظ هي زيادة العمر، وارتفاع نسبة خضاب الدم من النوع "س" وزيادة حجم كريات الدم الحمراء. كما لوحظت زيادة نسبة الحصى لدى الذكور عن الاناث، والسعوديين عن غيرهم، ومرضى فقر الدم المنجلي عن فقر الدم المنجلي والبحر المتوسط، لكن هذه الاختلافات لم تكن ذات مدلولات إحصائية.

الاستنتاجات: وجدت الدراسة أن نسبة حدوث حصى المرارة عالية لدى الأطفال المصابين بفقر الدم المنجلي. وكانت العلاقة مع العمر وزيادة نسبة خضاب الدم من النوع "س" وزيادة حجم كريات الدم الحمراء علاقة ذات دلالة إحصائية.

الكلمات المفتاحية: حصى المرارة؛ فقر الدم المنجلي

Abstract

Objective: Sickle cell disease is one of the most common inherited hemoglobinopathies in the world. Chronic haemolysis predisposes individuals to the development of bilirubinate cholelithiasis, which can be asymptomatic or can result in cholecystitis, choledocholithiasis, cholangitis, and gallstone pancreatitis. We aimed to determine the prevalence of cholelithiasis and associated gallstone disease among patients with paediatric sickle cell disease in a Saudi hospital.

Methods: This retrospective study was conducted among all patients aged between 2 and 18 years. We reviewed the medical records of patients diagnosed with sickle cell anaemia. Mean and standard deviation were calculated for quantitative variables, and the Student t-test was used to compare means. The chi-square test was used to assess those risk factors possibly associated with cholelithiasis. A P-value of ≤ 0.05 was considered statistically significant.

Results: Approximately 75% of participants developed cholelithiasis (27.5%) at a mean age of 6.9 $\pm$ 3.4 years. The frequency of cholelithiasis was significantly higher with increasing age (40.8% in participants 12 years and older) and among those with high levels of haemoglobin S (Hb S) and mean corpuscular volume (MCV). Moreover, cholelithiasis was more frequent among males than females, Saudis than non-Saudis, and in those with sickle cell disease than in those with sickle thalassemia. However, these differences were not statistically significant.

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Conclusion: In this study, the prevalence of cholelithiasis among children with sickle cell anaemia was found to be high. This association was significantly increased with age and high levels of MCV and Hb S.

Keywords: Cholelithiasis; Gallstones; Sickle cell anaemia

Introduction

Sickle cell disease (SCD) is one of the most common inherited hemoglobinopathies. SCD is caused by a haemoglobin S (Hb S) mutation, which is a single nucleotide substitution of normal hydrophilic glutamic acid with valine residue in the sixth codon of the β-globin gene. SCD indicates homozygosity for Hb S.[1] The polymerization of Hb S in deoxygenation is responsible for the pathophysiology of SCD within red blood cells (RBCs). Furthermore, rigid polymers of Hb S frequently form and disrupt the RBC membrane, shorten the lifespan of RBCs, and induce haemolysis. This makes RBCs inflexible and abnormally adhesive; therefore, they are prone to obstruct blood flow causing vaso-occlusion that can lead to infarction and ischemic injury to multiple organs and tissues.[2,3]

Sickle cell anaemia (SCA) accounts for most cases of SCD in the Kingdom of Saudi Arabia (KSA). In one study, Hb electrophoresis in 297 patients showed that 96.7% of patients had SCA and 3.3% had the sickle cell trait.[4] However, there is wide variability in phenotype among regions of the KSA,[5] with SCD more prevalent in the eastern and western areas.[2,3] A study performed at King Abdul-Aziz Medical City in Riyadh, KSA showed that SCD is relatively more frequent among males (56.4%) than females; however, the incidence of SCA is more common among children (48.5%).[4] Most children are diagnosed with SCA during the first or second year of life, and only a small percentage of children with SCA are diagnosed at birth due to decreased neonatal screening of the Saudi population.[6] Recent studies have demonstrated the success of a premarital Saudi program in reducing the incidence of SCA in the KSA.[7,8]

SCD is a systemic disease that affects all organs as a consequence of either haemolysis or vaso-occlusion. However, the presentation of SCD can be either acute or chronic. Acute manifestations include dactylitis, pain crisis, acute chest syndrome (ACS), and acute splenic sequestration (ASS). Both ACS and ASS are the leading causes of death among patients with SCD. Chronic manifestations include complications of the central nervous, cardiovascular, renal, and hepatobiliary systems.[2,3] Chronic haemolysis leads to bilirubinate cholelithiasis, which can be either asymptomatic or symptomatic, ranging from cholecystitis, choledocholithiasis, and cholangitis, to gallstone pancreatitis.[9]

Studies have shown that 70% of patients with SCA will develop gallstones once in their lifetime, which increases morbidity among these patients.[9,10] The incidence of cholelithiasis in SCA worldwide ranges from 5% to 55%.[10] A previous study in the KSA showed a prevalence of 16.4% for biliary sludge and 19.7% for gallstones among patients with SCA.[11] This prevalence increased significantly with age ranging from 8.7% in children ≤10 years to 36% in children between age 15 and 18 years.[11] Most patients are asymptomatic for cholelithiasis; therefore, there is a need for longitudinal studies to assess the course of asymptomatic gallstones. Biliary sludge is best managed with serial ultrasound examination at 12- to 24-month intervals, unless cholestasis occurs; at that point, laparoscopic cholecystectomy is indicated. Elective laparoscopic cholecystectomy has become the procedure of choice for symptomatic cholelithiasis owing to shortened hospital stay, lower cost, and fewer complications.[12]

In the present study, we aimed to estimate the prevalence and determine the risk factors of cholelithiasis among patients with paediatric SCD in Almadinah Almunawwarah, KSA.

Materials and Methods

Study design and duration

This study was based on a retrospective cohort analysis, conducted at Maternity and Children Hospital in Almadinah Almunawwarah from March 1, 2017 to September 11, 2017.

Study participants

The study was conducted by reviewing the medical records of 153 patients diagnosed with SCD. SCD was diagnosed using haemoglobin electrophoresis based on cellulose acetate (CA) electrophoresis at pH 8.2–8.6, including all phenotypes such as sickle S (SS), sickle C (SC), and sickle-beta thalassemia (Sβ).

Inclusion and exclusion criteria

Patients between the ages of 2 and 18 years with SCD and cholelithiasis were included in this study. However, patients with severe health complications were excluded.

Statistical analysis

Data analysis was performed using IBM SPSS, version 20.0 (IBM Corp., Armonk, NY, USA). Mean and standard deviation were calculated for quantitative variables (age, gallstone size, and baseline total haemoglobin, haemoglobin electrophoresis, mean corpuscular volume (MCV), white blood cells (WBCs), and platelets). The Student t-test was used to compare means. The chi-square test was used to determine the association of qualitative variables (sex, nationality, type of SCD, and haemoglobin electrophoresis type). A P-value ≤0.05 was considered to indicate statistical significance.

Ethical considerations

This study was ethically approved by the institutional review board (IRB) at Maternity and Children Hospital, Almadinah Almunawwarah. Appropriate ethics policies and regulations were followed in the study. The medical records

were reviewed for all included patients, without disclosure of patient identification.

Results

In this study, we reviewed the medical records of 153 patients with SCA who were registered in Maternity and Children Hospital of Almadinah Almunawwarah between March 1, 2017 to September 11, 2017. The mean patient age was 9.4 ± 3.9 years (ranging from 2 to 18 years). Almost half of the patients (51%) were in the age group 6–12 years.

Most patients were diagnosed with SCA (85%); the rest were diagnosed with sickle cell-beta thalassemia (15%). Two patients (1.8%) had been diagnosed at birth, 41 patients (36%) were diagnosed before reaching their first birthday, and 45 patients (39.5%) were diagnosed during their second year of life; the median age at diagnosis was 12 months (Table 1). More than half of patients (55.3%) had an average of one hospital admission per year due to complications of SCA; 13.8% of patients had an average of three hospital admissions per year or more. The most common causes of hospital admission were painful episodes (69.3%), infection (60.8%), ACS (43.8%), and ASS (28.8%). The least frequent hospitalization causes included aplastic episodes (3.3%), stroke (9.2%), and osteomyelitis (9.2%).

The data in Table 2 show that more than a quarter of patients (27.5%) developed cholelithiasis. The mean age for diagnosing cholelithiasis was 6.9 ± 3.4 years, which was mainly detected accidentally through radiography (24; 64.9%), with only about one-third (13; 35.1%) of patients presenting symptomatic manifestations. The main finding was the presence of gallstones (84.2%), which were mostly present in multiple numbers (71.4%) with an average size 5.5 ± 2.1 mm; 6 patients (15.8%) only had biliary sludge. Of all patients diagnosed with cholelithiasis, 23 underwent successful laparoscopic cholecystectomy.

The frequency of cholelithiasis was higher among males than females (29.6% vs. 25%), Saudi than non-Saudi patients (31.3% vs. 15.8%), and in those with SCA than those with sickle thalassemia (28.5% vs. 21.7%). However, these differences were not statistically significant, with P-values 0.522, 0.063, 0.505, respectively (Table 3). Moreover, the results of haemoglobin electrophoresis results no statistically significant association with the occurrence of cholelithiasis. However, the frequency of cholelithiasis was significantly associated with patients' age; proportions ranged between 11.5% in patients aged <6 years, to 24.4% in those aged 6 to <12 years, and up to 40.8% in patients aged 12 years or older (P = 0.018).

As shown in Table 4, the MCV was significantly larger among patients with cholelithiasis (85.1 ± 10.8) than those without cholelithiasis (78.2 ± 10.8, P = 0.001). Hb S concentrations were significantly higher among patients with (67.4 ± 17.2) than those without cholelithiasis (59.7 ± 22.0, P = 0.041). Otherwise, no statistically significant differences were observed between the two groups of patients regarding WBCs, platelets, total haemoglobin, and haemoglobin A, F, or A2 (P > 0.05). The data in Table 5 show that there was a high frequency of cholelithiasis among patients taking hydroxyurea (38.2%) and folic acid (28.6%); these differences were not statistically significant (P = 0.110 and 0.308, respectively). Moreover, no statistically significant difference was

Table 1: Clinical characteristics of patients with sickle cell disease (n = 153).

Characteristics	No.	Percentage
Type of sickle cell disease		
Sickle cell anaemia	130	85.0
Sickle cell thalassemia	23	15.0
Age at diagnosis (n = 114)		
Birth	2	1.8
<12 months	41	36.0
12–24 months	45	39.5
>24 months	26	22.7
Median	12 months	

Table 2: Clinical characteristics of patients with cholelithiasis (n = 42).

Characteristics	No.	Percentage
Age at diagnosis (n = 34)		
<6 years	12	35.3
6 to <9 years	11	32.4
≥9 years	11	32.4
Mean ± SD	6.9 ± 3.4 years	
Clinical presentation (n = 37)		
Symptomatic	13	35.1
Accidently in radiography	24	64.9
Type of findings (n = 38)		
Biliary sludge	6	15.8
Gallstones	32	84.2
Number of stones (21)		
Single	6	28.6
Multiple	15	71.4
Mean ± SD size of gallstones	5.5 ± 2.1 mm	

Table 3: Demographic and clinical factors possibly associated with cholelithiasis.

Factors	Occurrence of cholelithiasis				X^2	P*
	Yes		No			
	No	%	No	%		
Sex						
Male	24	29.6%	57	70.4%	0.410	0.522
Female	18	25.0%	54	75.0%		
Nationality						
Saudi	36	31.3%	79	68.7%	3.452	0.063
Non-Saudi	6	15.8%	32	84.2%		
Age						
<6 years	3	11.5%	23	88.5%	8.075	0.018**
6 to <12 years	19	24.4%	59	75.6%		
≥12 years	20	40.8%	29	59.2%		
Type of sickle cell disease						
Sickle cell anaemia	37	28.5%	93	71.5%	0.443	0.505
Sickle cell thalassemia	5	21.7%	18	78.3%		

*Based on chi-square test. ** Statistically significant.

Table 4: Results of laboratory investigations in cholelithiasis.

Lab results	Occurrence of cholelithiasis		t	P*
	Yes	No		
	Mean ± SD	Mean ± SD		
White blood cells	14.9 ± 5.0	15.2 ± 6.2	0.298	0.766
Platelets	482.9 ± 174.1	430.0 ± 252.1	1.252	0.213
Haemoglobin	8.3 ± 1.4	8.1 ± 1.3	0.829	0.408
Mean corpuscular volume	85.1 ± 10.8	78.2 ± 10.8	3.499	0.001**
Haemoglobin A	20.3 ± 22.5	22.1 ± 24.0	0.366	0.715
Haemoglobin F	11.5 ± 8.6	12.1 ± 9.2	0.315	0.754
Haemoglobin S	67.4 ± 17.2	59.7 ± 22.0	2.073	0.041**
Haemoglobin A2	3.6 ± 0.8	4.5 ± 3.1	1.094	0.276

*Based on independent samples t-test. ** Statistically significant.

Table 5: Frequency of cholelithiasis according to type of medication given for sickle cell anaemia.

Medication	Occurrence of cholelithiasis				X^2	P*
	Yes		No			
	No	%	No	%		
Hydroxyurea						
Yes	13	38.2%	21	61.8%	2.553	0.110
No	29	24.4%	90	75.6%		
Folic acid						
Yes	40	28.6%	100	71.4%	1.039	0.308
No	2	15.4%	11	84.6%		
Ospen						
Yes	28	26.4%	78	73.6%	0.186	0.666
No	14	29.8%	33	70.2%		

*Based on chi-square test.

observed regarding the frequency of cholelithiasis and intake of phenoxymethylpenicillin (P = 0.666).

Discussion

In the present study, we determined the prevalence of cholelithiasis among patients with paediatric SCD in Almadinah Almunawwarah, KSA. The results showed that a quarter of participants developed cholelithiasis at a mean age of 6.9 years. However, previous studies have reported prevalence of cholelithiasis in the range if 4.2%–58%.[11–21] This wide range in cholelithiasis frequency is mainly attributable to differences in geographic area and age group as well as differing inclusion and exclusion criteria among studies. In the present study, 27.5% of patients with SCA developed cholelithiasis. A higher rate was reported in a 1996 study in KSA by Al–Salem et al.[11] who reported a 35.5% prevalence of cholelithiasis.[11] A similar frequency (23.8%) was reported in Jamaica by Walker et al.[15] A significantly higher rate has been noted in other studies where adolescent and adult age groups were considered.[16,17] The prevalence of cholelithiasis was 45% among Brazilian participants in a study by Gumiero et al.[16] and 58% among British participants.[17]

When considering the risk factors for cholelithiasis in children with SCA, the present study revealed that sex and nationality were not significant risk factors. In a similar context, a Sudanese study found that there was no correlation between gallstones and patients' sex (P = 0.73)[20]. However, increased frequency of cholelithiasis was reported among patients with SS as compared with patients who had Sβ; these differences were not statistically significant (P > 0.05). In contrast, a Brazilian study reported a significantly higher prevalence of cholelithiasis in patients with SS than in those with SC or Sβ disease (P = 0.0044), and in SS and Sβ when considered as a group than in the SC group (P = 0.001).[16]

Age is considered a significant risk factor for gallstones among patients with SCA. Similar results were reflected in a study conducted by Attalla et al.[20] who reported that the youngest patient with cholelithiasis was 2.5 years old; when divided into subgroups, the proportion of patients with gallstones was 0.7% in those less than 5 years old, 13% in those aged 5–10 years, and 33% in patients aged 10–16 years.[20] Kamdem et al.[22] found a median age for gallstones of 9.2 (range: 2.5 to 17.9) years and the cumulative risk of gallstones was 5% by age 5 years, 20.7% by age 10 years, and 35.6% by age 15 years.[22] Gumiero et al.[16] reported a mean age at diagnosis of cholelithiasis of 12.5 years.[16] Two-thirds of the patients in our study were diagnosed through radiography, and only one-third had symptomatic manifestations. Attalla et al.[20] found that no patients were symptomatic at the time of diagnosis of cholelithiasis. Only one patient developed symptoms during the follow-up period.[20] In a study by Gumiero et al.,[16] 14 of 101 patients were symptomatic at the time of diagnosis of cholelithiasis and 34 became symptomatic during follow-up.[16]

In the present study, we found no significant difference between patients who developed gallstones and those who did not with respect to WBCs, platelets, total haemoglobin, and haemoglobin A, A2, and F levels. In agreement with these results, Attalla et al.[20] reported that total haemoglobin, reticulocyte %, and total bilirubin showed no significant differences between patients with and without gallstones.[20] Kamdem et al.[22] found that haemoglobin, WBCs, neutrophils, platelets, MCV, and bilirubin were not significant risk factors.[22] Moreover, their study showed that high MCV and Hb S levels were significant risk factors for cholelithiasis. Kamdem et al.[22] also reported that Hb F, reticulocyte count, and lactate dehydrogenase (LDH) significantly increased the risk for gallstones.[22] In the KSA, Perrine[23] found that lower incidence of cholelithiasis and milder clinical manifestations were related to high levels of foetal haemoglobin.

Our study findings demonstrated a non-significant higher frequency of cholelithiasis among patient taking folic acid and hydroxyurea for long-term treatment of SCD. There was no significant correlation between the intake of phenoxymethylpenicillin and formation of gallstones among our patients. Similar results were reported by Martin et al.[24] who found no significant differences in the frequency of cholelithiasis between patients who used

hydroxyurea (32.4%) and those who did not (21.4%, P = 0.215).[24]

The present study results are limited in that there were no available data for reticulocyte %, LDH, and bilirubin levels; therefore, we could not evaluate their correlation with cholelithiasis as compared with other factors in this study.

Conclusion

The present study found an increased prevalence of cholelithiasis (27.5%) among children with SCA in Almadinah Almunawwarah, KSA. The mean age at the time of diagnosis was 6.9±3.4 years. Most patients were asymptomatic and cholelithiasis was detected accidently during abdominal ultrasound follow-up.

Recommendations

Early screening with routine abdominal ultrasound and follow-up of laboratory findings, especially in high-risk patients with high levels of MCV and Hb S, may help in early detection and lower the incidence of cholelithiasis and its complications. Further prospective studies are recommended to establish the age at which to start screening and to assess the course of asymptomatic gallstones.

Conflict of interest

The author have no conflict of interest to declare.

Ethical approval

The ethical approval was obtained from institutional review board (IRB) at Maternity and Children Hospital, Almadinah Almunawwarah. Ethics policies and regulations were followed in the study. The medical records were reviewed for all targeted patients without disclosing patient identification.

Authors' contributions

AMS, AMQ, LKH conceived and designed the work, collected and contributed data and the analysis tool, interpreted the data and wrote the initial and final drafts of the manuscript. ZMH, WAT also conceived and designed the work, reviewed the manuscript, and provided logistical support. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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