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Biliary obstruction in pediatric hereditary spherocytosis: a clinical review of 16 cases

Xinjie Huang[1], Chunhui Peng[1*], Yajun Chen[1], Dongyang Wu[1], Wei Chen[1,2], Zengmeng Wang[1] and Kai Wang[1]

Abstract

Background Biliary obstruction is a rare complication in patients with hereditary spherocytosis (HS). The clinical course and optimal treatment strategies for HS patients complicated by biliary obstruction remain unclear.

Methods We conducted a retrospective review of 16 pediatric HS patients complicated by biliary obstruction who were treated at our hospital between January 2018 and October 2024. Based on previously published clinical severity classifications, patients were divided into Group A (non-severe group: trait, mild, and moderate) and Group B (severe group).

Results The study included 16 patients with a mean age of 9.0 ± 3.2 years, evenly distributed between the two groups (8 patients each). Preoperative routine blood tests showed no significant differences between the groups; however, Group B exhibited higher bilirubin levels and lower liver enzyme levels. Genetic testing was performed in 12 patients, revealing SPTB gene mutations in 7 (58.3%). Conservative management effectively resolved biliary obstruction in 10 patients (62.5%) within 14 days. Invasive interventions, such as endoscopic retrograde cholangiopancreatography (ERCP) or cholecystostomy, were required in 6 patients, with conjugated bilirubin levels normalizing within five days post-procedure. Complications occurred in two patients with prolonged intervals between diagnosis and surgery (> 3 months): one required stent replacement due to blockage after ERCP, and the other developed a gallbladder-skin fistula and coagulation disorder following laparoscopic cholecystostomy. Of the 14 patients who underwent subsequent splenectomy and/or cholecystectomy, 12 recovered without complications. Notably, the 6 patients who underwent splenectomy alone without cholecystectomy did not experience biliary colic during a mean follow-up period of 3.4 years (range: 0.5 – 5.5 years).

Conclusions Biliary obstruction can complicate HS in pediatric patients regardless of anemia severity, particularly in those with SPTB gene mutations. Conservative management is effective in most cases, while invasive procedures are required for refractory cases. Shortening the interval between diagnosis and subsequent surgery may help prevent complications. Splenectomy alone appears to be a viable option once biliary obstruction is resolved.

Keywords Hereditary spherocytosis, Biliary obstruction, Cholelithiasis, Gallstone

Background

Hereditary spherocytosis (HS) is a common inherited hemolytic disease characterize by anemia, jaundice and splenomegaly [1, 2]. The underlying defect in the spherocyte cell membrane predisposes these cells to entrapment and destruction in the spleen, leading to significantly elevated bilirubin levels in the biliary system and the formation of pigment gallstone. Consequently, complications

*Correspondence:
Chunhui Peng
chunhuipeng_bjh@126.com
[1] Department of General Surgery, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, No. 56 Nanlishi Road, Beijing 100045, China
[2] Department of Pediatric Surgery, Beijing Tsinghua Changgung Hospital, No.168 Litang Road, Beijing 102218, China

such as cholecystitis, cholangitis, pancreatitis and biliary obstruction are clinical concerns in HS patients.

The prevalence of gallbladder stone in pediatric HS patients is reported to be 17% [3], with this figure raising to 41% when regular biliary ultrasound scan is initiated earlier [4]. But most these gallstones remain asymptomatic, as evidence indicated that symptomatic cases requiring cholecystectomy mainly involve cholesterol stones [5, 6]. Most HS pediatric cases with biliary stone are diagnosed before the age of 13 [4, 7]. Acute biliary obstruction associated with gallstone in HS is a severe but rarely reported manifestation that sometimes be fatal [8]. Despite its clinical significance, there is limited consensus on the optimal management strategies, particularly regarding surgical interventions [3].

The aim of this study is to review the clinical presentation, management and outcomes of acute biliary obstruction in pediatric HS patients, with the goal of narrowing the existing knowledge gap and providing evidence-based recommendations for clinical practice.

Methods and materials

Patients

Medical records of HS patients who were admitted for biliary obstruction and received treatments in the Department of General Surgery, Beijing Children's Hospital between January 2018 and October 2024 were retrospectively reviewed. HS is diagnosed based on hemolytic anemia, microspherocytes in peripheral blood smears, positive osmotic fragility test, gene testing. Biliary obstruction was diagnosed based on (1) clinical presentations of biliary colic: sudden onset of abdominal pain and aggravated jaundice; (2) laboratory tests: high level of conjugated bilirubin; (3) abdominal imaging shows common bile duct stones and dilated. The inclusion criteria were pediatric HS patients who were treated at our institution for biliary obstruction. The exclusion criteria were patients with incomplete medical charts, other concomitant biliary duct diseases.

Study design

This is an Institutional Review Board (IRB) approved retrospective cohort study (IRB reference number 2025-E-002-R). Patients were classified into Group A and Group B based on clinical manifestations as previously published to identify if anemia severity is associated with biliary obstruction [3]: Group A (non-severe group: trait, mild and moderate), Group B (severe group). Medical charts were reviewed for age, sex, clinical manifestations, gene mutations, anemia severity, blood transfusion history, family history, imaging studies, blood tests, biliary obstruction treatment, subsequent surgery and complication. Following data were analyzed between Group A and Group B to identify any statistical difference: age, sex, laboratory test results (hemoglobin, total bilirubin (TBIL), conjugated bilirubin, unconjugated bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), total bile acid (TBA).

Study outcomes

The primary outcomes of the study were the success treatment of biliary obstruction, recurrent colic and invasive related complications. Secondary outcomes were symptoms.

Conservative treatments

During admission, patients remained fasting until bilirubin levels declined, progressing from low-fat to normal diet as conjugated bilirubin normalized. Sulperazon (cefoperazone-sulbactam, 20–40 mg/kg/day) was given until jaundice resolution for infection prevention, with supportive care comprising parenteral nutrition and ibuprofen analgesia.

Surgical indication and technique

For patients with severe jaundice (conjugated bilirubin >200 μmol/L) or those refractory to conservative management after 48 h, surgical bile duct exploration or endoscopic retrograde cholangiopancreatography (ERCP) is performed under general anesthesia. Except in emergency circumstances, splenectomy is deferred until completion of essential immunizations [3]. The standard approach involves laparoscopic splenectomy and/or cholecystectomy via a four-port technique, with intraoperative conversion to open surgery in cases of uncontrolled hemorrhage or technically challenging anatomy.

Follow-up

Patients were discharged upon meeting all of the following criteria: (1) resolution of symptoms, (2) normalization of conjugated bilirubin levels, and (3) adequate oral nutritional intake. Postoperative follow-up included clinical evaluation at one month for patients undergoing splenectomy and/or cholecystectomy. For non-cholecystectomized patients, surveillance biliary ultrasound was performed at six-month intervals. For patients who underwent ERCP, stent reevaluation was scheduled within 3–6 months to assess the need for replacement or removal.

Statistical analysis

All statistical analysis was performed with SPSS version 22.0. Continuous variables with normal distribution were presented as the mean (standard deviation) and were analyzed with Student's t-test. Continuous variables with

Table 1 Summary of 16 hereditary spherocytosis pediatric with biliary obstruction

	Case (n)
Sex	
Male	9
Female	7
Age	
< 120 months	10
> 120 months	6
Gene mutation	
SPTB	7
ANK1	4
SPTA1	1
Anemia at birth	**11**
Anemia degree	
Mild (Hb > 130 g/L)	4
Moderate (Hb 80 ~ 130 g/L)	4
Moderately severe (Hb 60 ~ 80 g/L)	5
Severe (Hb < 60 g/L)	3
Obstruction Treatment	
Conservative	10
ERCP	5
Laparoscopic cholecystostomy	1
Blood Transfusions[a]	
> 2	5
1 ~ 2	3
No	8
Surgery	
Laparoscopic splenectomy	6
Laparoscopic splenectomy & cholecystectomy	4
Open splenectomy & cholecystectomy[b]	1
Laparoscopic cholecystectomy	1
Laparoscopic splenectomy & cholecystolithotomy	2

Hb Hemoglobin

[a] Transfusions before admitted for biliary obstruction

[b] attempted laparoscopic failed and converted to open surgery

nonnormal distribution were presented as median (Inter Quartile Range, IQR) and were analyzed with Wilcoxon–Mann–Whitney's test. Nominal data were compared with chi-square test. Statistical significance was set at $p < 0.05$.

Results

Over the study period, 16 patients were identified with a mean age of 9.0 ± 3.2 years (range: 3.3–13.8 years old). Patients were evenly distributed between the two groups (8 patients each), their characteristics were summarized in Table 1. Group A was younger than Group B (8.0 ± 3.3 years, 10.0 ± 2.9 years, respectively), but no significant difference was found ($P = 0.226$).

A positive family history was noted in 8 patients (50%). Notably, half of the patients (8/16, 50%) were nots diagnosed with HS prior to the onset of biliary obstruction. Among the 12 patients who underwent genetic testing, SPTB gene mutations were the most prevalent(7/12, 58.3%), followed by ANK1(4/12, 25%) and SPAT1(1/12, 8.3%) gene mutations.

The laboratory test results of all patients on admission are summarized in Table 2. The findings revealed a significant elevation in total bilirubin levels, predominantly driven by conjugated bilirubin. Liver enzymes (AST, ALT) and hemoglobin levels remained within normal ranges or showed only mild alterations. Although no statistically significant differences were found between the two groups, Group B exhibited higher levels of bilirubin, GGT and TBA, along with lower levels of AST, ALT, hemoglobin level (Table 2).

Imaging studies, including abdominal ultrasound or MRI, confirmed splenomegaly in all patients in addition to findings consistent with biliary obstruction.

Treatment was initiated immediately after admission. Conservative treatment was effective in 10 patients (62.5%) within 14 days. Invasive treatment (ERCP or cholecystostomy) was indicated in 6 patients (three patients in each group) due to persistent cholestasis and

Table 2 Laboratory tests on admission

	Mean[a]	Group A	Group B	*P*	Reference
TBIL, μmol/L	478.7 ± 282.6	389.6 ± 188.9	567.9 ± 344.7	0.07	3.42 ~ 20.5
Conjugated bilirubin, μmol/L	318.5 ± 264.6	246.7 ± 182.9	390.2 ± 325.9	0.10	0 ~ 3.42
Unconjugated bilirubin, μmol/L	160.3 ± 58.1	142.8 ± 62.2	177.7 ± 52.3	0.42	0 ~ 17.1
AST, U/L	77.6 ± 43.7	85.0 ± 54.5	70.2 ± 32.1	0.18	21 ~ 80
ALT, U/L	154.0 ± 126.5	171.5 ± 150.4	136.6 ± 106.3	0.32	7 ~ 30
GGT, U/L	166.4 (197.3)[a]	168.9 (147.8)[a]	174.4 ± 128.3	0.66	6 ~ 31
TBA, μmol/L	12.8 (196.5)[a]	9.9 (439.1)[a]	15.8 (102.14)[a]	0.06	0 ~ 10
Hemoglobin, g/L	101 ± 11.5	102.4 ± 9.2	100.1 ± 14.2	0.14	112 ~ 149

TBIL Total bilirubin, *AST* Aspartate aminotransferase, *ALT* Alanine aminotransferase, *GGT* Gamma-glutamyl transferase, *TBA* Total bile acid

[a] Non-normally distributed data are reported as median (Inter Quartile Range, IQR)

significantly higher conjugated bilirubin levels compared to those managed conservatively (479.5 ± 113.6 μmol/L *vs* 197.7 ± 66.9 μmol/L, $P = 0.04$). In all 6 patients who underwent invasive procedures, conjugated bilirubin levels normalized within five days post-intervention. Postoperative complication occurred in two patients. One patient required replacement of an ERCP-implanted biliary stent three months after the initial stent was blocked. The other patient, who underwent laparoscopic cholecystostomy, developed a gallbladder-skin-fistula and subsequent coagulation disorder secondary to fat-soluble vitamin deficiency.

Among all patients, one patient is awaiting splenectomy, another with mild type underwent ERCP for symptoms relief but declined further surgical intervention. Twelve patients underwent splenectomy and/or cholecystectomy had uneventful recovery (Table 1). However, one patient who underwent synchronous cholecystolithotomy during splenectomy developed postoperative pleural effusion, which required closed drainage. Additionally, a 9-year-old girl developed streptococcus pneumoniae infection ten days after splenectomy due to insufficient preoperative vaccination.

Among six patients who underwent splenectomy without cholecystectomy, none experienced biliary colic during a mean follow-up period of 3.4 years (range: 0.5–5.5 years).

Discussion

Biliary obstruction and hyperbilirubinemia are rare symptoms of HS. Our study challenges the conventional assumption that anemia severity correlates with gallstone-related complications. Notably, 50% of the patients belongs to non-severe group, their mean age is younger than the severe group. This finding aligns with Han [8], suggesting that biliary complications may arise independently of anemia severity. Hyperbilirubinemia, in this scenario, is driven by three mechanisms: biliary obstruction, liver cell damage and recurrent hemolysis. In early-stage mild-type HS patients, liver cell damage may play a dominate role, as evidenced by the higher liver enzyme levels observed in our non-severe group (Group A). This finding suggests that symptomatic biliary complication can occur in mild-type HS regardless of age, highlighting the importance of regular biliary scan for both mild-type and severe-type HS patients.

The rarity of biliary obstruction in HS also leads to delayed diagnosis of hemolytic anemia. In our study, eight patients were neither diagnosed nor suspected of having HS on admission, as they exhibited mild to no anemia. This phenomenon can be explained by the fact that obstructive jaundice increases red cell membrane lipid, makes it to a less spheroidal shape and permits it to better transform in splenic circulation, thereby ameliorating hemolytic anemia [9]. Therefore, caution is required when unexplained anemia appears after the resolution of biliary obstruction, particularly in the presence of splenomegaly, as observed in our eight patients. A positive family history of HS further supports the diagnosis, making it more straightforward [3].

Several genes encoding red cell membrane proteins and cytoskeleton have been reported previously in HS, with specific mutations identified as causative factors [3]. Although studies showed that specific variants within these genes are not correlated with anemia severity or predictive of early splenectomy, patients with the same genotype tend to share similar clinical phenotype [10]. A previous example is the co-occurrence of Gilbert syndrome (caused by UGT1 A1 gene mutations) with HS, which increases the risk of gallstone formation fivefold and predisposes patients to early onset cholelithiasis [4, 11]. In our study, 58.3% (7/12) of patients harbored pathogenic SPTB gene mutations, which is consistent with reports from other similar studies [8, 12]. Moreover, SPTB variants are relatively uncommon in east-Asian HS population [1]. The high prevalence of SPTB gene mutations in our cohort suggests a potential association with biliary obstruction, however, further research is needed to elucidate underlying mechanisms.

Over half of our patients (62.5%) responded well to conservative management. However, for patients with severe jaundice and dilated common bile duct, active interventions are necessary. Both laparoscopic common bile duct exploration (LCBDE) and ERCP are equally effective options [13, 14]. In our study, five patients underwent ERCP, and their outcomes, along with findings from other reports [15, 16], support the use of ERCP due to its high immediate success and low complication rate. LCBDE represents an important alternative approach [17], particularly given its advantage of sphincter preservation and comparable efficacy to ERCP in pediatric studies [14, 18]. In a more recent multicenter study, when endoscopic access is technically challenging or unavailable, surgery first approach decreases length of stay and time to definitive intervention [19].

Questions concerning timing of subsequent splenectomy and cholecystectomy remains. On one hand, performing those procedures during the same-admission reduces the risk of recurrent gallstone-related complications [20]. On the other hand, some patients require additional time to confirm the diagnosis of HS and complete necessary immunizations [3]. Two patients in our study experienced complications: one required biliary stent replacement, and the other developed a gallbladder-skin fistula. These complications, we believe, were associated with prolonged intervals between initial and subsequent

surgeries (over three months). Therefore, we recommend performing subsequent surgeries within three months to prevent stent-related issues and reduce the risk of recurrent obstructive cholangitis [21].

While symptomatic gallstones are a clear indication for cholecystectomy, there is no consensus on the management of asymptomatic gallstone in patients undergoing splenectomy [3]. In our study, after removal of the initial obstructive stones, gallstones became clinically silent, leading six patients to refuse concomitant cholecystectomy. The decision behind this was supported by three key observations: First, pigment stones stop to form after splenectomy [22]. Second, our previous study demonstrated that asymptomatic stone often remain quiescent for extended periods [23]. Consistent with these findings, none of the six patients in this cohort developed biliary complications during a mean follow-up about three years, suggesting that residual biliary stones may persistent without clinical sequelae for several years. Furthermore, ongoing debate exists regarding whether cholecystectomy might increase long-term risk of colon cancer [24–27], potentially mediated by increasing deoxycholic acid levels [28]. Although more recent evidence generally refutes this association [29], parents in our study expressed concern about this potential risk. Additionally, traditional Chinese culture often favors gallbladder preservation and conservative management, even when potential biliary complications exist [30]. We emphasize that we do not advocate universal gallbladder preservation in these cases. However, based on our findings, splenectomy alone without cholecystectomy may be considered when: (1) biliary obstruction has been resolved, and (2) gallstones remain asymptomatic. We recommend close clinical surveillance for these patients, with laparoscopic cholecystectomy indicated upon development of any biliary complications.

This study is limited by its retrospective design and small sample size. Although patient numbers were restricted by disease rarity, future multicenter prospective studies may provide stronger evidence.

In summary, our study demonstrates that biliary obstruction can occur in pediatric patients with HS, regardless of anemia severity, particularly in those with SPTB gene mutations. For patients who do not respond well to conservative management, invasive interventions such as ERCP and LCBDE are effective in resolving obstruction. Shortening the interval between initial treatment and subsequent surgeries helps to prevent complications and recurrent symptoms. Splenectomy alone may be sufficient once biliary obstruction is resolved, provided gallstones remain asymptomatic.

Abbreviations

HS Hereditary spherocytosis
LCBDE Laparoscopic common bile duct exploration
ERCP Endoscopic retrograde cholangiopancreatography

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Not applicable.

Clinical trial number
Not applicable.

Author's contributions
XJH collected, analyzed the data and drafted the manuscript. CHP and YJC conceived the study. DYW, ZMW, KW, WC facilitated all project-related tasks.All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study was approved by the Medical Research Ethics Committee, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health (2025-E-002-R). written informed consent was obtained from all parents for participating in this study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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