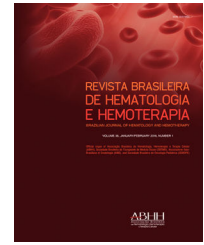




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Original article

**Cholelithiasis and its complications in sickle cell disease in a university hospital**



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ABSTRACT

**Introduction:** The clinical manifestations of sickle cell disease are related to the polymerization of hemoglobin S. The chronic hemolysis caused by this condition often causes the formation of gallstones that can migrate and block the common bile duct leading to acute abdomen.

**Objective:** This study aimed to evaluate the profile of patients with sickle cell disease and cholelithiasis.

**Methods:** Patients with sickle cell disease were separated into groups according to the presence or absence of cholelithiasis. Socioepidemiological and clinical characteristics, such as gender, age, use of hydroxyurea and the presence of other hemoglobinopathies were researched in the medical records of patients.

**Results:** A hundred and seven patients with sickle cell anemia were treated at the institution. Of these, 27 (25.2%) had cholelithiasis. The presence of cholelithiasis was higher in the 11–29 age group than in younger than 11 years and over 29 years. No association was found for the presence of cholelithiasis with gender, use of hydroxyurea or type of hemoglobinopathy (hemoglobin SS, hemoglobin SC or sickle beta-thalassemia). Sixteen of the patients had to be submitted to cholecystectomy with 14 of the surgeries being performed by laparoscopy. Complications were observed in three patients and one patient died for reasons unrelated to the surgery.

**Conclusion:** A quarter of patients with sickle cell disease had gallstones, more commonly in the 11- to 29-year age range. Patients should be monitored from childhood to prevent cholelithiasis with preoperative, intra-operative and postoperative care being crucial to reduce the risk of complications in these patients.

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## Introduction

Sickle cell anemia is caused by a mutation in chromosome 11 that results in the replacement of glutamic acid with valine at position 6 of the N-terminus of the globin chain. The clinical manifestations of sickle cell disease are directly associated with conformation changes in hemoglobin (Hb). In deoxygenation events (hypoxia, dehydration, stress, low temperature, acidosis, infection), because of the sickle shape of the red blood cells (hence the name), Hb S becomes relatively insoluble and aggregates into long polymers.<sup>1-4</sup>

Approximately 3500 people are estimated to be born with sickle cell disease in Brazil every year, with an estimated 25,000-30,000 people having sickle cell anemia and at least 7,200,000 people carrying the sickle cell trait. The prevalence of carriers of sickle cell trait ranges from 2% in the general population to 6-12% in African descents.<sup>5</sup>

As the cells are abnormal, they have a shorter life than normal red blood cells. Chronic hemolysis leads to continuous production of bilirubin, which is conjugated in the liver and excreted in the feces as urobilinogen; in large quantities, it may form calcium bilirubinate gallstones. Cholelithiasis can be detected even in under five-year-old children, but it is more common in adolescents and adults with sickle cell anemia. Gallstone migration can block the common bile duct leading to acute abdomen. 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 anemia, particularly when evaluating complications. Early diagnosis and appropriate treatment increase survival and improve the quality of life of patients with sickle cell anemia.<sup>6-8</sup>

This study aimed to evaluate the profile of patients with sickle cell disease and cholelithiasis, the incidence of cases at the Fundação Hemominas in Uberaba (FHU) and the Hospital das Clínicas of Universidade Federal do Triângulo Mineiro (HC/UFTM) and the importance of early diagnosis for proper treatment.

## Methods

This is a retrospective descriptive study. A computerized database was used to analyze patients with sickle cell disease referred to the FHU and to the HC/UFTM from 1995 to 2014. Diagnosis of cholelithiasis was performed by abdominal ultrasound and two groups of patients were formed: with and without cholelithiasis. The following absolute and relative data regarding some socioepidemiological characteristics were collected: gender (male, female), age (younger than 10 years, between 10 and 29 years, and older than 29 years), type of hemoglobinopathy (Hb SS, Hb S/beta-thal, and Hb SC) and use of hydroxyurea. The classification of the hemoglobinopathy was performed by electrophoresis on cellulose acetate at alkaline pH.

The data was first submitted to an analysis of absolute frequencies and percentages, and were organized in tables. An Odds Ratio was calculated in order to study the association between the characteristics of interest. The level of significance for all tests was set at 5%, and the data were analyzed

using the statistical software InStat 3.0 (GraphPad Software Inc, La Jolla, CA, USA).

## Results

One hundred and seven patients with sickle cell disease were followed up in the Hematology/Hemotherapy Services of the HC/UFTM and FHU during the study period. Twenty seven (25.2%) of the patients had cholelithiasis.

A mean prevalence of 25.2% was observed for the diagnoses of cholelithiasis. Of the 27 cases, 17 were investigated because of clinical symptoms, whereas ten patients were diagnosed during routine screening.

The percentage of cholelithiasis was higher in the 11-29 age group than in the age groups younger than 11 years and over 29 years ( $p$ -value = 0.018); the vast majority of the patients were diagnosed before 30 years of age, with an average age at diagnosis of 16 years. Only four cases were diagnosed after 30 years old.

There were no significant differences in frequency of cholelithiasis between males and females (29.3% and 22.0%, respectively;  $p$ -value = 0.400), between the group that used hydroxyurea and the group that did not use this medicine (32.4% and 21.4%, respectively;  $p$ -value = 0.215) and between Hb SS, Hb S/beta-thal and Hb SC groups (28.4%, 25.0% and 7.1%, respectively,  $p$ -value > 0.05; [Table 1](#)). All Hb S/beta-thal patients were Hb S/beta<sup>0</sup>.

Sixteen patients (59%) underwent cholecystectomy, fourteen patients underwent laparoscopic surgery, and two cases underwent open surgery. Although laparoscopy had been started in one of these two cases, laparotomy with emergency splenectomy was performed with satisfactory results due to excessive bleeding. Laparoscopy equipment was not available at the time of the procedure of the other patient.

Three cases (18.7%) of the 16 operated patients developed postoperative complications. One case required emergency splenectomy due to bleeding, and another patient was a cholelithiasis carrier submitted to endoscopic retrograde cholangiopancreatography progressing to acute pancreatitis. The patient was treated with a good response and then videolaparoscopic cholecystectomy was performed without major complications. One patient progressed to death 30 days after surgery due to splenic sequestration.

## Discussion

Cholelithiasis was significantly more prevalent in the 11-29 age group. These results suggest that this group should be made aware of the risk of gallstones, related symptoms, possible complications, and the need for regular follow-ups with routine preventive screenings. However, it should be highlighted that despite having found a higher occurrence in this group, the screening of lithiasis secondary to chronic hemolysis should be provided to all patients with sickle cell disease regardless of their profile in accordance with the Brazilian Handbook of Acute Events in Sickle Cell Disease.<sup>9</sup>

A study conducted at the Universidade de Campinas found a higher incidence of cholelithiasis in patients with sickle cell disease (45%), as well as predominance of younger patients

**Table 1 – Distribution of patients with and without cholelithiasis regarding gender, age, use of hydroxyurea, and type of hemoglobinopathy in the Hematology and Hemotherapy Service of the Universidade Federal do Triângulo Mineiro (UFTM).**

Epidemiological characteristic	Patients							
	Total (107)	Without cholelithiasis (80)		Cholelithiasis (27)		OR	95% CI	p-Value
n	n	%	n	%				
Female	59	46	77.97	13	22.03	–	–	–
Male	48	34	70.83	14	29.17	0.69	(0.3–1.6)	0.400
<10 years	23	22	95.65	1	4.35	–	–	–
11–29 years	62	40	64.52	22	35.48	12.10	(1.5–95.9)	0.018 <sup>a</sup>
≥30 years	22	18	81.82	4	18.18	4.90	(0.5–47.7)	0.172
Used hydroxyurea	37	25	67.56	12	32.43	–	–	–
Did not use hydroxyurea	70	55	78.57	15	21.42	1.76	(0.7–4.3)	0.215
Hb SS	81	58	71.60	23	28.40	2.4	(0.5–11.5)	0.280
Hb S/beta thalassemia	12	9	75.00	3	25.00	2.0	(0.3–14.6)	0.492
Hb SC	14	13	92.86	1	7.14	–	–	–

OR: Odds Ratio; 95% CI: 95% confidence interval.

<sup>a</sup> Significant difference.

(<15 years). Sixty-three percent were Hb SS, with a statistically significant predominance. Nonetheless, this study was performed only in children and adolescents and this may have contributed to the differing results. It is also important to note that sickle cell disease has great variations in clinical presentation, natural history and severity of hemolysis. Some populations may have a lower frequency of cholelithiasis because of haplotype variations, environmental factors, and different clinical managements.<sup>6</sup>

The use of hydroxyurea was not associated with gallstones. This contradicted our expectations as increased levels of fetal hemoglobin caused by this medication promote a decrease in hemolysis of patients and it was expected that this would decrease the formation of gallstones. However, the findings are not conclusive on this point because the study has the limitation of not having been able to check the patients' adherence to the use of hydroxyurea. It was also not possible to identify whether patients had already had gallstones before the use of this medicine.

This study observed sixteen cases of symptomatic cholelithiasis subjected to laparoscopy. The incidence of procedure-related complications was minimal and the vast majority of patients progressed satisfactorily after surgery.<sup>7,8</sup> The surgical approaches used are laparotomy and laparoscopy, with most authors considering the latter safer for patients, with less complications related to surgery, shorter operative time and faster postoperative recovery, as well as a shorter hospital stay.<sup>10–14</sup> However, a study published in the International Journal of Surgery in 2009 found a positive relationship between acute chest syndrome and laparoscopic surgery. The study stated that the pneumoperitoneum and respiratory acidosis secondary to the procedure are predictors of the syndrome and that, in order to minimize the risk, surgery should be performed by an experienced team with less intrabdominal pressure and shorter operative time.<sup>8</sup>

Elective removal of asymptomatic gallstones, diagnosed by chance, is a controversial matter.<sup>7,8</sup> Most experts, similar to in the hematology service at UFTM, do not recommend surgery before symptoms appear. There is evidence that this profile can be clinically managed for long periods,<sup>8,14</sup> so the medical team usually prescribe antispasmodic agents for minor pain and recommend preventative measures such as a low-fat diet for these patients.

Episodes of acute cholecystitis ought to be treated conservatively with antibiotics, analgesia, and general care until the crisis is over. Cholecystectomy should then be performed.<sup>7,8</sup> Recently, the National Heart, Lung, and Blood Institute of the United States recommended, from evidence-based management of sickle cell disease, that asymptomatic gallstones should be treated with watchful waiting in children and adults. In those who develop symptoms specific to gallstones, cholecystectomy should be performed with the laparoscopic approach being preferred if surgically feasible and available.<sup>15</sup>

Walker et al. observed a large number of asymptomatic patients over 25 years of follow-up, and suggested that research and surgery be indicated only for symptomatic patients.<sup>16</sup> However, cholecystectomy in asymptomatic patients with sickle cell disease prevents the risk of gallstone crises in this patient group. Authors advocating prophylactic cholecystectomy claim that this procedure reduces the risk of complications such as acute chest syndrome, painful vaso-occlusive crises, and hepatic and splenic sequestration associated with cholecystitis crises in sickle cell patients. The authors also note that cholecystectomy in gallstone patients allows the exclusion of this differential diagnosis in individuals with recurrent abdominal pain, thus facilitating the diagnosis of abdominal vaso-occlusive crisis, which is quite frequent and has similar symptoms.<sup>10,16</sup> Another argument against the indication of cholecystectomy in the absence of symptoms would be the fact that surgery

exposes patients to several factors that precipitate the sickling of red blood cells, thus facilitating the onset of a severe hemolytic crisis.<sup>7</sup>

Patients with sickle cell disease who are to be submitted to anesthetic and surgical procedures require specific care. Conditions associated with these procedures, such as hypoxia, acidosis, hypothermia, infection, hematologic instability and hypovolemia may have particularly serious consequences for these patients. Therefore, in order to minimize the risk of these complications, it is recommended that a multidisciplinary preoperative evaluation be performed, as well as special attention be given to hydration and oxygenation, and less invasive surgical procedures be chosen, for example, laparoscopic surgery as well as special postoperative care. Even though patients with sickle cell disease are cared for, morbidity rates are as high as 25%.<sup>7,8,10</sup>

The major postoperative complications described are as follows: atelectasis, pneumonitis, pulmonary infarction and infections.<sup>7,11-13,17,18</sup> Three of the cases (18%) in this study developed complications. The first case was due to organ damage during the procedure that required laparotomy and emergency splenectomy with the patient having a good evolution. In another case, the patient developed acute pancreatitis after endoscopic retrograde cholangiopancreatography, but progressed well and subsequently underwent laparoscopic cholecystectomy. Finally, in the third case, the patient developed splenic sequestration 30 days after the procedure, was unresponsive to clinical measures, and evolved to death. As the incident occurred days after the surgical process, we discarded the association of death with cholecistectomy.

In patients with pain in the right upper abdominal quadrant it is important to perform differential diagnoses of viral hepatitis, vaso-occlusive crisis of the liver, common bile duct obstruction, or drug-induced hepatotoxicity. Assessments of the liver and gallbladder must be periodically made by laboratory and imaging exams (radiography and ultrasound), and the patient must be referred to specialized services.<sup>14</sup>

## Conclusion

This study showed that a prevalence of 25.2% of gallstones was observed in patients with sickle cell disease and 11- to 29-year-old patients have a higher incidence of gallstones. So, patients with sickle cell disease should be monitored in specialized centers on a regular basis by undergoing regular screening tests and by preventing this complication of chronic hemolysis. Nonetheless, early diagnosis, and preoperative, intra-operative and postoperative care are mandatory for a good progression of sickle cell disease and for less risk of complications.

## Conflicts of interest

The authors declare no conflicts of interest.

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