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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

# Gilbert syndrome as a risk factor for the development of cholelithiasis in children

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**SUMMARY**

**Introduction/Objective** Gilbert syndrome (GS) is the most common hereditary hyperbilirubinemia. As well as mild unconjugated hyperbilirubinemia, it is characterized by the excess of bilirubin monoglucuronide over diglucuronide in the bile and thus increases the risk of biliary calculosis. The aim of the study was to determine the importance of GS as a risk factor in the development of cholelithiasis in children.

**Methods** The study included a sample of 31 children (14 male and 17 female, mean age 12.16 ± 4.11 years, range 3–16.75 years) with symptomatic cholelithiasis. The diagnosis of cholelithiasis was based on an ultrasonographic finding, and for GS the diagnosis was based on at least a double increase of unconjugated bilirubin fraction after a three-day hypocaloric diet (400 kcal per day).

**Results** GS was confirmed in five or 16.13% of patients (three male and two female, mean age 14.71 ± 0.55 years, range 14–15.3 years). In addition to GS, in the history of the disease they all had some of the additional risk factors for the development of cholelithiasis. One of them had an identical problem as its mother, one had hereditary elliptocytosis, one had sudden weight loss, one was overweight, and one had premature birth and sepsis.

**Conclusion** GS registers in one-sixth of children with cholelithiasis, but in none of them as the only risk factor for developing this disease. This finding suggests that GS is a risk factor for the development of cholelithiasis, but not sufficient in itself in that respect.

**Keywords:** Gilbert syndrome; cholelithiasis; children

## INTRODUCTION

Gilbert syndrome (GS) is the most common hereditary hyperbilirubinemia [1–4]. It is registered in 2–13% of the general population and characterized by a mild, intermittent unconjugated hyperbilirubinemia without evidence of hemolysis or liver injury caused by the autosomal recessive deficit of bilirubin uridine diphosphate glucuronosyltransferase (UGT1A1), a microsomal enzyme of the hepatocyte, which is of crucial importance in the conjugation of bilirubin with glucuronic acid [1–6]. The *UGT1A1* gene located on the long arm of chromosome 2 (2q37.1) is responsible for the expression of this enzyme [1]. The consequence of this genetic defect, the most common due to extra bases (TA) in the TATAA box sequence of the promoter region of the *UGT1A1* gene, is reduced synthesis of UGT1A1 by at least 50%, and consequently lower capacity of bilirubin conjugation and excretion [4, 6]. An additional pathogenetic significance in the occurrence of hyperbilirubinemia is a shorter lifespan of erythrocyte present in about one-half of cases, as well as the defect of the uptake and transport of unconjugated bilirubin at the hepatocyte level [4, 7]. Beside unconjugated hyperbilirubinemia, the UGT1A1 deficit is followed by the excess of bilirubin monoglucuronide compared to bilirubin diglucuronide in bile, which makes individuals with GS more prone to bilirubin (pigment) cholelithiasis [5, 7–14]. In the expression of GS, sex hormones, especially androgens, have significant effect, which explains its rare manifestation before puberty, and two to seven times higher incidence in males than in females [7, 11]. Higher erythrocyte count and muscle mass in men compared to women contribute significantly to this difference [7]. Earlier expression of GS is seen in young infants with hypertrophic pyloric stenosis, annular pancreas, congenital atresia and stenosis of small intestine, and other diseases accompanied with caloric deficits, as well as within the breastfeeding jaundice [1, 6, 15].

In GS without associated disorders, such as hemolytic and liver disease, serum bilirubin levels usually vary between normal values and 35–70 μmol/L, and rarely above that value [2]. Hyperbilirubinemia is precipitated and potentiated by low calorie intake, physical exertion, and fever [3, 7]. GS is not followed by other complications except for an increased risk for the development of biliary calculosis, significant involvement in incidence and degree of unconjugated hyperbilirubinemia in newborns and patients with hemolysis and hepatic impairment, as well as irinotecan intolerance [7].

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The aim of the study was to determine the importance of GS as a risk factor in the development of cholelithiasis in children.

## METHODS

The study was based on a sample of 31 children (14 male and 17 female, mean age 12.16 ± 4.11 years, range 3–16.75 years) hospitalized due to symptomatic cholelithiasis.

The diagnosis of cholelithiasis was performed by ultrasonographic examination of the abdomen. In addition to the details related to the symptoms and signs of cholelithiasis, as well as the presence of risk factors for its occurrence, all patients were subjected to a detailed physical examination and appropriate laboratory tests. In patients with unconjugated hyperbilirubinemia, in addition to insight into reticulocyte count and the appearance of erythrocytes, Coombs's test and measurement of osmotic resistance of erythrocytes were made. Since all patients had uncomplicated symptomatic cholelithiasis, all of them underwent laparoscopic cholecystectomy [16, 17]. According to the number of biliary concrements, cholelithiasis is classified into solitary and multiple, and, depending on their appearance, into pigment, cholesterol, and mixed [17, 16].

In all patients with unconjugated hyperbilirubinemia, verified during diagnosis of cholelithiasis or during recovery from cholecystectomy, tests for GS were performed. The diagnosis of GS is based on at least a double increase in the unconjugated serum bilirubin fraction after 72 hours of the hypocaloric diet (400 kcal per day), as well as its normalization or significant decrease after two to three days of administration of phenobarbitone (2–3 mg/kg) (Figure 1) [18]. This procedure was done in three patients before cholecystectomy and in two of them two months after surgery. The study was approved by the local ethics committee.

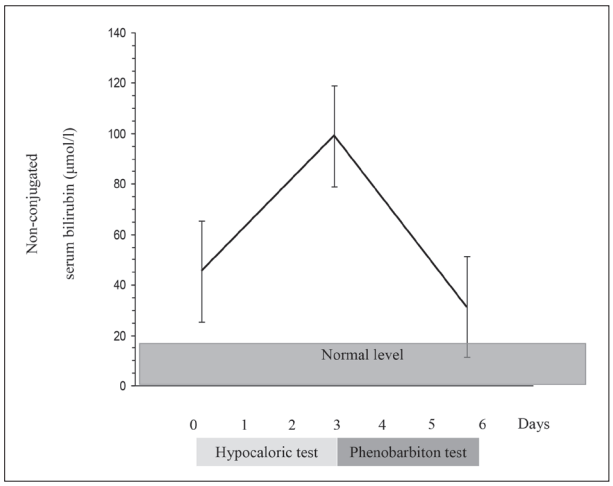


**Figure 1.** Serum non-conjugated bilirubin level after hypocaloric and phenobarbital test

## RESULTS

GS and cholelithiasis association was established in five (16.13%) of 31 patients (three male and two female, mean age 14.71 ± 0.55 years; range 14–15.3 years) with cholelithiasis. Unconjugated hyperbilirubinemia was observed in three patients during the diagnosis of cholelithiasis and in two at the time of recovery from cholecystectomy. The underlying symptom that preceded the diagnosis of cholelithiasis was intense abdominal pain, recurrent in four and acute in one, localized in epigastrium and/or right hypochondrium, followed by emesis and occasional vomiting. All patients with cholelithiasis and GS had some of the additional risk factors for the development of biliary calculosis (Table 1). Except for a boy with hereditary elliptocytosis, with a transient choledocholithiasis and cholestasis three months before admission, other complications of cholelithiasis were not recorded.

Apart from palpatory pain and sensitivity in the epigastrium and/or right hypochondrium, which was present in all of the patients, a slight scleral icterus in three of them, palpable spleen by 1 cm in a boy with hereditary elliptocytosis, and being slightly overweight in one girl (+12.5%), other physical findings on admission were normal in all.

With exclusion of a boy with hereditary elliptocytosis, in whom, together with an unconjugated hyperbilirubinemia (114 μmol/L), characteristic erythrocyte appearance and significant reticulocytosis was found (4.2%), and two more with elevated unconjugated fraction of bilirubin in the serum (36 and 38 μmol/L), other laboratory analysis on admission, including blood hemoglobin values and additional liver tests, were normal in all.

Laparoscopic cholecystectomy was uneventful in all five patients. The number and appearance of their concretions are given in Table 1.

**Table 1.** Additional risk factors for the development of cholelithiasis in children with Gilbert's syndrome and appearance and number of biliary calculi

| Patient | Risk factors | Appearance and number of calculi |
|---|---|---|
| 1 | Hereditary elliptocytosis | Black pigment, multiple |
| 2 | Cholelithiasis in mothers | Brown pigment, solitary |
| 3 | Premature birth (32 GW) neonatal sepsis | Black pigment, multiple |
| 4 | Overweight (+12.5%) | Black pigment, multiple |
| 5 | Reduction diet (sudden weight loss) | Black pigment, multiple |

GW – gestational weeks

## DISCUSSION

Thanks to ultrasound diagnostics, it is known today that cholelithiasis is not so rare in children, especially in those at the final stage of childhood [16, 17, 19]. Its prevalence in this age has been reported to be 0.13–0.22% [16, 19]. The main risk factors for gallstone formation in childhood, in addition to the family predisposition, are the diseases accompanied by reduced solubility of the biliary content,

such as hemolysis, obesity, anorexia nervosa, long-lasting total parenteral nutrition, hepatobiliary disorders, hypercholesterolemia, terminal ileum resection, cholecystitis, cystic fibrosis, and others, as well as premature birth and rapid weight loss [16, 17, 19–23]. With the onset of puberty, cholelithiasis is more common in girls than in boys [17, 20–23]. Due to the excess of the less hydrolysable bilirubin monoglucuronide to bilirubin diglucuronide and bile, GS is also ranked as the risk factor for the development of biliary calculosis [5, 7–14]. This fact is particularly present in the association of GS with hemolysis and other diseases accompanied by high inclinations to biliary calculosis [5, 16, 24].

The clinical picture of cholelithiasis in older children is similar to that of adults and is characterized by episodes of spasmodic postprandial pain localized in the right hypochondrium or epigastrium, accompanied by nausea, and often by vomiting [17, 20, 25]. However, in younger children it can be quite atypical, and resemble acute appendicitis, intussusception, volvulus and other acute surgical conditions that must be ruled out [25]. In a significant number of cases, cholelithiasis is complicated by cholecystitis, and rarely by gallbladder empyema and choledocholithiasis, followed by ascending cholangitis, and pancreatitis [16, 17, 19, 21]. Also, gallbladder perforation with bile peritonitis, and life-threatening sepsis is possible [26, 27].

Therapy of symptomatic cholelithiasis is surgical [16, 19, 28], and in uncomplicated cases the laparoscopic approach is preferred and widely adopted [16, 19, 28, 29, 30].

Symptoms and signs of cholelithiasis in our patients were quite characteristic [16, 23, 25]. None of them had complications of the disease, so laparoscopic cholecystectomy was performed in all of them, without conversion to open procedure.

Our data suggests that GS is a risk factor in the development of cholelithiasis, but not sufficient in itself in that respect. The presence of GS in patients with cholelithiasis is encountered more frequently (16.13%) in comparison to cholelithiasis prevalence in the general population (2–13%) and shows that GS can be considered a biliary lithogenic factor [1–5]. An additional argument in favor of this is the fact that out of five patients with cholelithiasis and GS three were boys and two were girls, while this relationship in the group of those without GS was reversed (11 *vs.* 15). Also, in four out of five patients, the biliary concrements were black-pigmented [5]. However, what disables this conclusion in the full sense is the fact that in all of them, besides GS, another risk factor for the development of cholelithiasis is also registered. In addition, patients with cholelithiasis and GS were on average significantly older than those without GS (14.71 *vs.* 11.67 years).

## CONCLUSION

According to our study, GS registers in every sixth child with cholelithiasis, or more than twice as often compared to its average frequency in the general population, but never as the only risk factor for the development of this disease. This finding suggests that GS is a risk factor for the development of cholelithiasis, but not sufficient in itself in that regard.

**Conflict of interest:** None declared.

## REFERENCES

1. King D, Armstrong MJ. Overview of Gilbert's syndrome. Drug Ther Bull. 2019;57(2):27–31. [DOI: 10.1136/dtb.2018.000028] [PMID: 30709860]
2. Kamal S, Abdelhakam S, Ghoraba D, Massoud Y, Aziz KA, Hassan H, et al. The frequency, clinical course, and health related quality of life in adults with Gilbert's syndrome: a longitudinal study. BMC Gastroenterol. 2019;19(1):22. [DOI: 10.1186/s12876-019-0931-2] [PMID: 30717703]
3. Wagner KH, Shiels RG, Lang CA, Seyed Khoei N, Bulmer AC. Diagnostic criteria and contributors to Gilbert's syndrome. Crit Rev Clin Lab Sci. 2018;55(2):129–39. [DOI: 10.1080/10408363.2018.1428526] [PMID: 29390925]
4. Radlović N. Hereditary hyperbilirubinemias. Srp Arh Celok Lek. 2014;142(3–4):257–60. [DOI: 10.2298/sarh1404257r] [PMID: 24839786]
5. Bale G, Avanthi US, Padaki NR, Sharma M, Duvvur NR, Vishnubhotla VRK. Incidence and risk of gallstone disease in Gilbert's syndrome patients in Indian population. J Clin Exp Hepatol. 2018;8(4):362–6. [DOI: 10.1016/j.jceh.2017.12.006] [PMID: 30563996]
6. Gazzin S, Masutti F, Vitek L, Tiribelli C. The molecular basis of jaundice: An old symptom revisited. Liver Int. 2017;37(8):1094–102. [DOI: 10.1111/liv.13351] [PMID: 28004508]
7. Radu P, Atsmon J. Gilbert's syndrome – clinical and pharmacological implications. Isr Med Assoc J. 2001;3(8):593–8. [PMID: 11519385]
8. Kitsiou-Tzeli S, Kanavakis E, Tzetis M, Kavazarakis E, Galla A, Tsezou A. Gilbert's syndrome as a predisposing factor for idiopathic cholelithiasis in children. Haematologica. 2003;88(10):1193–4. [PMID: 14555319]
9. Tsezou A, Tzetis M, Giannatou E, Spanos I, Roma E, Fretzayas A, et al. Gilbert syndrome as a predisposing factor for cholelithiasis risk in the Greek adult population. Genet Test Mol Biomarkers. 2009;13(1):143–6. [DOI: 10.1089/gtmb.2008.0095] [PMID: 19309288]
10. Ravikanth VV, Rao GV, Govardhan B, Sasikala M, Subramanyam C, Vivekananda Murthy HV, et al. Polymorphisms in UGT1A1 gene predispose South Indians to pigmentous gallstones. J Clin Exp Hepatol. 2016;6(3):216–23. [DOI: 10.1016/j.jceh.2016.08.004] [PMID: 27746618.
11. Buch S, Schafmayer C, Völzke H, Seeger M, Miquel JF, Sookoian SC, et al. Loci from a genome-wide analysis of bilirubin levels are associated with gallstone risk and composition. Gastroenterology. 2010;139(6):1942–51.e2. [DOI: 10.1053/j.gastro.2010.09.003] [PMID: 20837016]
12. Van Erpecum KJ. Pathogenesis of cholesterol and pigment gallstones: an update. Clin Res Hepatol Gastroenterol. 2011;35(4):281–7. [DOI: 10.1016/j.clinre.2011.01.009] [PMID: 21353662]
13. Lammert F, Miquel JF. Gallstone disease: from genes to evidence-based therapy. J Hepatol. 2008;48 Suppl 1:S124–35. [DOI: 10.1016/j.jhep.2008.01.012] [PMID: 18308417]
14. Milton JN, Sebastiani P, Solovieff N, Hartley SW, Bhatnagar P, Arking DE, et al. A genome-wide association study of total bilirubin and cholelithiasis risk in sickle cell anemia. PLoS One. 2012;7(4):e34741. [DOI: 10.1371/journal.pone.0034741] [PMID: 22558097]
15. Prameela KK. Breastfeeding during breast milk jaundice – a pathophysiological perspective. Med J Malaysia. 2019;74(6):527–33. [PMID: 31929480]

16. Suchy FJ, Feldman AG. Diseases of the gallbladder. In: Kliegman RM, St Geme III JW, Blum NJ, Shah SS, Tacker RC, Wilson KM, Behrman RE, editors. Nelson Textbook of Pediatrics. 21st edition. Philadelphia: Elsevier; 2020. p. 2139–40.
17. Wong MCY, Incerti F, Avanzini S, Palo F, Sertorio F, Damasio MB, et al. Cholelithiasis management in a third-level pediatric center: case series and literature review. Updates Surg. 2022;74(3):963–8. [DOI: 10.1007/s13304-021-01227-9] [PMID: 35094309]
18. Berk K, Korenblat K. Approach to the patient with jaundice or abnormal liver test. In: Goldman L, Schafer AI, editors. Goldman's Cecil Medicine. 24th edition. Philadelphia: Elsevier; 2012. p. 956–66.
19. Frybova B, Drabek J, Lochmannova J, Douda L, Hlava S, Zemkova D, et al. Cholelithiasis and choledocholithiasis in children; risk factors for development. PLoS One. 2018;13(5):e0196475. [DOI: 10.1371/journal.pone.0196475] [PMID: 29763444]
20. Zdanowicz K, Daniluk J, Lebensztejn DM, Daniluk U. The Etiology of cholelithiasis in children and adolescents – A literature review. Int J Mol Sci. 2022;23(21):13376. [DOI: 10.3390/ijms232113376] [PMID: 36362164]
21. Diez S, Müller H, Weiss C, Schellerer V, Besendörfer M. Cholelithiasis and cholecystitis in children and adolescents: Does this increasing diagnosis require a common guideline for pediatricians and pediatric surgeons? BMC Gastroenterol. 2021;21(1):186. [DOI: 10.1186/s12876-021-01772-y] [PMID: 33882844]
22. Lia E, Amri K. Cholelithiasis in children: A characteristic study. Med J Malaysia. 2022;77(Suppl 1):59–61. [PMID: 35899891]
23. Xu ZR, Dan HL, Yu F. Risk factors, manifestations, diagnosis and treatment of cholelithiasis in children. World J Meta-Anal. 2021;9(1):54–63. [DOI: 10.13105/wjma.v9.i1.54]
24. Batista JVGF, Arcanjo GS, Batista THC, Sobreira MJ, Santana RM, Domingos IF, et al. Influence of UGT1A1 promoter polymorphism, α-thalassemia and βs haplotype in bilirubin levels and cholelithiasis in a large sickle cell anemia cohort. Ann Hematol. 2021;100(4):903–11. [DOI: 10.1007/s00277-021-04422-1] [PMID: 33523291]
25. Goldman DA. Gallbladder, Gallstones, and Diseases of the Gallbladder in Children. Pediatr Rev. 2020;41(12):623–9. [DOI: 10.1542/pir.2019-0077] [PMID: 33262152]
26. Khetarpal A, Khetarpal A. Case report – acute pre-operative gall bladder perforation (Type-1) with generalized biliary peritonitis in younger age group without any comorbid illness. Ann Med Surg (Lond). 2021;64:102253. [DOI: 10.1016/j.amsu.2021.102253] [PMID: 33889403]
27. Rhoads K, Snyder J, Lee H. Cholelithiasis and perforated gallbladder in an infant. J Pediatr Surg. 2002;37(9):1374–5. [DOI: 10.1053/jpsu.2002.35029] [PMID: 12194140]
28. Kılıç ŞS, Özden Ö, Çolak ST. Comparative analysis of reliability and clinical effects of the critical view of safety approach used in laparoscopic cholecystectomy in the pediatric population. Pediatr Surg Int. 2021;37(6):737–43. [DOI: 10.1007/s00383-021-04869-3] [PMID: 33586011]
29. Pogorelić Z, Lovrić M, Jukić M, Perko Z. The Laparoscopic cholecystectomy and common bile duct exploration: A single-step treatment of pediatric cholelithiasis and choledocholithiasis. Children (Basel). 2022;9(10):1583. [DOI: 10.3390/children9101583] [PMID: 36291520]
30. Lammert F. Gallstones: The thing in itself. Clin Liver Dis (Hoboken). 2022;20(Suppl 1):57–72. [DOI: 10.1002/cld.1269] [PMID: 36518788]

## Жилберов синдром као фактор ризика за развој холелитијазе код деце

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**САЖЕТАК**

**Увод/Циљ** Жилберов (*Gilbert*) синдром (ЖС) представља најчешћи хередитарни поремећај метаболизма билирубина. Сем благе неконјуговане хипербилирубинемије, карактерише га ексцес билирубин-моноглукоронида у односу на диглукуронид у жучи и тиме повећан ризик од билијарне калкулозе. Циљ студије је био да се утврди значај ЖС као фактора ризика у развоју холелитијазе код деце.

**Методе** Студија је обухватала узорак од 31 детета (14 дечака и 17 девојчица, узраста три до 16,75 година, просечно 12,16 ± 4,11 година) са симптоматском холелитијазом. Дијагноза холелитијазе је заснивана на ултрасонографском налазу, а ЖС на најмање двоструком порасту неконјуговане фракције билирубина после тродневне хипокалоријске дијете (400 *kcal* дневно).

**Резултати** ЖС је доказан код пет или 16,13% болесника (три дечака и две девојчице, узраста 14 до 15,3 година, просечно 14,71 ± 0,55 година). Поред ЖС сви су у анамнези имали и неки од додатних фактора ризика за развој холелитијазе. Један болесник је имао идентичан проблем као мајка, један је имао хередитарну елиптоцитозу, један нагло мршављење, један вишак телесне тежине и један превремено рођење и сепсу.

**Закључак** ЖС се региструје код једног од шесторо деце са холелитијазом, али ни код једног од њих као једини фактор ризика за развој овог обољења. Овај налаз указује да је ЖС фактор ризика за развој холелитиазе, али не и да је у том смислу довољан.

**Кључне речи:** Жилберов синдром; холелитијаза; деца