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Cholelithiasis in Patients with Sickle Cell Disease and Sickle/Beta-Thalassemia in Akre City, Kurdistan Region of Iraq

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Abstract:

Background and objectives: Sickle cell disease and sickle β-thalassemia are hemolytic diseases characterized by chronic destruction of the abnormal red cells with consequent hyperbilirubinemia. The present study aimed to determine the association of gallstone with Sickle cell disease and sickle β-thal patients compared to the control healthy group and to determine gallstone's association with several demographic and laboratory parameters among the patients themselves.

Methods: Patients visiting the Akre thalassemia center for routine checks have been recruited for this study (patients=73; control=36). Blood samples were collected for biochemical and haematological analyses. All participants were subjected to abdominal ultrasonography for confirmation of gallstones. These parameters were compared with patients' subtype traits. Additional information regarding blood transfusion, hospital admission, and the use of chelating agents was also allocated.

Results: The prevalence of gallstone was significantly higher in patients (12%) than in the control (3%) group ($P<0.05$), with similar prevalence in both trait; homozygous haemoglobin S (14%) and compound heterozygous of hemoglobin S and β-thalassemia (11%), together with significant differences in the biochemical and haematological parameters. The haemoglobin concentration was significantly ($P<0.05$) reduced in patients (8.5±0.86) versus control (12±1.6). Reticulocytes, lactate dehydrogenase enzyme, and bilirubin were significantly ($P<0.05$) elevated in patients compared to the control. No differences existed between control versus patients regarding hospital admission, blood transfusion, and the use of medication including chelating agent or hydroxyurea.

Conclusion: Sickle-diseased and sickle beta-thalassemia patients have a higher risk of developing gallstones than the general population alongside interruption of metabolic and biochemical parameters with co-association with sub-traits of type of haemoglobin.

Keywords: Gallstones, Hb, Sickle cell Anaemia, Thalassemia.

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Introduction:

Sickle cell disease (SCD) and Sickle/β-thal are common chronic hemolytic diseases in Africa, the Mediterranean area and the Middle East. A chromosome 11 mutation that causes valine to substitute glutamic acid at position 6 of the N-terminus of the globin

Sickle cell disease 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 mostly vasooclussive phenomenon.[6,7] Chronic haemolysis leads to bilirubinate cholelithiasis, which can be either asymptomatic or symptomatic, ranging from cholecystitis, choledocholithiasis, and cholangitis, to gallstone pancreatitis[8].

Chronic hemolysis leads to the continuous production of bilirubin, which is conjugated in the liver and excreted in the faeces as urobilinogen; in large quantities, it may form calcium bilirubin gallstones. Cholelithiasis can be detected even in under five-year-old children, but it is more common in adolescents and adults with sickle cell anaemia. Because of the potential complications and severity of this condition, early diagnosis is of paramount importance. Diagnostic imaging methods play a major role when managing patients with sickle cell anaemia, particularly when evaluating complications. Early diagnosis of SCD and appropriate treatment increase survival and improve the quality of life of patients with sickle cell anemia.[9–12]

No exclusion criteria mentioned like someone with other risk factors for GS disease etc. When a patient with SCD has recurring abdominal pain, cholelithiasis should be taken into consideration as a possible diagnosis.[13-chain is the root cause of sickle cell anaemia. Because of the sickle-shaped red blood cells that are precipitated by deoxygenation events, like hypoxia, dehydration, acidosis and infection, HbS becomes highly insoluble and assembles into long polymers.[1-4] Carriers make up around 2% of the general population to 6-12% of people of African descent.[5]

Cholelithiasis has been found to be more common in SCD patients as they get older, affecting up to 15% of children with the condition under the age of 10 and 50% of those over the age of 30.[15,16] The present study aimed to investigate the prevalence rate of gallstones among SCD patients compared to the control group in the Akre thalassemia centre. The study also aimed at identifying the differences in haematological and biochemical profiles in these patients with SCD compared to control groups.

Patients and methods

In this prospective observational study, 73 patients, 29 homozygous SCD (HbS/S) and 44 compounds heterozygous for HbS and β-thalassemia (HbS/β-thal) were studied together with 34 normal subjects served as a control group. The exclusion criteria include severely ill patients. The patients were recruited at Akre thalassemia Centre while the normal subjects were enrolled from Gulan hospital. The control group was visitors or employees in Gulan Hospital. The participants were informed about the study; written consent has been obtained from the patients and/or their guardians.

Demographic and clinical data including age, gender, age at diagnosis, age of first blood transfusion and frequency of blood transfusion, and the annual rate of hospital admissions were recorded. Venous blood samples were collected for haematological and biochemical laboratory analysis.

Complete blood count together with peripheral blood film and reticulocyte count was done. Serum was collected and sent for determination of blood urea, creatinine, total bilirubin (TSB) aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH) and ferritin levels. All the participants were sent for ultrasonography to confirm or exclude the presence of gallstones.

GraphPad Prism was used for data analysis. Data were expressed as mean and standard deviation. For non-parametric data, Kruskal-Wallis and Chi-square test and for parametric data, the student t-test was used for evaluating statistical differences among different subgroups. A *p*-value < 0.05 was considered significant, and this study was approved by the Kurdistan Higher Council of Medical Specialties KHCMS committee.

Results

The demographic characteristics of the enrolled patients and normal control subjects are illustrated in Table (1). The mean age of the patients was 17.4 (±9.9) years, ranging between 2-46 years. The prevalence of gallstones in the patients was significantly higher (P=0.01) compared to the control group (12% vs. 3%, respectively). The laboratory parameters of the patients and normal subjects are illustrated in Table (2). The serum bilirubin and LDH levels were significantly higher in the patient's group compared to the normal control group (P<0.05).

Out of 73 patients, nine had gallstones. Table (3) compares the characteristics of patients with gallstones (GS+ve) with those without gallstones (GS-ve). The mean age of GS+ve patients was significantly higher than that of GS-ve patients (23.1± 8.9 vs. 16.5±9.8 years; P=0.001). Female patients constituted 89% of the GS+ve group. The prevalence of gallstones among homozygous (HbS/S) patients was higher than in the compound heterozygous (HbS/β-thal) patients. The age at first blood transfusion was significantly lower in the GS+ve group (Table 3).

Table (4) shows illustrates the differences in the frequency of blood transfusion, hospital admission, and the use of hydroxyurea and chelation agents in the GS-ve and GS+ve groups. No differences were found between the GS-ve and GS+ve groups of patients. In this study, two subtypes of sickle cell patients were included, HbS/S and HbS/β-thal. The mean age of HbS/S patients was significantly lower than the HbS/β-thal patients. The rate of gallstone formation did not differ between the two subtypes (Table 5).

Table (1): Demographic characteristics of the studied groups.

Characteristics		Controls (n=34)	Cases (n=73)	p value
Age (Year)	Mean±SD	16.7±9.8	17.4±9.9	0.1
	Range	1-44	2-46	
Gender (M/F)	No.	13/21	26/47	0.8
	%	38/62	36/64	
Gall stone	+ve	1(3%)	9(12%)*	0.01
	-ve	33(97%)	64(88%)	

Table (2): Laboratory parameters of the control and patient groups.

Parameters	Controls Mean±SD	Cases Mean±SD	p value
Hb	12±1.6*	8.5±0.86	0.01
WBC	12±1.2	11.3±3.8	0.4
MCV	73±6	80±7.6	0.1
Retic	1.3±0.4	10.8±6.3*	0.001
MCH	24.3±3.8	24.8±7.1	0.1
MCHC	33.4±3.1	33.4±4.3	0.3
TSB	1±0.26	3±1.0*	0.001
direct	0.9±0.1*	0.5±0.2	0.01
indirect	0.9±0.25	2.8±0.28*	0.001
LDH	315±46	600±217*	0.002

Table (3): Demographic characteristics of gallstone negative and gallstone positive patients groups.

Characteristics		GS-ve (n=64)	GS+ve (n=9)	p value
Age (Year)	mean±SD	16.5±9.8	23.1±8.9*	0.001
	Range	3-46	7-34	
Gender (M/F)	No.	26/38*	1/8	0.04
	%	41/59	11/89	
Age of Diagnosis (Years)	mean±SD	5.4±5.5	6±7.4*	0.06
	Range	1-29	1-24	
Type of Sickle cell diseases	HbSS(n=29)	25(86%)*	4(14%)	0.07
	HbS/B(n=44)	39(89%)	5(11%)	
Age of first blood transfusion (Years)	mean±SD	5.4±5.4*	4.9±8.1	0.01
	Range	1-29	1-24	

Table (4): Frequency of blood transfusion, hospital admission, and the use of hydroxyurea and chelation agents in gallstone negative and gallstone positive groups.

	Frequency n(%)	GS-ve (n=64)	GS+ve (n=9)	p value
Blood Transfusion	No Transfusion	25 (39%)	6 (67%)	0.1
	Occasional transfusion	28 (44%)	1 (11%)	
	Few transfusion	11 (17%)	2 (22%)	

	Regular transfusion	0 (0%)	0 (0%)	
Admission to Hospital	No Admission	40 (62%)	5 (55%)	0.3
	Occasional Admission	15 (23%)	1 (11%)	
	Few Admission	9(15%)	3 (34%)	
Hydroxy urea	Yes	6 (9%)	2 (22%)	0.25
	No	58 (91%)	7 (78%)	
Chelating agents	Yes	15 (23%)	2 (22%)	0.9
	No	49 (77%)	7 (78%)	
No transfusion: has never been transfused Occasional transfusion: has been transfused once or less than once per year. Few transfusions: has been transfused more than once per year (but not regular). Regular transfusion: has been transfused once or more than once per month. No admission: has never been admitted, Occasional admission: has been admitted once or less than once per year. Few admissions: has been admitted more than once per year (but not regular).				

Table (5): Demographic characteristics in HbS/S versus HbS/β-thal groups.

Characteristics		HbS/S (n=29)	HbS/β-thal (n=44)	p value
Age (Year)	mean±SD	5.7±6.8	18±10.4*	0.001
	Range	1-29	4-46	
Gender (M/F)	No.	11/18	16/28	0.09
	%	38/62	36/64	
Gall stone	+ve	4(45%)	5(55%)	0.8
	-ve	25(39%)	39(61%)	
Age of Diagnosis (Years)	mean±SD	7.6±8.1*	5.3±5.2	0.01
	Range	1-29	1-24	
Age of first blood transfusion (Years)	mean±SD	5.6±6.8	5.1±4.9	0.8
	Range	1-29	1-24	

Discussion

Gallstones develop in non-SCD people as a result of intricate interactions between hereditary, environmental, metabolic, and other risk factors. The feminine gender, age of over 40, being overweight, becoming pregnant, eating a meal laden with fats and low in fibre, using oral contraceptives, hormone therapy, or experiencing liver disease are all potential risk factors for gallstone formation.[17] Gallstones can occur more frequently in SCD patients.[18-24] Due to the variations in epidemiological methods, many lifestyle factors are still ambiguous.[23]
The present study has focused on a detailed review of characteristic features of the patients with SCD, whether HbS/S or HbS/β-thal, in correlation to the presence or absence of gallstones. The present study has

confirmed that gallstones are more prevalent among patients with SCD (12%) compared to the healthy subject group (3%). Many studies have reported variable rates of gallstone formation among sickle patients.

According to the research, choledocholithiasis occurs in 4.4% to 18.8% of instances and is present in 9% of female and 6% of male instances of cholelithiasis in the general public. In our study, cholelithiasis is more prevalent (9%) in sickle patients compared to normal but still, gender-matched in the previous study.[24] In the present study, the rate of cholelithiasis is 12% in sickle patients compared to 3% in the control group. In contrast, a study conducted by Al-Salem et al. observed a rate of cholelithiasis of 35.5%[25]. Alternatively, the prevalence in two studies, conducted by Walker (23.8%) [20] and the other study by Alhawsawi et al. (27.5%)[26]. Akinyanju observed a low prevalence of cholelithiasis of 6% in individuals under the age of 15.[27] In 226 children between the ages of 5 and 13 who underwent abdominal ultrasound testing, Webb et al. found a 13% frequency of cholelithiasis.[28] In another study conducted by Attalla, the frequency of cholelithiasis was found to be 11.5% overall and to rise with age. [29]

When adolescents and adults were taken into account, a greater rate has indeed been recorded in other researches.[29,30] Research conducted by Bond et al. found that 95 individuals aged 10 to 65 who underwent ultrasonography examinations for cholelithiasis had incidence rates of 55% in HbS/S and HbS/C groups.[16]

Age is a significant risk factor for gallstones among SCD individuals. The frequency of such a consequence dramatically rises in patient populations who are 5 years old or more. Several researchers have reported this pattern.[31-34] According to Alhawsawi et al., there was a significant correlation between the prevalence of cholelithiasis and the age of patients, with percentages ranging from 11.5% in patients under the age of six to 24.4% in patients between six and twelve, and up to 40.8% in patients over twelve years[26]. Similar findings were reported in a research by Attalla, who found that 0.7% of patients under the age of five had gallstones, compared to 13% of patients over the age of 55.[29]

Gender differences also have a role in increasing the risk for the development of cholelithiasis. Similar to our results, some other studies revealed a higher incidence of gallstones in females. [35-37]

Our study has found that the rate of gallstone formation was higher among patients who started early blood transfusion compared to those who started transfusion later. However, the frequency of blood transfusion did not have any correlation to the rate of gallstone formation. Several studies have reported that blood transfusion magnitude increases the susceptibility of gallstone formation. Patients with more frequent blood transfusion have a higher rate of gallstones than those with no blood transfusion[32]; however, several other reports have confirmed that the frequency of blood transfusion has no relation with the development of gall stones.[38-40]

There was no significant variation between sickle patients with and without gallstones regarding hospital admission. Similarly, the use of hydroxyurea and iron chelation by sickle patients did not reduce the risk and incidence of gallstone formation. Many studies have reported that hydroxyurea and iron chelating agents in SCD do not minimize the pathology of sickling including their effects on the development of gall stones.[41,42] The subtypes of the disease traits have shown differences in the measured parameters.

Homozygous SCD patients were diagnosed later and received blood later than the compound heterozygous sickle patients. However, the rate of gallstone formation did not differ in the two subgroups.

Conclusion

We conclude that sickle patients in Akre are prone to develop gallstones with haematological and biochemical parameters derangement in association with the presence of gallstones.

Conflict of interest:

The authors declare no conflict of interest concerned in the present study.

References

1. Herrick JB. Peculiar elongated and sickle-shaped red blood corpuscles in a case of severe anaemia. Yale J Biol Med. 2001; 74(3): 179–84
2. Kutlar A. Sickle cell disease: a multigenic perspective of a single gene disorder. Hematol. 2005; 10(sup1):92-9.
3. Kan YM, Dozy AM. Polymorphism of DNA sequence adjacent to human-globin structural gene: relationship to sickle mutation. Proc Natl Acad Sci U S A. 1978; 75(11):5631–5.
4. Antonarakis SE, Kazazian HH Jr, Orkin SH. DNA polymorphism and molecular pathology of the human globingene clusters. Hum Genet. 1985; 69(1):1–14.
5. Copelan A, Kapoor BS. Choledocholithiasis: diagnosis and management. Tech Vasc Interv Radiol. 2015; 18(4):244-55.
6. Manwani D, Frenette PS. Vaso-occlusion in sickle cell disease: pathophysiology and novel targeted therapies. Blood, the Journal of the American Society of Hematology. 2013 Dec 5; 122(24):3892-8.
7. Ballas SK, Lieff S, Benjamin LJ, et al. Definitions of the phenotypic manifestations of sickle cell disease. Am J Hematol. 2010; 85(1):6-13.
8. Wethers DL. Sickle cell disease in childhood: Part I. Laboratory diagnosis, pathophysiology and health maintenance. American Family Physician. 2000; 62(5):1013-20.
9. Gumiero AP, Bellomo-Brandão MA, Costa-Pinto EA. Gallstonesin children with sickle cell disease followed up at a Brazilian hematology center. Arq Gastroenterol. 2008; 45(4):313–8.
10. Ebert EC, Nagar M, Hagspiel KD. Gastrointestinal and hepatic complications of sickle cell disease. Clin. Gastroenterol. Hepatol. 2010; 8(6):483-9.
11. Dan D, Seetahal S, Harnanan D, Singh Y, Hariharan S, Naraynsingh V. Laparoscopic cholecystectomy in sickle cell disease patients: does operating time matter? Int J Surg.2009; 7(1):70–3.
12. Abdullah UY, Jassim HM, Baig AA, et al. Gallstones in patients with inherited hemolytic diseases. Int J Pharm Pharm Sci 2015; 7:9–15.
13. Okuonghae HO, Szlachetka R, Sagay AS. Cholelithiasis in children with homozygous sickle cell anaemia in northern Nigeria. Trop. Geogr. Med. 1993; 45(1):44-5.
14. Serjeant GR. Mortality from sickle cell disease in Africa. BMJ. 2005; 330(7489):432-3.
15. Hendricks-Ferguson V, Nelson MA. Treatment of cholelithiasis in

children with sickle cell disease. AORN J. 2003; 77(6):1169-82.
16. Currò G, Meo A, Ippolito D, Pusiol A, Cucinotta E. Asymptomatic cholelithiasis in children with sickle cell disease: early or delayed cholecystectomy? Ann. Surg. 2007; 245(1):126.
17. Kratzer W, Walcher T, Arnold F, et al. Gallstone prevalence and risk factors for gallstone disease in an urban population of children and adolescents. Zeitschrift für Gastroenterologie. 2010; 48(06):683-7.
18. Al-Qurashi MM, El-Mouzan MI, Al-Herbish AS, Al-Salloum AA, Al-Omar AA. The prevalence of sickle cell disease in Saudi children and adolescents. A community-based survey. Saudi Med. J. 2008; 29(10):1480-3.
19. Al-Salem AH, Qaisruddin S. The significance of biliary sludge in children with sickle cell disease. Pediatr Surg Int 1998; 13:14-6.
20. Walker TM, Hambleton IR, Serjeant GR. Gallstones in sickle cell disease: Observations from The Jamaican Cohort study. J Pediatr 2000; 136:80-5.
21. Agholor CA, Akhigbe AO, Atalabi OM. The prevalence of cholelithiasis in Nigerians with sickle cell disease as diagonosed by ultrsound. Br J Med Med Res 2014; 4(15): 2866-73.
22. Parez N, Quinet B, Batut S, et al. Cholelithiasis in children with sickle cell disease: experience of a French pediatric hospital. Archives de Pediatrie. 2001; 8(10):1045-9.
23. Bencini L, Tommasi C, Manetti R, Farsi M. Modern approach to cholecysto-choledocholithiasis. *World J. Gastrointest. Endosc.* 2014; 6(2):32.
24. Yoo EH, Lee SY. The prevalence and risk factors for gallstone disease. Clin. Chem. Lab. Med. 2009; 47(7):795-807.
25. Al-Salem AH, Qaisaruddin S, Al-Dabbous I, et al. Cholelithiasis in children with sickle cell disease. Pediatr Surg Int 1996; 11:471-3.
26. Alhawsawi ZM, Alshenqeti AM, Alqarafi AM, Alhussayen LK, Turkistani WA. Cholelithiasis in patients with paediatric sickle cell anaemia in a Saudi hospital. J Taibah Univ Med Sci 2019; 14:187-92.
27. Akinyanju O, Ladapo F. Cholelithiasis and biliary tract disease in sickle-cell disease in Nigerians. Postgrad. Med. J.1979; 55(644):400-2.
28. Webb DK, Darby JS, Dunn DT, Terry SI, Serjeant GR. Gall stones in Jamaican children with homozygous sickle cell disease. Arch Dis Child 1989; 64:693-6.
29. Attalla BI. Abdominal sonographic findings in Sudanese children with sickle cell anaemia. J Diagn Med Sonography 2010; 26:276-80.
30. Taylor C, Carter F, Poulose J, Rolle S, Babu S, Crichlow S. Clinical presentation of acute chest syndrome in sickle cell disease. Postgrad. Med. J.2004; 80(944):346-9.
31. Balci A, Karazincir S, Sangün Ö, et al. Prevalence of abdominal ultrasonographic abnormalities in patients with sickle cell disease. *Diagn Interv Radiol*. 2008; 14(3):133.
32. Shahramian I, Behzadmehr R, Afshari M, Allahdadi A, Delaramnasab M, Bazi A.

Cholelithiasis in Thalassemia major patients: A report from the South-East of Iran. Int J Hematol Oncol Stem Cell Res. 2018; 12(2):117.
33. Martins RA, Soares RS, De Vito FB, et al. Cholelithiasis and its complications in sickle cell disease in a university hospital. Rev Bras Hematol Hemoter. 2017; 39(1):28–31.
34. Papadaki MG, Kattamis AC, Papadaki IG, et al. Abdominal ultrasonographic findings in patients with sickle-cell anaemia and thalassaemia intermedia. Pediatr. Radiol. 2003; 33(8):515-21.
35. Suell MN, Horton TM, Dishop MK, Mahoney Jr DH, Olutoye OO, Mueller BU. Outcomes for children with gallbladder abnormalities and sickle cell disease. J. Pediatr. 2004; 145(5):617-21.
36. Kosiyo P, Otieno W, Gitaka J, Munde EO, Ouma C. Haematological abnormalities in children with sickle cell disease and non-severe malaria infection in western Kenya. BMC Infect. Dis. 2021; 21(1):1-1.
37. Al-Jafar HA, Hayati HA, AlKhawari H, Al Thallab FS, Al-Ali M. The prevalence and severity of gallstones in sickle cell disease in Kuwait. Open J. Epidemiol. 2020; 10(4):346-54.
38. Origa R, Galanello R, Perseu L, et al. Cholelithiasis in thalassemia major. Eur. J. Haematol. 2009; 82(1):22-5.
39. Tankanitlert J, Morales NP, Fucharoen P, et al. Association between promoter and coding region mutations of UDP-glucuronosyltransferase 1A1 and beta-thalassemia/Hb E with cholelithiasis. Eur J Haematol. 2008; 80(4):351-5.
40. AlFadhli S, Al-Jafer H, Hadi M, et al. The effect of UGT1A1 promoter polymorphism in the development of hyperbilirubinemia and cholelithiasis in hemoglobinopathy patients. PLoS One. 2013; 8(10): e77681
41. Agrawal RK, Patel RK, Nainiwal L, Trivedi B. Hydroxyurea in sickle cell disease: drug review. Indian J. Hematol. Blood Transfus. 2014; 30(2):91-6.
42. Ware RE. How I use hydroxyurea to treat young patients with sickle cell anemia. Blood, Am. J. Hematol. 2010; 115(26):5300-11.