ANNALES
UNIVERSITATIS MARIAE CURIE-SKŁODOWSKA
LUBLIN – POLONIA
VOL. LIX, N 1, 84 SECTIO D 2004

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Congenital nonhemolytic hyperbilirubinemias

Congenital nonhemolytic hyperbilirubinemias (CNH) are non-rare pathology of liver. They occur most often in children, but are common in adults too. A common feature of congenital nonhemolytic hyperbilirubinemias is an abnormal serum bilirubin level without other abnormalities in routine liver functional tests. Hereditary genetics defect of enzymes taking part in metabolism of bilirubin is the cause of CNH.

All CNH are divided into two groups: I. CNH with unconjugated hyperbilirubinemia; II. CNH with conjugated hyperbilirubinemia. They are all characterised by periodical elevation of serum bilirubin level. Patients do not present any clinical syndromes. Physical examination findings are generally normal. No abnormalities of gallbladder and biliary tract in ultrasound and computed tomography are observed. Elevated serum bilirubin level occurs usually after physical efforts, alcohol use, during viral infection, or menstruation in women. Liver histology on light microscopy is normal. Diagnosis of CNH is based on clinical syndromes and liver histology on electron microscopy.

There are three well-defined genetically transmitted congenital nonhemolytic unconjugated hyperbilirubinemias: Crigler-Najjar syndrome (type I and type II), and Gilbert syndrome. Crigler-Najjar syndrome is an autosomal recessive disease and is characterised by the complete absence of glucuronyltransferase activity (type I), or partial deficiency in glucuronyltransferase activity (type II) (2, 3, 5, 6). In Crigler-Najjar syndrome type I disease appears soon after birth and about 40% of patients die in the neonatal period from kernicterus. This kind of disorders is pediatrists' domain. Crigler-Najjar syndrome type II occurs in adults patients. The plasma bilirubin level is usually less than 20 mg/dL and the prognosis is excellent in the great majority of patients. Jaundice usually manifests itself in the first year of life, but may not present until early adulthood. Liver histology on light microscopy and results of other routine liver tests (like aminotransferases, alkaline phosphatase, gamma--glutamylo-transpeptydase activities and serum albumin level) are normal. Ultrasonography and tomography computed of liver and biliary tree do not present any abnormalities too (5, 6).

Gilbert syndrome is a relatively common disorder and the most common among CNH. It occurs in up to 7% of the population and has a male preponderance. Gilbert syndrome is caused by mutation in the UDP-glucuronosyltransferase gene. Mutations in the same gene cause the Crigler-Najjar syndrome, which is a more severe and dangerous form of hyperbilirubinemia such as it was described above. The gene for Gilbert syndrome has been mapped to chromosome 2. The syndrome is inherited in an autosomal dominant manner. If someone has Gilbert syndrome, the chance of transmitting the Gilbert gene to each of their children is 50% and each child who receives the gene has Gilbert syndrome.

The syndrome is characterised by a mild unconjugated hyperbilirubinemia (1–6 mg/dL) in the absence of overt hemolysis or any histologic or biochemical evidence of liver disease. The elevated serum bilirubin level can sometimes cause mild yellowing of the eyes and is the only one symptom of disease. The condition may be detected serendipitously (purely by accident) in the course of routine

blood screening. The hyperbilirubinemia is usually recognised during the second or third decades of life. This often occurs in the setting of an acute febrile episode or prolonged fasting, both of which result in transient increases in plasma bilirubin concentration. There is considerable fluctuation in serum bilirubin concentration in individual patients. In fact the serum bilirubin value may remain in the normal range for extended periods of time in one third of the patients. Nonspecific symptoms such as fatigue, malaise and abdominal discomfort may be event, although they do not correlate with the serum bilirubin concentration. Thus, the major goal of clinician is to distinguish this benign disorder from more serious causes of jaundice.

The diagnosis of Gilbert syndrome is established by observing a persistent, unconjugated hyperbilirubinemia in the absence of increased bilirubin production from hemolysis and the presence of repeatedly normal results of routine liver function tests. Liver histology on light microscopy is normal. But on electron microscopy hypertrophy of the endoplasmic reticulum of hepatocyte in 50% of patients can be observed. Gilbert syndrome is no need for treatment, and the prognosis is excellent (2, 5, 6).

The disorders proceeding with elevated conjugated bilirubin concentration in the serum include two syndromes: Dubin-Johnson syndrome and Rotor syndrome. Dubin-Johnson syndrome is a type hereditary hyperbilirubinemia that was described independently in 1954 by D u b i n and J o h n s o n and by S p r i n z and N e l s o n (4).

Both of conjugated hyperbilirubinemias have a relatively benign course, but it is important to establish the diagnosis to spare patients from undergoing multiple unnecessary procedures and to exclude other serious causes of hyperbilirubinemia. They are characterised by chronic or intermittent nonpruritic conjugated hyperbilirubinemia with results of other liver function tests including liver enzymes, serum albumin, hematological studies (e.g. complete blood count, reticulocyte count) being normal and autosomal recessive inheredităńce. The cause of these syndromes is defect in the cojugated bilirubin excretion from hepatocyte into bile. Hyperbilirubinemia is characterized as mild to moderate, with bilirubin levels usually between 2–5 mg/dL.

Dubin-Johnson syndrome is a rare disorder. It has been described in all nationalities, ethnic groups. Prevalence reported is the highest among Iranian Jews (1 : 300). This group may have an associated deficiency in clotting factor VII that is not observed in other populations. Dubin-Johnson is caused by a mutation in the gene responsible for the human canalicular multispecific organic anion transporter (cMOAT) protein. This protein mediates ATP-dependent transport of certain organic anions across the canalicular membrane of the hepatocyte. In Dubin-Jonhson patients brown-black pigmentation of the liver is observed. Despite this the liver is otherwise histologically normal on light microscopy. A defect in the cMOAT protein results in impaired hepatobiliary transport of non-bile salt organic anions and is thought to be responsible for the conjugated hyperbilirubinemia and for the accumulation of hepatocellular pigment. This pigment can cause the liver to appear dark or almost black.

Most of the patients are asymptomatic, some can present hepatosplenomegaly. Subclinical cases can become evident during pregnancy or following the initiation of oral contraceptives. The diagnosis of Dubin-Johnson syndrome can be confirmed by demonstrating an increase in the ratio of urinary coproporphyrin I to coproporphyrin III or elevated urinary coproporphyrin I only. Coproporphyrins are byproducts of heme biosynthesis. Normally, coproporphyrin I is preferentially excreted in bile, whereas coproporphyrin III is preferentially excreted in urine. While total urinary coproporphryrin levels can be increased in patients with various hepatobiliary disorders, only patients with Dubin-Johnson syndrome have an increased ratio of coproporphyrin I to coproporphyrin III in the urine. This finding is therefore a pathognomonic feature of this Dubin-Johnson syndrome. Results of laboratory tests of liver function are usually normal. Only prothrombin time can be prolonged in Iranian Jewish patients associated with factor VII deficiency. Diagnosis can be confirmed by the test for urinary coproporphyrins. A liver biopsy is not necessary for diagnosis. Patient may be noted to have dark liver

during routine surgeries (e.g. cholecystectomy), prompting biopsy. When the biopsy is performed histologic findings include: accumulation of coarsely granular pigment, most pronounced in the centrolobular zones. No associated scarring, hepatocellular necrosis, or distortion of zonal architecture is present. The amount of pigment can vary among patients and within an individual. Certain diseases (e.g. viral hepatitis) can cause the pigment to disappear. The pigment reaccumulates slowly once the acute process is resolved. Deposition of melaninlike pigment occurs in the livers of patients with Dubin-Johnson syndrome but not in Rotor syndrome, which helps to differentiate the two diseases. As in Dubin-Johnson syndrome, patients with Rotor syndrome are asymptomatic (1, 7, 8, 9).

Because CNH in adults are benign disorders and the prognosis is excellent, patients do not require any specific therapy. In the past, patients were treated with phenobarbital, which was primarily used to reduce serum bilirubin levels. This is no longer recommended. At present, CNH are treated as a cosmetic defects and no therapy is applied. But it is important to take the differential diagnosis. Disease categories to consider include the following: hepatocellular disease – acute or chronic viral hepatitis, autoimmune hepatitis, hepatitis caused by drugs or alcohol; infiltrative liver diseases – metastatic or primary cancer, pyogenic abscesses; extrahepatic causes – gallstone disease, cholangiocarcinoma, pancreatic head tumor (1). Once the diagnosis of congenital nonhemolytic hyperbilirubinemia is confirmed, patients should be informed of the disease process and its benign nature to prevent needless workup in the future.

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SUMMARY

Congenital nonhemolytic hyperbilirubinemias (CNH) are quite rare pathology of liver. They occur most often in children, but are common in adults too. A common feature of congenital nonhemolytic hyperbilirubinemias is an abnormal serum bilirubin level without other abnormalities in routine liver functional tests. Liver histology on light microscopy is normal. Hereditary genetics defect of enzymes taking part in metabolism of bilirubin is the cause of CNH. They are divided into two groups: with unconjugated hyperbilirubinemia (Crigler-Najjar syndrome, Gilbert syndrome) and conjugated hyperbilirubinemia (Dubin-Johnson syndrome and Rotor syndrome). Because CNH in adults are benign

disorders and the prognosis is excellent, patients do not require any specific therapy. Is important to take the differential diagnosis. Once the diagnosis of congenital nonhemolytic hyperbilirubinemia is confirmed, patients should be informed of the disease process and its benign nature to prevent needless work-up in the future. In present, CNH are treated as cosmetic defects and no therapy is applied.

Wrodzone niehemolityczne hyperbilirubinemie

Wrodzone niehemolityczne hyperbilirubinemie (WNH) są stosunkowo rzadką patologią wątroby. Częściej występują u dzieci, niemniej jednak są obecne w klinice osób dorosłych. Charakteryzują się okresowymi niewielkimi zwyżkami poziomu bilirubiny bez towarzyszących objawów klinicznych. Nie stwierdza się nieprawidłowości w badaniach biochemicznych ani badaniach obrazujących wątrobę i układ żółciowy. Obraz histopatologiczny wątroby w mikroskopie świetlnym jest prawidłowy. Przyczyną ich są zaburzenia związane z defektem enzymów uczestniczących w przemianie bilirubiny. Obejmują dwie grupy zespołów chorobowych: I przebiegające z podwyższonym poziomem bilirubiny nieskoniugowanej (z kwasem glikuronowym) – zepół Crigler-Najjara i zespół Gilberta, oraz II przebiegające z podwyższonym poziomem bilirubiny skoniugowanej – zespół Dubin-Johnsona i zespół Rotora. Ze względu na łagodny przebieg i brak niepożądanych następstw nie wymagają one jakiegokolwiek postępowania terapeutycznego. Istotne jest przeprowadzenie diagnostyki różnicowej i wykluczenie innych patologii wątroby i dróg żółciowych. Pacjenta z rozpoznaną wrodzoną niehemolityczną hyperbilirubinemią należy poinformować o łagodnym przebiegu schorzenia i braku konieczności stosowania leczenia. Obecnie zespoły te są traktowane jako defekty kosmetyczne.