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

Жилберов синдром као фактор ризика за развој холелитијазе код деце

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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 to 16.75 years) with symptomatic cholelithiasis The diagnosis of cholelithiasis was based on an ultrasonographic finding and for GS 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 5 or 16.13% of patients (3 male and 2 female, mean age 14.71 ± 0.55 years, range 14 to 15.3 years). In addition to the 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 in its mother, one had hereditary elliptocytosis, one ofthem 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 the GS is a risk factor for the development of cholelithiasis, but not that it is sufficient in that sense.

Keywords Gilbert syndrome; cholelithiasis; children

САЖЕТАК

Увод/Циљ Жилберов (*Gilbert*) синдром (ЖС) представља најчешћи хередитарни поремећај метаболизма билирубина. Сем благе некоњуговане 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 узорк од 31 детета (14 дечака и 17 девојчица, узраста 3 до 16,75 година, просечно 12,16 ± 4,11 година) са симптоматском холелитијазом. Дијагноза холелитијазе је заснивана на ултрасонографским налазу, а ЖС на најмање двоструком порасту некоњуговане фракције билирубина након тродневне хипокалоријске дијете (400 *kcal* дневно).

Резултати ЖС је доказан код 5 или 16,13% пацијената (3 дечака и 2 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 пацијент 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 шест 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

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 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 significant effect had sex hormones, especially androgens, which explains its rare manifestation before puberty, and 2-7 times higher incidence in males than females [7, 11]. Higher erythrocyte count and muscle mass in men compared to women are contributing 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 the 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 was not followed by other complications except for an increased risk for the development of biliary calculosis, significant involvement in incidence and degree of unconjugated hyperbilirubinaemia in newborns and patients with hemolysis and hepatic impairment, as well as irinotecan intolerance [7].

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 to 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 cholelitiasis, 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 hyperbilirubinaemia, 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 on pigment, cholesterol and mixed [17, 16].

In all patients with unconjugated hyperbilirubinemia, verified during diagnosis of cholelithiasis or during recovery from cholecystectomy, test 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 2-3 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 local ethics committee.

RESULTS

GS and cholelithiasis association is established at 5 (16.13%) of 31 patients (3 male and 2 female, mean age 14.71 ± 0.55 years; range 14 to 15.3 years) with cholelithiasis. Unconjugated hyperbilirubinaemia was observed in 3 patients during the diagnosis of cholelithiasis and in 2 at the time of recovery from cholecystectomy. The underlying symptom that preceded the diagnosis of cholelithiasis was intense abdominal pain, in 4 recurrent and in 1 acute, 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 a boy with hereditary elliptocytosis, with a transient choledocholithiasis and cholestasis 3 months before admission, other complications of cholelithiasis have not been recorded.

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

With exclusion of a boy with hereditary hereditary elliptocytosis, in which, together with an unconjugated hyperbilirubinemia (114 μmol/L), was found characteristic erythrocyte

apearance and significant reticulocytosis (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 5 patients. The number and appearance of their concretions are given in Table 1.

DISCUSSION

Thanks to ultrasound diagnostics, it is known today that cholelithiasis is not so rare in children, especially those at the final stage of childhood [16, 17, 19]. Its prevalence in this age has been reported to be 0.13% to 0.22% [16, 19]. The main risk factors for gallstones formation in childhood, in addition to the family predisposition, are the diseases accompanied by reduced solubility of the billiar content, such as hemolysis, obesity, anorexia nervosa, long-lasting total parenteral nutrition, hepatobiliary disorders, hypercholesterolemia, terminal ileum resection, cholecystitis, cystic fibrosis and other, 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 haemolysis and other diseases accompanied by high inclinations to bilary 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, intususception, 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 with gallbladder empyema and choledocholithiasis followed by ascending cholangitis, and pancreatitis [16, 17, 19, 21]. Also, a 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 laparoscopic approach is preferred one 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 that it is sufficient in that respect. Presence of GS in patients with cholelithiasis is encountered more frequently (16.13%) in comparison to cholelithiasis prevalence in the general population (2% to 13%) and shows that GS can be considered as a biliary lithogenic factor [1-5]. An additional argument in favor of this is the fact that out of 5 patients with cholelithiasis and GS 3 were boys and 2 girls, while this relationship in the group of those without GS was reversed (11 vs. 15). Also, in 4 out of 5 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 cholelithisis 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 six children with cholelithiasis, or more than twice as often in comparison with its average frequency in general population, but none of them as the only risk factor for the development of this disease. This finding suggests that the GS is a risk factor for the development of cholelithiasis, but not that it is sufficient in that sense.

Conflict of interest: None declared.

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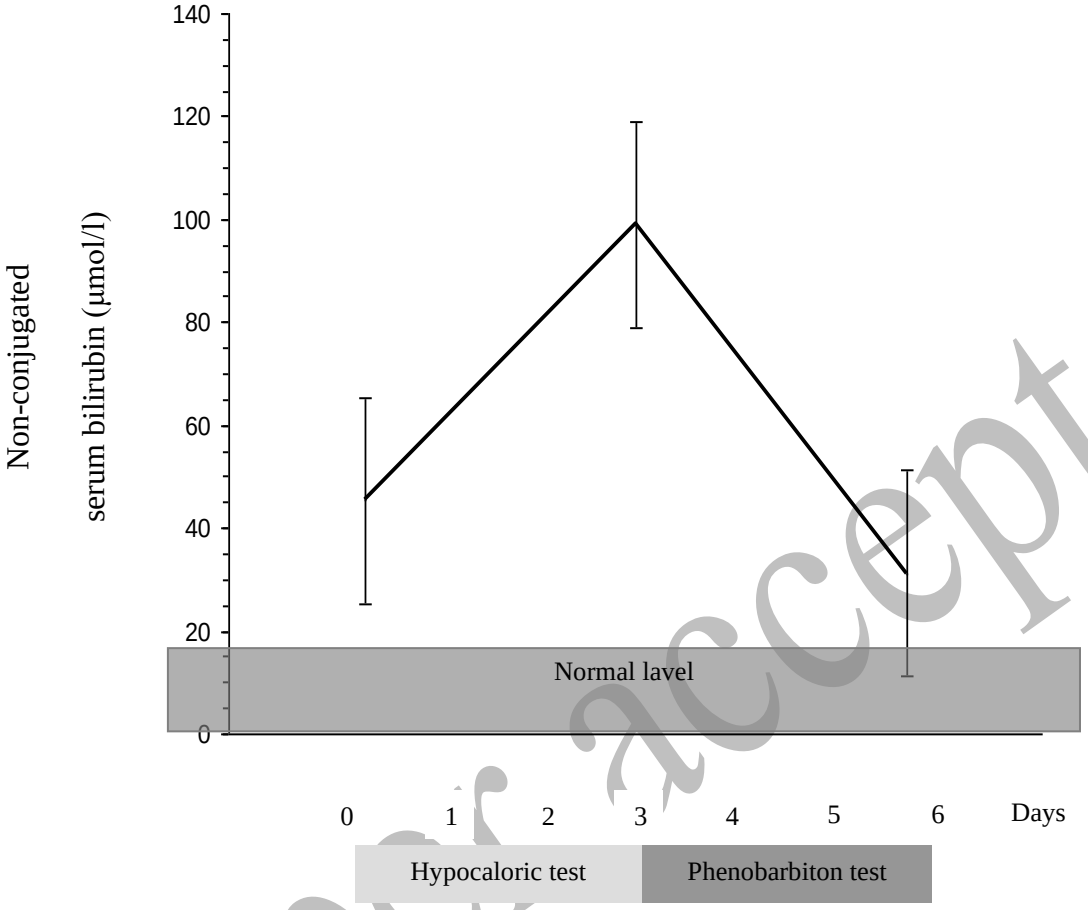

Figure 1. Serum non-conjugated bilirubin level after hypocaloric and phenobarbital test

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

