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Frequency of Cholelithiasis in Sickle Cell Disease and Thalassemic Patients at Hereditary Blood Diseases Center in Karbala Teaching Hospital for Children

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Abdulkareem A. Jasim[1], Israa Mustafa Salih AL-Musawi[2,*], Zahraa Alaa Abdul Zhara[3]

1.C.A.B.A.P. Asst.Prof.College of Medicine,University of Karbala.

2.C.A.B.A.P. Pediatrecian Karbala Teaching Hospital for children.

3.M.B.Ch.B. Senior registrar Karbala Teaching Hospital for children.

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ABSTRACT

Background: Cholelithiasis is defined as formation of stones in gallbladder, it is unusual in infants, and in children but it is not rare. Hemolytic anemia (sickle cell disease and thalassemia) cause chronic hemolysis which is a risk factor for gallstones formation. **Objective**: To determine the frequency of cholelithiasis in patients with sickle cell disease and thalassemia treated at hereditary blood diseases center in Karbala Teaching Hospital for children in Karbala city. **Methods**: A retrospective study is performed by reviewing medical records of a Four hundred thirty-three patients with sickle cell disease and thalassemia, patients aged six months to 18 years, between December, the 1st, 2015 to December the 30th, 2016. Data collected include type of hemolytic anemia, frequency of blood transfusion, and the mode of diagnosis of cholelithiasis whether symptomatic or asymptomatic (diagnosed by doing abdominal ultrasound for each patient).**Results:** Cholelithiasis occurred in 50 patients 32(7.39%) patients with sickle cell disease and 18 (4.15%) patients with thalassemia, with no significant difference between genders. The overall percentage of cholelithiasis was 11.54% and it increased with age. A thirty-four (7.8%) patients with gallstones were asymptomatic at the time of diagnosis discovered by routine abdominal ultrasound and 16 (3.7%) patients were symptomatic by history of abdominal pain, jaundice, fever, nausea and vomiting. **Conclusion:** The frequency of cholelithiasis in patients with sickle cell disease and thalassemia in this study was significant. The frequency of gallstones in patients with sickle cell disease more than in the patients with thalassemia. The majority of patients remained asymptomatic. Patients with sickle cell disease who had infrequent blood transfusion had more chance to develop gallstones than others. In patients with beta thalassemia the frequency of gallstones where more in patients who transfused blood transfusion every 3 weeks than others.

INTRODUCTION

When compared with adults, cholelithiasis (gallstones) is unusual in infants, and in children but it is not rare. Increased frequency of gallstones may be due to an increase in recognition of disease due to widespread use of ultrasonography (U/S) for abdominal complaints in recent years [1]. Cholelithiasis classified into three groups; hemolytic, non-hemolytic, and idiopathic [2,3,4] table (1).

Table (1) ETIOLOGY OF GALLSTONES IN CHILDREN (5,6).

Type	Proportion	Etiology of gallstone
Hemolytic	20%-30%	Sickle-cell disease, Hereditary spherocytosis, Thalassemia syndrome
Non-hemolytic	30%	TPN, prolonged fasting ileal disease (like Crohn's disease) or resection, prematurity, furosemide therapy, cardiopulmonary bypass, congenital biliary malformations, PFIC, chronic liver disease, cystic fibrosis, teenage pregnancy
Idiopathic	30%-40%	No predisposing factor

About (20-30%) of all gallstones in children are due to Hemolytic diseases and mainly occurs after the age of 5years and is directly related to the severity and to the intensity of hemolysis. The cholelithiasis is one of the important manifestations of sickle cell disease in the digestive tract [5]. The incidence of cholelithiasis in thalassemia in children is (10-15%) [6] and increasing progressively with the age to reach (50%) in adult [7]. The highest frequency of gallstones has been reported in beta thalassemia associated with Gilbert's syndrome genotype because of the combined effect of increased bilirubin production and reduced bilirubin-diphosphate-glucuronyl transferase enzyme activity [7,8]. The frequency of gallstones in patients with hereditary spherocytosis is 10-20% in children and in adult, it is 40% [9]. Gallstones are (30-40%) idiopathic mainly among adults and adolescent girls [3,4,10]. In about 30% of cases, gallstones are due to non-hemolytic causes such as use of total parenteral nutrition [which cause cholecystokinin and enterohepatic circulation impairment lead to gallbladder contraction resulting in biliary stasis, and stones], phototherapy and furosemide in the infants, congenital biliary diseases such choledochal cyst, chronic liver disease, progressive familial intrahepatic cholestasis, prolonged fasting, and ileal disease or resection [2,3]. Biliary sludge or biliary pseudolithiasis has been reported complication of ceftriaxone which is reversible and disappears on discontinuation, (60% excreted unchanged into the urine and 40% in the bile, concentrate in bile 20 times more than in serum and forms an insoluble salt with calcium that deposit in gallbladder).

In hemolytic anemias, the liberated hemoglobin (from chronic hemolysis and also multiple blood transfusions) is broken down, and its heme component is eventually, degraded into bilirubin by the liver. Increased bilirubin production leads to formation of pigment gallstones. Even in cholesterol stones, a bilirubin nidus has been documented [11]. Patients who are homozygous have the higher incidence of gallstones development than those who are heterozygous for that particular gene defect and disease [12].

Gallstones have different types; Pigment gallstones (black or brown) which are the common type of gallstones associated with chronic haemoglobinopathies composed mainly of bilirubin and calcium salts with 20% cholesterol; Pure cholesterol gallstones; and Mixed gallstones which are more common in adults composed mostly of cholesterol (70-80%), calcium salts and bilirubin compounds (20-30%).

There is variation of the frequency of cholelithiasis in the haemoglobinopathic patient with the age. As patients grow older, gallstones are more likely to develop. In Sickle Cell Disease, which is the commonest hemolytic anemia, the frequency of pigmented gallstones in SCD is directly related to the rate of hemolysis [5,13]. Stones occur in children as young as three to four years of age. The frequency of gallstones is more in patients with Hb-SS disease. The risk of gallstone in patient with Hb-SB thalassemia syndrome is moderately high. Thalassemia intermedia patients may develop gallstones, which occur more commonly than in thalassemia major [8,14]. Gallstones either asymptomatic discovered by routinely abdominal ultrasound or symptomatic inflammation of gallbladder (cholecystitis). Cholecystitis should be suspected in a patient present with right upper quadrant or epigastric pain, jaundice, vomiting, fever, and a leukocytosis. A positive Murphy's sign supports the diagnosis [15]. History, physical examination, and laboratory test findings are not enough to establish the diagnosis. In most cases, the diagnosis can be confirmed with an abdominal ultrasound with sensitivity and specificity exceeding 95%. [16]. Gallstones are usually mobile, single or multiple and characteristically cast an acoustic shadow. Biliary sludge appearing echogenic on ultrasound does not cast an acoustic shadow. A stone, as small as 1.5 mm, can be detected by ultrasonography [17]. In children 20% to 50% gallstones are radiopaque (18). If the diagnosis remains unclear, cholescintigraphy or magnetic resonance cholangiography can be obtained.

Treatment of gallstones depends on the age and the symptoms of the patient. Symptomatic gallstones and complicated gallstones need cholecystectomy, but there is controversy about

the treatment of asymptomatic gallstones in children [19]. Asymptomatic children or children with nonspecific symptoms need monitoring and followed up till adulthood to determine their life risks for developing symptoms of gallstones. Before surgery, blood transfusion therapy is required and aimed to get the hemoglobin up to 10m g/dl to prevent potentially life-threatening Intra-and postoperative complications [20]. Laparoscopic cholecystectomy is associated with lower rates of postoperative complications and a shorter hospital stay [21,22,23].

Aim of the study: We aim to increase the awareness about the frequency of gallstone disease with particular emphasis on its pathogenesis, genetics, risk factors and management in child patients with sickle cell disease and thalassemia treated at hereditary blood diseases center in Karbala teaching hospital for children.

METHOD

A retrospective study was performed by reviewing medical records of 433 patients (6 months to 18 years old) followed up till December the 30th 2016 in hereditary blood diseases center at Karbala teaching hospital for children in Karbala city. Iraq. Data collected for this study include type of hemolytic anemia sickle cell disease or thalassemia (we exclude patients with hereditary spherocytosis), frequency of blood transfusion, treatments of hemolytic anemia, compliance with treatment, regularity of visits to the center for follow up, and complications of hemolytic anemia (namely the gallstones). the diagnosis of cholelithiasis had been done either by routine abdominal ultrasound for each patient or by history of cholecystitis.

The SPSS for Windows software, version 20 (SPSS, Inc., Chicago, IL, USA) was used for analysis of the data. Descriptive analysis consisted of allocating continuous variables for position and dispersion and arranging categorical variables in frequency tables. The chi-square was used to determine associations or to compare proportions. A level of significance of 0.05 was adopted. The study protocol was approved by the hereditary blood diseases center, with no need for informed consent of the patients or their parents since the study was retrospective and based on records review.

RESULTS

A total of 433 patient records were studied. Totally the sample included 229 (52.88 %) males and 204 (47.12 %) females. The mean patients' age of the patient's sample was 9.80 ± 4.70

years and the age range was between 6 months and 18 years. There was no gender difference in the mean age (9.45 ± 4.762 years for males and 10.10 ±4.632 years for females). No significant difference in frequency of cholelithiasis between genders (P = 0.747). From 433 patients, fifty patients had gallstones, males 22 (44%) and females 28 (56%). According to the age groups studied, most of the cases are at the age group of 5-10 years 191 (44.1%) with 12 (24%) patients had gallstones while the age group 11-15 years108(25%) with 12(24%) gallstones and age group of 16-18 years 71(16.4 %) with 25(50 %) with gall stone these groups represented the highest numbers of patients with gallstones in the studied groups, which means the frequency of gallstones increased with age as shown in table (2).

Table (2): Frequency of gallstones among Thalassemic patients and sickle cell disease patients according to age and gender.

Age group (years)	Boys				Girls				Total			
	NO gallstones		Have gallstone		NO gallstones		Have gallstone		NO gallstones		Have gallstone	
	No	%	No	%	No	%	No	%	No	%	No	%
6m-4 y	36	9.4	1	2	26	6.7	0	0.0	62	16.1	1	2
5-10 y	95	24.8	7	14	84	22	5	10	179	46.8	12	24
11-15 y	49	12.8	5	10	47	12.3	7	14	96	25.1	12	24
16-18 y	27	7	9	18	19	5	16	32	46	12	25	50
Total	207	54	22	44	176	46	28	56	383	100	50	100

The sample included 249 (57.5%) patients with thalassemia and 184 (42.5%) patients were with sickle cell disease. The frequency of gallstones in thalassemia group 18(4.15%), and in sickle cell group 32(7.39%) so increase frequency of gallstones in patients with sickle cell disease than in patients with thalassemia table, (3).

Table (3): Frequency according to the type of hemoglobinopathy

Disease	Gall Stone				Total
	No Stone	%	Have gallstone	%	
Thalassemia	231	53.35	18	4.15	249(57.5%)
SCD	152	35.10	32	7.39	184(42.5%)
Total	383	88.45	50	11.54	433(100%)

Table (4) show that the total number of patients of sickle cell anemia (HbSS) was 118 (27.3%) from them 16 (3.7%) (HbSS) patients had gallstones, the number of Sβ disease patients were 66 (15.2%) cases, only16 (3.7%) patients had gallstones. Beta thalassemia major was included 203(46.9%) patients from them 13(3%) have gallstones while beta thalassemia intermedia were included 33(7.6%) patients, only 5(1.1%) patients had gallstones. The overall frequency of cholelithiasis was (11.5%), was higher in patients with SS and Sβ disease and with highly significant difference (p-value 0.001).

Table (4): The distribution of the subtype of disease by history of gallstone.

Disease type	GallStone		Total
	No Stone	Have gallstone	
HbSS	102(23.6%)	16(3.7%)	118(27.3%)
HbS-B	50(11.5%)	16(3.7%)	66(15.2%)
TM	190(43.9%)	13(3.0%)	203(46.9%)
TI	28(6.5%)	5(1.1%)	33(7.6%)
Alpha T	12(2.8%)	0(0%)	12(2.8%)
HbE	1(0.2%)	0(0%)	1(0.2%)
Total	383(88.5%)	50(11.5%)	433(100%)
Chi-square	16.08	p value	0.001

Table (5) shows that 16 (3.7%) patients were symptomatic at the time of diagnosis of cholelithiasis and 34 (7.8%) patients asymptomatic discovered by routinely done abdominal ultrasound, for a total 50 patients with gallstones. Symptoms included nonspecific abdominal pain, abdominal pain located in the right hypochondrium radiated to back, fatty food intolerance, nausea and emesis after meals, jaundice, and fever.

Patients with sickle cell anemia (Hb SS) who had gallstones, only 6(1.4%) were symptomatic. While patients with Hb S-B disease who had gallstones from them only 3(0.7%) patients were symptomatic. Five patients (1.1%) with thalassemia major who had stones were symptomatic and 2(0.5%) patients with thalassemia intermedia who had gallstones were symptomatic. This is highly significant with (p-value =0.004).

Table (5): Symptomatic gallstone according to subtype of hemolytic disease.

Disease type	Have gallstone			Total
	No stones	Asymptomatic by Ultrasound	Symptomatic	
HbSS	102 (23.6%)	10 (2.3%)	6 (1.4%)	118 (27.3%)
HbS-B	50 (11.5%)	13 (3%)	3 (0.7%)	66 (15.2%)
TM	190 (43.9%)	8 (1.8%)	5 (1.1%)	203 (46.9%)
TI	28 (6.5%)	3 (0.7%)	2 (0.5%)	33 (7.6%)
Others	13 (3%)	0	0	13 (3%)
Total	383 (88.5%)	34(7.8%)	16(3.7%)	433 (100%)
Chi-square	19.28	P value	0.004	

Regarding the 236 patients who had beta thalassemia, 12 patients had no blood transfusion, and all of them didn't have stone while only 6 patients infrequently transfused blood and had no stone, 21 patients who had 2 weekly transfused blood from them only 7 patients had stones and others had no stones. The number of patients who had three weekly transfused blood were 111 patients, from them 9 patients had stones and 102 had no gallstones, patients with 4 weekly blood transfusion were 78, from them just one patient had stone, while patients with 5 weekly transfused were 4 patients and all of them had no stone, one patient was 6 weekly transfused and had no stone, 8 weekly transfused were 3 patients from them only 1 patient had gallstone. The occurrence of gallstone in patients with thalassemia was increased with increased frequency of blood transfusion with (p-value 0.004) as shown in table (6).

Table (6) Association between blood transfusion and gallstone.

	Gallstone	Frequency of Blood Transfusions in weeks								Total
		No BT	Inf BT	2w	3w	4w	5w	6w	8w	
Thalassemia	No Stone	12	6	14	102	77	4	1	2	218
	Have gall stone	0	0	7	9	1	0	0	1	**18**
	Total	12	6	21	111	78	4	1	3	236
	Chi –square	28.90	P value		0.004					
	Gall Stone	**Frequency of Blood Transfusions in weeks**								**Total**
		No BT	Inf BT	2w	3w	4w	5w	12w		
Sickle cell anemia	No Stone	112	32	0	1	4	2	1		152
	Have gall stone	12	14	1	0	4	1	0		**32**
	Total	124	46	1	1	8	3	1		184
	Chi-square	22.21	P value		0.002					

In our study we have 184 patients had sickle cell disease, 124 had no blood transfusion from them 12 had stones ,46 patients had infrequently blood transfusions from them only 14 had gallstones, one patient had every two weeks transfused blood who had stone, one patient had 3 weekly transfused blood but did not have stone, while 8 patients had 4 weekly transfused blood, from them 4 patients only had stones .There were three patients had 5 weekly transfused blood only one patient and had stone, while one patient who had yearly transfused blood had no stone. The occurrence of gallstone in sickle cell patients was significantly positively associated with infrequent blood transfusion and 4 weekly transfusions with p-value 0.002.

DISCUSSION:

In current study, we tested 433 patients (sickle cell disease and thalassemia). Totally the sample included 229 (52.88 %) males and 204 (47.12 %) females. From them, 50 (11.54%) patients had cholelithiasis, males 22 (44%) and females 28 (56%). The sex ratio of cholelithiasis was equal in childhood groups, while adolescent age group (16–18 years) was a female predilection for gallstones since males who had gallstone in this age group were 9 (18%) while females were 16 (32%). Our study is consistent with the results what was reported in Saudi Arabia, in which there is a female predilection in adolescent age group [24] (see table 2). Most of the cases who had hemolytic anemia were at the age group of 5-10 years 191(44.1%) patient from them 12(24%) patients had gallstones while the highest number of patients with gallstones in the age group from 16 to18 years 71(16.4 %) patients from them 25(50 %) patients had gallstones. This may be due to increased incidence of gallstones in patients with chronic hemolytic disease with increasing age and by the time at which bile pigment saturation in the bile increases [9]. Our study was different from Noor AL Huda's study (2015) in Basra [25] most of cases with gallstones were at age group 11-16 year (66.1%). In the current study, the frequency of gallstone in patients with sickle cell disease was 7.39% while the frequency of gallstone in thalassemia syndrome was 4.15%. This percentage of gallstones in Sickle cell disease is different to what was reported by Wesdorp and Schweizer studies, which was 20% of patients [2,3] and the percentage of gallstones in thalassemia major is less than reported with Gallanello et.al [8]. The frequency of cholelithiasis in patients with sickle cell disease varies according to different studies [5]. The selection of distinct populations and different age ranges may explain some differences, but other authors have reported high rates, usually 50% [5]. The frequency of cholelithiasis in

sickle cell disease in our study was different to that reported by WALKER et al [5], who found frequency of cholelithiasis of 52.7% in SS disease; however, that study did not include patients with Hb S -B thalassemia, (table 3).

In current study, the percentage of gallstones in HbSS and HbS –B thalassemia were similar (3.7%) although the total number of patients in both diseases were different this may relate to rate of hemolysis was more in patients HbS-B thalassemia. The frequency of gallstones in patients with beta thalassemia major was 3% while in patients with thalassemia intermedia was 1.1%, this percentage were different what was reported in Italian study, which is a large study performed in 2001, gallstones were more observed in thalassemia intermedia than in Thalassemia major [9]. There are several possible explanations for this observation, including the older age of intermedia patients, the high degree of ineffective erythropoiesis, and peripheral hemolysis not suppressed by regular transfusions, (table 4).

In present study, the majority of children were asymptomatic 34 (%) at the time of diagnosis of cholelithiasis and 16 (%) patients were symptomatic. This result was less than that reported by other studies in Canada (49.5%) and Italy (64.7%) [7,9]. This may be explained partly by the present of routine screening abdominal ultrasound for patients with haemoglobinopathies. The results of this study regarding ultrasound were consistent with results of other studies. [2]. This may be explained by that most of cholelithiasis remain asymptomatic until complications develop (table 5). In our study the number of patients with beta thalassemia and had gallstone who transfused blood every 3 weeks were 9 patients which represented the highest one among others, due to gallstone formation related to severity of hemolytic disease and intensity of the episodes of hemolysis [5], as multiple transfusions are a recognized risk factors for gallstone formation in thalassemia due to those patients exposed to recurrent attacks of hemolysis from more frequent blood transfusions [7] (table 6).

We found that the number of patients with SCD who had gallstone and infrequent transfused blood were 14 patients which represented the high number among others because those patients complaint from hemolytic crisis as part of their disease and they suffering from occlusive crisis so lead to decrease blood supply and stasis of gallbladder contents which lead to stone formation , and patients who transfused blood every 4 week were 8 from them 4 patients had gallstone also represent high number due to recurrent attacks of hemolysis from more frequent blood transfusions(table 6)

CONCLUSION

1) The frequency of cholelithiasis in study population with SCD and thalassemia at hereditary blood diseases center at Karbala teaching hospital of children was 11.54%.

2) The majority of patients remained asymptomatic 34 (7.8%).

3) Patients with HbSS or Hb S-B disease were at a higher risk for the development of gallstones both of them same results (3.7%) compared to patients with beta thalassemia major and thalassemia intermedia (3%, 1.1%) respectively.

4) Most of patients were diagnosed between the ages 16 years to 18 years and were 25(50%) patients

5) Patients with SCD who had infrequent blood transfusion and who transfused blood 4 weekly had more chance to develop gallstones than other. In patients with thalassemia the frequency of gallstones more in patients who transfused blood transfusion every 3 weeks than other.

RECOMMENDATIONS

1) Usefulness of abdominal ultrasound screening program in pediatric patients with hemolytic disease especially when they presented with suggestive symptoms, with special attention to age group between 16 years to 18 years.

2) Further studies should be done to identify other risk factors for the formation of gallstones in hemolytic diseases [like multiple transfusions in beta thalassemia patients and genetic factors (like UGTIA)].

3) Cholecystectomy must be done to symptomatic patients and follow up of symptomatic patients to prevent complications like obstructive jaundice and cholangitis.

REFERENCES

1. Klar A, Branski D, Akerman Y. Sludge ball, pseudolithiasis, cholelithiasis and choledocholithiasis from intrauterine life to 2 years: 13 years follow up. J Pediatr Gastroenterol Nutr 2005; 40: 477-480.
2. Wesdorp I, Bosman D, de Graaff A, Aronson D, vander Blij F, Taminiau J. Clinical presentations and predisposing factors of cholelithiasis and sludge in children. J Pediatr Gastroenterol Nutr 2000; 31: 411-417.
3.Schweizer P, Lenz MP, Kirschner HJ. Pathogenesis and symptomatology of cholelithiasis in childhood. Dig Surg 2000; 17: 459-467.

4. Deepak J, Agarwal P, Bagdi RK, Balagopal S. Pediatric cholelithiasis and laparoscopic management: A review of twenty-two cases. J Mini Assess Surg. 2009;5(4):93-6.
5. Walker TM, Hambleton IR, Serjeant GR. Gallstones in sickle cell disease: observations from the Jamaican cohort study. J Pediatr 2000; 136:80-5
6. Lotfi M, Keramati P, Assadsangabi R, Nabavizadeh SA, Karimi M. Ultrasonographic assessment of the prevalence of cholelithiasis and biliary sludge in beta-thalassemia patients in Iran. Med SciMonit 2009; 15; CR398-402.
7. Origa R, Galanello R, Perseu L, TavazziD,Cappellini MD, Terenzani L, et al. Cholelithiasis in thalassemia major. Eur J Hematol 2008; 82: 22-25.
8. Galanello R, Piras S, Barella S, Leoni GB, Cipollina MD, Perseu L, et al. Cholelithiasis and Gilbert's syndrome in homozygour beta-thalassemia. Br J Haematol 2001; 115: 926-928.
9. Kar R, Rao S, Srinivas UM, Mishra P, Pati HP. Clinico-hematological profile of hereditary spherocytosis: experience from a tertiary care center in North India. Hematology 2009; 14: 164-167.
10. Herzog D, Bouchard G. High rate of complicated idiopathic gallstone disease in pediatric patients of a North American tertiary care center. World J Gastroenterol. 2008;14(10):1544-1548.
11. Grünhage F, Lammert F. Gallstone disease. Pathogenesis of gallstones: A genetic perspective. Best Pract Res Clin Gastroenterol 2006; 20: 997-1015
12. Tüzmen S, Tadmouri GO, Ozer A, Baig SM, Ozçelik H, Başaran S, Başak AN. Prenatal diagnosis of beta-thalassaemia and sickle cell anaemia in Turkey. Prenat Diagn 2000; 16: 252-258.
13.Adam S, Jonassaint J, Kruger H, et al. Surgical and obstetric outcomes in adults with sickle cell disease. Am J Med 2008; 121:916.
14. Taher AT, Musallam KM, Karimi M, et al. Overview on practices in thalassemia intermedia management aiming for lowering complication rates across a region of endemicity: the optimal care study. Blood 2010; 115:1886.
15.Trowbridge RL, Rutkowski NK, Shojania KG. Does this patient have acute cholecystitis? JAMA 2003; 289:80.
16. Millar AJW, Prasad H. Gallstone disease in children. Indian Pediatric. 2010;47(11):945-5312.
17. Poddar U, Thapa BR, Bhasin DK, Prasad A, Nagi B, Singh K. Endoscopic retrograde cholangiopancreatography in the management of pancreatobiliary disorders in children. J GastroenterolHepatol 2001; 16: 927-931.
18. Millar AJW. Surgical disorders of the l.Kiewiet JJ, Leeuwenburgh MM, Bipat S, et al. A systematic review and meta-analysis of diagnostic performance of imaging in acute cholecystitis. Radiology 2012; 264:708..
19. National Institutes of Health. The management of sickle cell disease 2002, 111-112. Accessed March 15, 2017.
Available at http://www.nhlbi.nih.gov/health/prof/blood/sickle/index.ht.
20. Vichinsky EP, Haberkern CM, Neumayr L, Earles AN, Black D, Koshy MM, et al. A comparison of conservative and aggressive transfusion regimens in the perioperative management of sickle cell disease. Preoperative transfusion in sickle cell disease study group. N Engl J Med 1995; 333:206-14.
21. Chan S, Currie J, Malik AI, Mahomed AA. Pediatric cholecystectomy: shifting goalposts in the laparoscopic era. SurgEndosc 2008; 22: 1392-1395.
22. Tannuri CA, Gonçalves AJ, Velhote M, Gonlçalves ME, Tannuri U. Management of gallstone disease in children: a new protocol based on the experience of a single center. J Pedia Surg. 2012; 47:2033-8.
23.Vichinsky EP, Haberkern CM, Neumayr L, Earles AN, Black D, Koshy MM, et al. A comparison of conservative and aggressive transfusion regimens in the perioperative management of sickle cell disease. Preoperative transfusion in sickle cell disease study group. N Engl J Med 1995; 333:206-1466.
24. Al-Mulhim AS, Abdulatif MM, Ali AM. Laparoscopic cholecystectomy in children with sickle cell disease. Saudi J Gastroenterol 2006; 12: 130-134.
25. Al-Huda, Noor & Al-Asadi, Jasim & Alhasani, Abbas. THE MEDICAL JOURNAL OF BASRAH UNIVERSITY. Cholelithiasis in children 16 years and below in Basrah: Epidemiological and Clinical study. The Medical Journal of Basrah University. 2015;33. 85-92. A.