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ПРИКАЗ БОЛЕСНИКА / CASE REPORT
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Association of Hereditary Elliptocytosis and Gilbert's Syndrome as the Cause of Biliary Calculosis: Case Report

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SUMMARY

Introduction Biliary calculosis is rare in children. It occurs associated with different haemolytic and non-haemolytic disorders, which are sometimes also combined.

Case Outline A 15-year-old male was hospitalized due to biliary calculosis and non-conjugated hyperbilirubinemia. A mild non-conjugated hyperbilirubinemia, without anaemia and other symptoms of liver dysfunction, was registered at age 8 years, and 7 years later cholelithiasis with transitory choledocholithiasis. The finding of ellyptocytes in blood smear, which was also verified in mother, normal haemoglobin count and the absence of diseases followed by secondary dysmorphic erythrocytes of this type, indicated a clinically milder (compensated) hereditary ellyptocytosis, while more than a double increase of non-conjugated serum bilirubin fracture after a three-day hypocaloric diet (400 kcal per day) showed the concurrent presence of Gilbert's syndrome. In the laparascopically removed gallbladder a larger number of small pigmented calculi were disclosed.

Conclusion Gilbert's syndrome is an essential precipitating factor of biliary calculosis in patients with chronic haemolytic condition. Thus, in all cases of biliary calculosis and non-conjugated hyperbilirubinemia with absent clinical and laboratory parameters of liver disorders and anaemia, except in compensated haemolytic disease and Gilbert's syndrome as isolated disorders, a possibility of their association should be taken into consideration.

Keywords: biliary calculosis; hereditary elliptocytosis; Gilbert's syndrome

INTRODUCTION

Cholelithiasis is a rare disease in children (0.13-0.31%) [1, 2]. Although it can be seen already during the first postpartum months, and even intrauterally, the highest incidence has been recorded in the period during and after puberty [1, 2, 3]. Except for chronic haemolytic conditions, cystic fibrosis, resection of the terminal ileum, long-term total parenteral nutrition, anorexia nervosa, cholecystitis, anomalies of the ductus choledocus, chronic hepatitis and hypercholesterolemia, the essential factors for the development of cholelithiasis are familial predisposition, obesity, a rapid weight-loss, Gilbert's syndrome, as well as being of female gender at the onset of puberty [2-9]. Pigmented gallstones, particularly in younger children, are considerably more frequent than cholesterol or mixed ones, as well as multiple compared to solitary gallstones [3, 10, 11]. If they are impregnated with calcium salts, which is not rare in children, this can be verified, not only by ultrasound, but also by native x-ray imaging [2]. Although it can be asymptomatic and even reversible, both in children and adults cholelithiasis, except for biliary colic, often atypical and difficult to detect in the youngest age, can lead to serious complications, such as choledocholithiasis, cholangiohepatitis, pancreatitis, rupture of ductus choledocus, cholecystitis, cholecystic perforation and other [3, 6]. Therapy of choice of symptomatic cholelithiasis is cholecystectomy which is now most often performed by laparoscopy [3].

If considered pathogenetically, biliary calculosis presents a complex and mostly insufficiently clarified problem [3, 6]. Except for a too high concentration of cholesterol and/or bilirubin, desolubilization of biliary content is induced by the deficit or inadequate content of bile acid and phospholipids, a high bilirubin content in the form of bilirubin-monoglucuronide, hypotonia and gallbladder dyskinesia, obstruction of ductus cysticus and choledocus, the presence of inflammatory detritus or mucus and other factors [3, 12, 13]. In conditions where these factors occur associated the risk of biliary calculosis is significantly increased [14-20]. This can be particularly seen in disorders with a moderate lithogenic potential, such as a compensated clinical form of hereditary spherocytosis and Gilbert's syndrome, which is the case of the patient we are presenting.

CASE REPORT

A 15-year-old male referred due to cholelihtiasis and etiologically unexplained non-conjugated hyperbilirubinemia. The enclosed data

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showed that the first episode of non-conjugated hyperbilirubinemia (60 μmol/L), without either anaemia or clinical and laboratory findings of liver disease, was registered at age 8 years. During further period the patient was without any problems until 3 months before arrival to our hospital when he had an attack of intensive epigastric pain associated with nausea, vomiting, jaundice, acholic stools and darkened urine. Physical examination, except for icterus, mild dehydration, moderate epigastric sensitivness and spleen palpable 1 cm below the costal margin, revealed no other pathological changes. Laboratory blood analysis showed a high serum bilirubin level (total 423, conjugated 164 μmol/L), gamma-glutamyl transpeptidase (115 U/L), alkakaline phosphatase (1248 U/L) and transaminase (AST 229, ALT 435 U/L). Bile colour of urine was positive (urobilinogen ++, bilirubin +), while haemoglobin count was normal (150 g/L). In blood smear, except for reticulocytosis (3.51%) and a mild erythrocyte anisocytosis, no other abnormalities were found. Other laboratory findings, including the serological markers for hepatitis A, B and C, microscopic agglutination-lysis-test for leptospirosis, serum cholesterol level, ferritin, lactate dehydrogenase (LDH), ceruloplasmin, C-reactive protein (CRP), as well as Coombs test, haemoglobin electrophoresis, urine and blood amylase levels, and erythrocyte sedimentation, were all normal. Beside moderate splenomegaly and multiple cholelithiasis, abdominal ultrasound also showed a suspected calculus in the ductus choledocus, so that the child was sent to our hospital for further investigation.

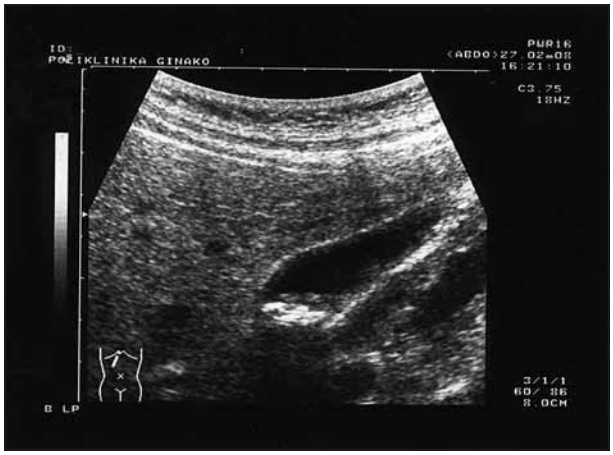


Figure 1. Abdominal ultrasound, multiple cholelithiasis

According to the data obtained by parents, he was the child of the second normal term pregnancy. During the first 3 months he had breast-feeding jaundice, but without anaemia neither at that period nor later. His growth and development were normal. Except for these findings, he had no other health problems.

On admission the child was without subjective problems, normally developed and nourished, with signs of full sexual maturity. Complete physical findings were normal, except for a mild icterus of the sclera, hard palate, frontal chest skin, as well as of the left costal arch of the palpable spleen. Abdominal ultrasound confirmed the presence of multiple cholelithiasis and moderate splenomegaly, but without the elements of choledolithiasis (Figure 1). Haemoglobin level was normal (147 g/L), while in the peripheral blood smear, except for high reticulocytosis (4.2%), there was a significant elliptocyte count (Figure 2). Erythocyte osmotic resistance was normal, and qualitative test to glucose-6-phosphate dehydrogenase deficiency was negative. Except for non-conjugated hyperbilirubinemia (114 μmol/L), other laboratory blood findings were within referent values, including conjugated bilirubin fraction, gamma-glutamyl transpeptidase, LDH, iron, ferritin, amylase and CRP. Also, erythrocyte count with mean corpuscular volume (MCV), white blood cell (WBC), WBC formula and platelet counts were normal.

Asymptomatic elliptocytosis was also confirmed in mother, while father's peripheral blood smear was normal. According to the data obtained by parents, the patient's older brother was healthy. Also, biliary calculosis was not registered in any of the second degree relatives.

The concurrent presence of Gilbert's syndrome was determined by a hypocaloric diet test (Graph 1). After a three-day hyporcaloric diet (400-kcal per day) non-conjugated bilirubinemia was increased 2.1-fold. Next, a three-day phenobarbiton test (2 mg/kg/day) was performed after which the non-conjugated serum bilirubin fracture decreased 2.76-fold.

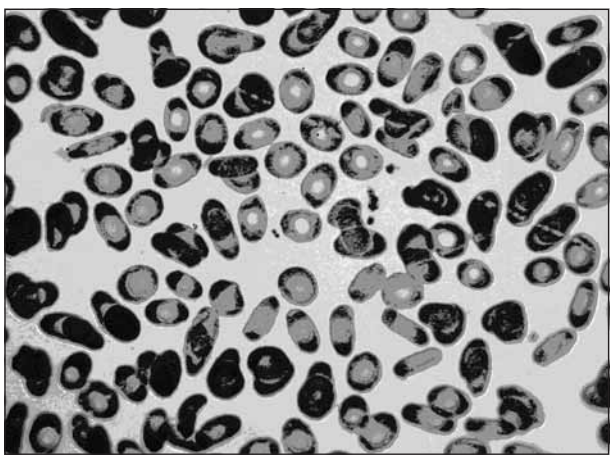
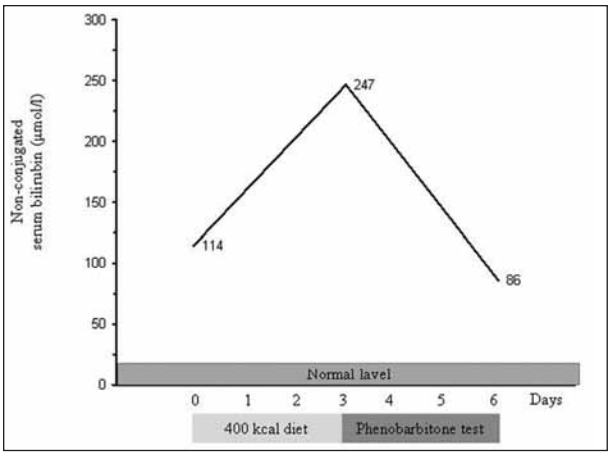


Figure 2. Peripheral blood smear of our patient. Visible normal erythrocyte and considerably increased elliptocyte counts.



Graph 1. Serum non-conjugated bilirubin level after hypocaloric and phenobarbitone test

Having in mind symptomatic cholelithiasis with transitory choledolithiasis, the child underwent laparoscopic cholecystectomy. The obtained stones were of pigmented character, multiple and of tiny size. The intervention and postoperative course were normal. Two years and 3 months after surgery the patient was without subjective problems. Except for a moderate splenomegaly, abdominal ultrasound was normal. Except for non-conjugated hyperbilirubinemia (143 μmol/L), other serum findings (conjugated bilirubin fraction, gamma-glutamyl transpeptidase, alkali phosphatase, cholesterol, AST, ALT, LDH, ferritin, amylase, LDH and CRP) were within referent values. In blood smear, beside elliptocytosis, there were 0.9% of reticulocytes, while haemoglobin, MCV and other parameters were normal.

DISCUSSION

The paper presents an adolescent with biliary calculosis caused by association of a compensated clinical form of hereditary elliptocytosis and Gilbert's syndrome. A mild asymptomatic non-conjugated hyperbilirubinemia, with normal haemoglobin level and other liver function findings were registered at age 8 years, while at age 15 years this association resulted in cholelithiasis with an episode of choledolithiasis.

Hereditary elliptocytosis represents a rare autosomal dominant membranopathy followed by elliptoid appearance and increased fragility of erythrocytes [21]. It occurs in 0.3-0.5 per 1000 newborns, and in about 90% of cases it passes asymptomatically [22, 23]. In about 95% of patients it develops due to gene mutation responsible for α- and β-spectrin expression, i.e. polypeptides which in tetrameric form compose the basis of cell cytoskeleton [23, 24]. Mutations bound to the protein 4.1 and glycoforin C are rare [21, 24]. If the mutation occurs on one allele only, the disease passes asymptomatically, while in cases when it is bilateral it features moderate or more severe haemolytic anaemia [21-24]. Although without genetic confirmation, based on the permanent finding of elliptocytes in blood smear, which was also verified in mother, as well as the fact that the child did not have either overmarked or prolonged neonatal jaundice, both at early and later age, it can be concluded that our patient had a heterozygotic, i.e. a milder clinical form of hereditary elliptocytosis [21, 23, 24]. In addition, the hereditary nature of the disorder is also supported by the absence of elements indicating other conditions that are followed by the presence of elliptocytes, such as the deficiency of iron, folic acid and vitamin B12 [21, 22, 23].

Contrary to hereditary elliptocytosis, Gilbert's syndrome is a frequent disorder. It occurs in 3-10% of general population featuring a benign and mild non-conjugated hyperbilirubinemia potentiated by hunger, fever and physical strain [25]. A low non-conjugated bilirubin clearance is primarily caused by autosomal recessive defect in the promoter region of the UGT1A1 gene (2q37) responsible for the expression of bilirubin uridine-diphosphate glucuronosyl transferase (UGPGT), a hepatic microsomal enzyme of key significance for bilirubin conjugation [26]. This results in decreased synthesis of bilirubin UDPGT which reduces to about 30% compared to the normal level that in turn leads to a lower capacity of bilirubin conjugation with glucuronic acid [27]. The additional pathogenetic significance are also a shorter life span of erythrocytes that is seen in about 50% of cases, as well as the defect in uptake and transport of non-conjugated bilirubin at the hepatocyte level [28]. In the expression of Gilbert's syndrome sex hormones, particularly androgens, play the major role, which explains its occurrence at the onset of puberty, as well as a 2-fold higher incidence in sexually mature males as compared to females [29, 30]. In addition, adult males are characterized by higher erythrocyte and muscular mass [29]. The presence of Gilbert's syndrome in our patient was confirmed by the occurrence of more than double increase of non-conjugated serum bilirubin fraction after a three-day hypocaloric diet test [28].

As well known, haemolytic conditions and Gilbert's syndrome present risk factors for the development of biliary calculosis, and also that it is probably more frequent in cases of their association [14-19]. The risk factor for the development of biliary calculosis in the first case is bilirubin hyperproduction and in the latter its elimination in the form of low water-soluble bilirubin monoglucuronide [14-19]. Although hereditary elliptocytosis and Gilbert's syndrome are congenital disorders, our patient did not develop biliary calculosis before the end of puberty, i.e. in the condition of marked androgenous suppression of bilirubin UDPGT, as well as additionally higher bilirubin production caused by the increased erythrocyte and muscular mass [29, 30]. As expected, in our patient the stones were composed of bilirubin.

Gilbert's syndrome contributes considerably to the development of biliary calculosis in patients with chronic haemolytic condition. This refers both to patients with decompensated, as well as those with compensated haemolytic disease. Therefore, if etiopathogenetically considering the cases of biliary calculosis and non-conjugated hyperbilirubinemia with absent clinical and laboratory parameters of liver disorders and anaemia, except in compensated haemolytic disease and Gilbert's syndrome as isolated disorders, the possibility of their association should be taken into consideration.

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Удруженост хередитарне елиптоцитозе и Жилберовог синдрома као узрок билијарне калкулозе: приказ болесника

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КРАТАК САДРЖАЈ

Увод Билијарна калкулоза је ретка код деце. Јавља се у склопу различитих хемолизних и нехемолизних поремећаја, некада и комбинованих.

Приказ болесника Петнаестогодишњи дечак је примљен на болничко лечење због билијарне калкулозе и неконјуговане хипербилирубинемије. Блага асимптоматска неконјугована хипербилирубинемија, без анемије и других показатеља дисфункције јетре, дијагностикована му је у осмој години, а седам година касније холелитијаза с пролазном холедохолитијазом. Налаз елиптоцита у размазу крви, који је потврђен и код мајке, нормалан ниво хемоглобина и изостанак обољења праћених секундарном дисморфијом еритроцита овог типа указивали су на клинички блажу (компензовану) хередитарну елиптоцитозу, а више на двоструко повећање неконјуговане фракције серумског билирубина након тродневног хипокалоријског теста (400 *kcal* дневно), на истовремено постојање Жилберовог синдрома. У жучној кесици, одстрањеној лапароскопски, нађен је већи број малих пигментних калкулуса.

Закључак Жилберов синдром је важан пратећи чинилац билијарне калкулозе код болесника с хроничним хемолизним стањем. Отуда у свим случајевима билијарне калкулозе и неконјуговане хипербилирубинемије, при изостанку клиничко-лабораторијских показатеља оштећења јетре и анемије, сем на компензовано хемолизно обољење и Жилберов синдром као изоловане поремећаје, треба у обзир узети и могућност њихове удружене појаве.

Кључне речи: билијарна калкулоза; хередитарна елиптоцитоза; Жилберов синдром

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