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Hereditary Hyperbilirubinemias

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SUMMARY
Inherited disorders of bilirubin metabolism involve four autosomal recessive syndromes: Gilbert, Crigler-Najjar, Dubin-Johnson and Rotor, among which the first two are characterized by unconjugated and the second two by conjugated hyperbilirubinemia. Gilbert syndrome occurs in 2%-10% of general population, while others are rare. Except for Crigler-Najjar syndrome, hereditary hyperbilirubinemias belong to benign disorders and thus no treatment is required.
Keywords: hereditary hyperbilirubinemias; UGT1A1 gene; uridine diphosphate glucuronosyltransferase 1A1; MRP2 gene

INTRODUCTION

Hereditary hyperbilirubinemias represent specific disorders of bilirubin metabolism independently of structural liver disease or hemolytic condition [1-4]. They involve four syndromes: Gilbert, Crigler-Najjar, Dubin-Johnson i Rotor, among which the first two are characterized by unconjugated hyperbilirubinemia and the second two by conjugated hyperbilirubinemia [1-5]. Except for Gilbert syndrome, which occurs in 2%-10% of general population, other hereditary syndromes are exceptionally rare [1-3, 6].

GILBERT SYNDROME

Gilbert syndrome, first described by Augustine Gilbert and Pierre Lereboullet in 1901, represents a benign autosomal recessive disorder followed by mild and varying unconjugated hyperbilirubinemia caused by the deficit of bilirubin uridine diphosphate glucuronosyltransferase (UGT1A1), a microsomal enzyme hepatocyte which is of crucial importance in bilirubin conjugation [2, 4, 7]. UGT1A1 gene located on the chromosome 2q37.1 is responsible for the expression of this enzyme [1, 8]. A normal promoter region of the UGT1A1 gene implies the presence of six thymine-adenine (TA) repeats /A(TA)6TAA/, as well as the absence of changes in its coding region [8, 9]. Contrarily, in persons with Gilbert syndrome there is an elongation or deletion of TA sequences in the promoter region and/or structural changes in the coding region of the UGT1A1 gene [4, 8, 9]. The basis of disorder in people of the European origin with Gilbert syndrome is formed by the homozygous A(TA)7TAA mutation in the promoter of the UGT1A1 gene [8, 9]. In population groups by origin outside Europe, beside A(TA)7TAA, there are also other polymorphisms of the promoter of the UGT1A1 gene /A(TA)5TAA and A(TA)8TAA/ or their combination, while in the Asians the mutations in the coding part of this gene are far more frequent [2, 4]. In addition, associated mutations in both parts of the UGT1A1 gene are also possible [10]. The result of this genetic defect is decreased synthesis of the UGT1A1 by 70%-80%, and consequently lowered capacity of bilirubin conjugation [1, 11, 12]. Beside unconjugated hyperbilirubinemia, the UGT1A1 deficit is followed by the excess of bilirubin monoglucuronide to bilirubin diglucuronide in bile, which makes the persons with Gilbert syndrome more prone to bilirubin (pigment) cholelithiasis [13]. The risk of biliary calculosis is especially marked in the association of Gilbert syndrome with some hemolytic diseases, such as thalassemia, congenital spherocytosis, glucose-6-phosphate dehydrogenase deficiency, congenital elliptocytosis, and other [14]. An additional pathogenetic significance in the occurrence of hyperbilirubinemia is a shorter erythrocyte lifespan that is seen in about 40% of cases, as well as the defect of the uptake and transport of the unconjugated bilirubin at the hepatocyte level [5]. Sex hormones, particularly androgens, also essentially participate in the expression of Gilbert syndrome, which explains its rare occurrence before puberty, as well as 2-7-fold higher incidence in male adolescents and adults [2, 6, 15]. More frequent clinical expression of Gilbert syndrome in males as related to females is additionally contributed by the sex-matched erythrocyte count and muscle mass [6]. However, up-to-date studies show that Gilbert genotype can be also expressed very early, as seen in newborns and younger infants with the congenital hypertrophic pyloric stenosis, annular pancreas, atresia of the small intestine, hypogalactia and other conditions followed by calorie deficit, as well as those with breastfeeding jaundice [6, 12, 16, 17, 18]. Besides negative energy balance in the first group of disorders and the inhibitory effect of maternal milk in breastfeeding jaundice, the additional factors of

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early expression in Gilbert syndrome include physiological immaturity of the liver and postnatal reduction of the fetal hemoglobin level [19]. In addition, Gilbert syndromes can be also precipitated by some drugs with suppressive effect on the UGT1A1, such as tyrosine-kinase inhibitors (sorafenib, nilotinib, pazopanib), virostatics indinavir and atazanavir, antiallergic tranilast and biological immunosuppressor tocilizumab, while phenobarbitone and glucocorticoids have a reverse effect [1, 2, 15, 20-25].

The level of serum bilirubin in Gilbert syndrome, without associated disorders, mostly varies from 30-90 μmol/l and rarely over [4, 11, 15]. Hyperbilirubinemia is potentiated by hunger, physical strain, febrility, dehydration and chromosome fluctuations within the menstrual cycle [2, 4, 15, 26]. Except for slightly higher risk of biliary calculosis and poorer irinotecan tolerance, other complications of this hereditary defect have not been recorded up-to-now [6, 9, 13, 27]. Due to antioxidant properties of the unconjugated bilirubin, some studies indicate that Gilbert syndrome could represent a positive mutation [1, 28-32].

Beside exclusion of hemolysis and liver disease as the cause of unconjugated hyperbilirubinemia, the basis of the clinical diagnosis of Gilbert syndrome lies in the significant increase of unconjugated bilirubinemia (more than twice higher as compared to initial rate) after 2-3 days on hypercaloric diet (≤400 kcal/24 hrs) as well as its considerable decrease or normalization 1- 3 days after phenobarbitone testing (1 mg/kg/24 hrs) [2, 6, 11, 15]. The method of choice in the diagnostics of Gilbert syndrome that has been increasingly used until these days is a genetic verification of disorder [33]. Genetic confirmation of Gilbert syndrome gains a particular expression by the explanation of unconjugated hyperbilirubinemia in patients with transplanted liver or on drug therapy with the inhibitory effect on the UGT1A1, as well as in its over-elevated findings during the neonatal period, and in different hemolytic and hepatic diseases [20-24, 34-41]. Liver biopsy performed to confirm low activity of the UGT1A1 and normal histological aspect of the liver is unnecessary [1, 11]. In the diagnostics of Gilbert syndrome, some other tests are also used, such as rifampicin, nicotine and other [2, 11].

Gilbert syndrome does not require treatment [2, 4, 12, 15]. In cases where subicterus presents a cosmetic problem, phenobarbitone can be administered in doses of 50-150 mg at night.

CRIGLER-NAJJAR SYNDROME

Crigler-Najjar syndrome involves two exceptionally rare (less than $1/10^6$ live births) autosomal recessive disorders – types I and II, which differ in the degree of UGT1A1 deficit, and accordingly in the clinical expression as well [2-5, 42, 43]. In both types, mutations are present in the coding region of the UGT1A1 gene; in the type I in exons 2-5, resulting in a truncated non-functional enzyme, or in exon 1, resulting in a complete loss of substrate recognition for bilirubin, while the genetic defect in the type II is somewhat subtler and is followed by decreased affinity of the enzyme for its substrate [4, 43].

Crigler-Najjar syndrome type I is characterized by the complete absence of the UGT1A1 activity and severe unconjugated hyperbilirubinemia occurring in the first 3 days of life [3]. If unrecognized on time and inadequately treated, it becomes complicated by kernicterus and ends lethally [11]. Prevention of kernicterus requires repeated exsanguinotransfusions, plasmapheresis, phototherapy and cholestyramine application [2-5, 11]. Phenobarbitone is ineffective [43, 44]. The only effective method of therapy is liver transplantation [2-4, 43, 44].

Crigler-Najjar syndrome type II occurs as the result of partial deficit of the UGT1A1 (<10% of normal) [1]. Hyperbilirubinemia is much milder as compared to the type I, and is rarely complicated by kernicterus [1, 3]. Beside the measures indicated for the type I during the first days after birth, administration of phenobarbitone can be used, too [1-4, 11].

DUBIN-JOHNSON SYNDROME AND ROTOR SYNDROME

Dubin-Johnson syndrome and Rotor syndrome belong to conjugated hereditary hyperbilirubinemias. They are the result of autosomal recessive defect of the hepatocyte excretion of conjugated bilirubin and some other organic anions [2-4, 45]. Mutation of the MRP2 gene, which encodes the bile canalicular membrane transporter for anion conjugates, underlies Dubin-Johnson syndrome, while mutation responsible for Rotor syndrome has not been identified [1, 46-49]. Dubin-Johnson syndrome and Rotor syndrome represent rare disorders, which are usually detected during adolescence or early adulthood but can occur as early as the second year of life [3]. They are characterized by mild asymptomatic and changeable conjugated hyperbilirubinemia in the absence of other laboratory parameters of cholestasis [4, 11]. Bilirubin concentration in serum ranges most often from 35-85 μmol/l, of which 60% forms the conjugated fraction [11]. Hyperbilirubinemia is potentiated by intercurrent infections, surgical interventions, gravidity, oral contraceptives and alcohol [3, 11]. Contrary to Rotor syndrome, Dubin-Johnson syndrome is characterized by negative cholecystography, normal coproporphyrinuria with over-elevated presence of coproporphyrin I (>75%) and histological finding of dark pigmentation in hepatocytes [2, 3, 4]. Conjugated hereditary hyperbilirubinemias are benign disorders and do not require any treatment [2-4, 45, 50].

CONCLUSION

Hereditary hyperbilirubinemias involve isolated autosomal recessive disorders of hepatocyte function. Except for Crigler-Najjar syndrome, these are benign disorders not requiring any treatment. Contrary to Gilbert syndrome, which has the frequency of even up to 10%, other hereditary hyperbilirubinemias are very rare. Therefore, this syndrome represents a frequent diagnostic problem, sometimes also a very complicated one, as in cases when it occurs in the combination with some liver diseases or hemolytic condition.

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Хередитарне хипербилирубинемије

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КРАТАК САДРЖАЈ

Урођене поремећаје метаболизма билирубина чине четири аутозомно рецесивна синдрома: Жилберов (*Gilbert*), Криглер–Најаров (*Crigler-Najjar*), Дабин–Џонсонов (*Dubin-Johnson*) и Роторов (*Rotor*), при чему прва два обележава неконјугована, а друга два конјугована хипербилирубинемија. Жилберов синдром се јавља код 2–10% припадника опште популације, док су остали изузетно ретки. Изузимајући Криглер–Најаров синдром, хередитарне хипербилирубинемије припадају групи бенигних поремећаја, те не изискују лечење.

Кључне речи: хередитарне хипербилирубинемије; ген *UGT1A1*; уридиндифосфат-глукуронозилтрансфераза 1A1; ген *MRP2*

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