Outcome of cholelithiasis in Sudanese children with Sickle Cell Anaemia (SCA) after 13 years follow-up

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Abstract

Background: SCA causes chronic haemolysis which is a risk factor for cholelithiasis.

Objective: To determine the prevalence and outcome of children with SCA complicated with gallstones treated at the sickle cell clinic at the children emergency hospital Khartoum state.

Methods: 261 patients age 4 months to 16 years were studied. AUS examination was carried out. The 30 patients in whom gall stones were detected followed prospectively from June 1996 to September 2009 when a second AUS examination was obtained.

Results: Gall stones occurred in 30 patients of whom four were lost to follow up in the first year. The overall prevalence of cholelithiasis was 11.5% and it increased with age. The youngest patient with cholelithiasis was 2 1/2 years old. Haematological variables, bilirubin and sex did not identify a subgroup of patients at higher risk for gallstones. All the patients were asymptomatic at the time of diagnosis. One patient developed symptoms 3years after the diagnosis and he was submitted to surgery. The 25 remaining asymptomatic patients were followed up for 13 years and none of them presented complications related to cholelithiasis during this period.

Conclusion: The prevalence of cholelithiasis in Sudanese children and adolescents with SCA was significant. The large majority patients remained asymptomatic over a long period.

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Introduction

Sickle cell disease (SCD) is the commonest inherited haemoglobinopathy. Its most common clinical manifestation is anemia due to chronic haemolysis. The occurrence of gallstones is one of the most important manifestations of SCD in the digestive tract[1, 2, 3, 4, 5]. Excessive production of bilirubin from chronic haemolysis is an important factor for formation of pigment gallstones[6, 7]. However, many SCD patients with marked haemolysis do not develop gallstones. Thus, abnormalities in gallbladder function or bile acid metabolism may contribute to gallstone formation in these patients[8].

The prevalence of cholelithiasis is high in patients with HbSS/SCA and increases progressively with age, affecting 15% of children with SCA younger than 10 years of age and more than 80% of those older than 30 years[9, 10]. Other studies reported a range of 6% in patients under 15 years and increases progressively with age, affecting 50% of young adults[11, 12]. Despite the increased incidence of gallstones in SCA, many have felt that symptomatic biliary tract disease was rare.

Cholecystectomy is indicated for symptomatic patients, but controversy still exists regarding the appropriate treatment for asymptomatic patients with cholelithiasis[13]. Although a low complication rate has been reported in some studies, suggesting an expectant conduct[14, 15], others have proposed elective surgery because of lower mortality and fewer surgical complications compared to an emergency surgery or procedure after an acute cholecystitis episode[16].

In a previous study we determined the prevalence of cholelithiasis in Sudanese children with SCA. Most of the patients were asymptomatic and we recommended a larger longitudinal study to describe the course of the asymptomatic gallstones[17].

The objective of the present study was to determine the frequency of gallstones in children with

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SCA treated at the sickle cell clinic children emergency hospital Khartoum state, and to describe the follow-up and outcome after the diagnosis of cholelithiasis.

Methods

This study was performed by studying all patients attended the sickle cell clinic in June 1996 when the clinic was established at Khartoum children emergency hospital. The clinic offers services including diagnosis, treatment, follow up, family education and counseling. It is a focus for research on sickle cell disease and it offers training for the medical staff.

261 SCA patients were recruited in June 1996. They were questioned for biliary tract disease which is an abdominal pain typical of biliary colic and defined as pain in the right hypochondrial or epigastric region of a study unremitting nature lasts for more than one hour with indigestion, fat intolerance, abdominal pain or discomfort, nausea or vomiting related to food. Children less than five years, this information was obtained from the parents. At that time (i.e. June 1996) they were all underwent blood tests for Hb concentration, reticulocyte count and Hct which were performed by standard haematological techniques (Dacie & Lewis, 1984)[18]. Total S-bilirubin was measured by the dichlorophenyldiazonium chloride method (Wahiefeld et al 1972)[19].

Ultrasonography of the gallbladder was performed using real time scanner with a frequency of 3.5 MHz using sonojelly. Sonographic tests were performed without sedation on the morning following an overnight fast; (they were allowed to take water or juice in the morning). Longitudinal and transverse scans of the right abdomen were obtained. Examination was obtained in supine positions and it took 5-10 minutes. Sonographic findings were considered positive for the presence of gallstones when an echodense images casting an acoustic shadows were seen. The findings were recorded in sonography sheets and kept with the follow –up records to be compared with the final results.

Of the 261patients studied, 30 were found to have gall stones; these 30 patients were then apparently followed on a regular basis until Sept 2009; follow-up included questioning for symptoms of cholecystitis. September 2009 a follow-up AUS examination was obtained. There was no change in the AUS technique between June 1996 and Sept 2009.

Statistical Analysis

The analysis of data was performed using SPSS - statistical package for social sciences computer programme. The mean and standard deviation were calculated for all quantitative data. Student's T-test was used to compare between means. A level of significance of 5% was adopted.

Results

A total of 261 SCA patients were studied. The sample included 165 (63%) males and 96(37%) females. The mean age of the patients was 6.8 years (SD =0.94, range: 4 months to 16years.

An initial abdominal ultrasound reported that gall stones occurred in 30 patients (18 boys, 12girls). The findings were multiple gall stones with thick bladder wall. The overall frequency of cholelithiasis was 11.5%. The frequency of gallstones increased with age, with the condition being diagnosed before the age of 5 in 0.7%, between 5 and 10 years of age in 13%, between 10 and 16 years in 33%. The youngest patient with cholelithiasis was 2 1/2 years old. There was no significant sex difference in patients with gall stones (chi square = 0.12 p = 0.73) (table 1).Hematological data showed no significant difference between patients with and without gall stones (table 2)

No patients were symptomatic at the time of diagnosis of cholelithiasis. Four were lost to follow up. They were followed for 5, 8, 9 and 11 months. One patient became symptomatic during follow-up. He underwent cholecystectomy with no postoperative complications. The time interval between the diagnosis of cholelithiasis and surgical treatment was 3 years. His symptoms were relieved and did not show any recurrence of symptoms for a period of 10 years follow-up. The remaining 25 asymptomatic patients were followed up prospectively after the diagnosis of cholelithiasis for a period of 13 years. As the clinic is the only specialized place for sickle cell disease and it offers free service, close follow-up was maintained for all that time.

Data was collected in the follow up records of the study. None of the patients developed symptomatic gallbladder disease during that period. A follow-up abdominal ultrasound was done after 13 years and the findings at follow-up compared with the findings on the initial examinations showed no difference for each patient.

Table 1: Prevalence of gall stones according to age and sex

Age group	Boys		Girls		Total	
(years)	No	No gall stones (%)	No	No gall stones (%)	No	No gall stones (%)
4 months-5years	93	1 (1)	45	0 (0)	138	1 (0.7)
5-10years	36	5 (13.9)	24	3 (12.5)	60	8 (13)
10-16 years	36	12 (33)	27	9 (33)	63	21 (33)
Total	165	18 (10.9)	96	12 (12.5)	261	30 (11.5)

Sex chi square = 0.12 p = 0.73

Table 2: Haematological data in patients with and without gallstones

Variable	Patients with gallstones		Patients without gallstones			
	Mean	SD	Mean	SD	T-Test	P
Hb (gm/dI)	6.4	0.9	6.7	1.7	0.21	> 0.05
PCV%	22.3	2.7	22.6	4.16	0.044	> 0.05
Retics %	10.4	5.1	10.7	6.4	0.14	> 0.05
Total bilirubin umol/L	87.5	2.3	83	2.5	0.83	> 0.05

Discussion

The prevalence of gallstones in patients with SCA varies according to different studies[1, 2, 3, 4, 5, 13, 15, 16]. The selection of different age ranges may explain some differences. In the present study, of the 261patients studied initially, 30 were found to have gall stones. This prevalence was similar to that reported by a previous study in Sudan [17], Barrett-Connor [20] and Webb et al[21]. In Nigeria a low prevalence of cholelithiasis of 6% in patients under 15 years was reported by Akinyanju et al [11]. This low prevalence was attributed to the less sensitive diagnostic method of oral cholecystography, but later studies using ultrasonography reported similar low prevalences of 4.4% under 17 years patients [22] and 5% under 15 years[23]. It therefore seems likely that gallstones are truly infrequent in young Nigerian patients with SCA consistent with the infrequency of all gallstones in that population[24]. In contrast, the prevalence of gallstones in Sudanese population is high and its occurrence is common[25, 26].

In a Saudi Arabian study [27]cholelithiasis was observed in only 8% of 62 patients aged 10 - 64 years. The youngest of whom was 17 years old. The lower incidence of cholelithiasis and the milder clinical manifestations in these patients were related to an unusually high level of foetal haemoglobin which averaged more than 20%.

Other studies [28, 29, 30, 31, 32, 33] reported higher prevalence than this study. In these studies some have used the same diagnostic method as ours [29, 31, 33], other used less sensitive methods [30] and the rest used more than one method[28, 32]. This is because they studied older children and adults [29, 30], and those who studied only children did not include those under 2 years of age[28, 31, 32, 33].

In this study the number of patients studied was large and the period of follow-up was long however the fact that the ultrasound technique was not optimal – in terms of MHz used – for infants and very young children was a limitation.

The results of the present study showed that age was a significant factor in gallstones formation. This trend was also reflected in other studies when they were categorized into age groups[20, 28, 29, 30, 32, 33]. In this study there was no evidence for a subgroup at higher risk of gallstones because of the haematological factors or sex. In contrast to other studies Bond et al[29] reported no correlation to sex, haematological variables or abnormal results of liver function tests. Rennels et al[31] and Sarnaik et al[33] found no significant differences in mean haemoglobin levels and reticulocyte counts, but higher mean bilirubin concentration in patients with gallstones was reported by Sarnaik[33]. Webb et al[21] reported that children with gallstones had significantly lower total haemoglobin and higher bilirubin concentrations. Perrine [27] reported no significant difference in haemoglolin and reticulocyte count between the two groups. Barrett-Connor [20] reported that abnormal liver function tests were poor guide to the presence of the gallstones.

This study did not show any correlation between gallstones and the haematologic values while other studies have shown a correlation between the presence of gallstones and the rate of haemolysis. We studied patients in the steady state and the compared haematologic values were done once initially.

Other apparent risk factor for gallstones formation is low foetal haemoglobin. Bond et al [29] reported no correlation in his study, but, Webb et al[21] reported low level of foetal haemoglobin in those with gallstones, while Perrine [27] reported high level in Saudi Arab population, where the prevalence of gallstones is low. Because we did not monitor foetal haemoglobin levels, we were unable to evaluate whether this correlation was present in our patients with gallstones. The patients with gallstones in this study were asymptomatic. A previous study reported40% of patients with gallstones had symptoms suggestive of biliary colic, and 60% of them were asymptomatic[17]. This finding is the same as what has been reported by Barrett-Connor [20], Webb et al[21] and Perrine [27], where most of their patients were asymptomatic. While Sarnaik[33], Cameron et al [30], Karayalcin [32] and Bond et al [29] reported that symptoms typical of biliary tract was common in patients with gallstones. One patient in this study developed symptoms three years after diagnosis. He had cholecystectomy that relieved his symptoms and he had no post-operative complications. In other studies authors reported good relief of symptoms following elective cholecystectomy with no postoperative complications[28, 30, 32, 34, 35, 36, 37]. Bond et al[29] reported postoperative complications which were common, but not generally serious. Stephens et al [34], who reported no complications with elective cholecystectomy, has reported that urgent cholecystectomy resulted in multiple major postoperative problems. The minimization of postoperative complications has been attributed to the careful management of these patients.

The 25 asymptomatic patients were followed-up for 13 years and had no symptoms during the follow-up period. The role of cholecystectomy for symptomatic gallstones as shown by one of our patients is unquestioned. Follow-up of patients with gallstones suggested that half would develop symptoms or complications within three years [34], and in another study half developed complications within the first five years[38]. In contrast, no symptoms have occurred in the follow-up of 30 Jamaican children with gallstones, and follow-up of 32 adults known to have gallstones for 15 years showed only one patient developing specific symptoms during this period. Walker et al[4] followed up patients for 25 years and found a large number of asymptomatic patients and a low 7% proportion of surgical indications. The U. S. National Institutes of Health [13] stated that there are sufficient data in the medical literature to indicate a non-surgical approach to asymptomatic patients, but there is still marked controversy.

Bogue et al suggested a conservative treatment for clinically silent, uncomplicated gallstones in children and infants because they are associated with low rates of complications, but patients with sickle cell disease, spherocytosis, and elliptocytosis had high complication rates and required surgery more often[39]. Hendricks-Ferguson V, reported that a great number of surgeons now remove asymptomatic stones in SS disease patients[40].

Laparoscopic cholecystectomy is one of the most frequently performed laparoscopic operations. It is a safe and effective procedure in almost all patients with cholelithiasis. Proper preoperative work up, knowledge of possible complications and adequate training makes this operation a safe procedure with favorable result and lesser complications[41]. Curro et al, recommend elective early laparoscopic cholecystectomy in children with chronic hemolytic anemia and asymptomatic cholelithiasis in order to prevent the potential complications of cholecystitis and choledocholithiasis which lead to major risks, discomfort and longer hospital stay[42]. The British guidelines for management of hereditary spherocytosis recommended that; in children undergoing splenectomy, the gall bladder should be removed concomitantly if there are symptomatic gallstones. If stones are an incidental finding without symptoms, the value of cholecystectomy remains controversial. If the gallbladder is left in situ (including when a cholecystostomy with stone extraction has been done), close follow-up using ultrasound is necessary[43].

What is already known about this subject?

Sickle cell disease causes chronic and recurrent haemolysis which is a recognized risk factor for cholelithiasis;

The prevalence of cholelithiasis is high in patients with SCA and increases progressively with age;

Cholecystectomy is indicated for symptomatic patients, but controversy still exists regarding the appropriate treatment for asymptomatic patients with cholelithiasis.

What are the new findings?

The prevalence of cholelithiasis in Sudanese children and adolescents with SCA treated at the sickle cell clinic was significant;

The large majority (25/30) patients remained asymptomatic over a long (13 year) period;

The youngest patient with gallstones was 2 ½ years old.

How might it impact on clinical practice in the foreseeable future?

Routine screening with AUS is not necessary in children with SCA and that AUS for the detection of cholelithiasis need only be done in the presence of symptoms and/or signs suggestive of cholelithisasis;

Cholecystectomy must be considered in symptomatic patients;

In asymptomatic patients, conservative management seems to be the better choice.

Conclusion

The prevalence of cholelithiasis in Sudanese children and adolescents with SCA treated at the sickle cell clinic was significant. The large majority patients remained asymptomatic over a long period.

AUS in SCA patients for the detection of cholelithiasis need only be done in the presence of symptoms and/or signs suggestive of cholelithisasis. Symptomatic patients' surgery must be considered after stabilization of the patient; asymptomatic conservative management appears to be a safe and possibly the better option, but further studies to confirm this recommendation are suggested.

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