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Genetic disorders of bilirubin metabolism

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Bilirubin (BR) is a yellow pigment formed by enzymatic cleavage of haem (ferroprotoporphyrin) of haemoglobin and other haem-containing proteins. Its chemical structure is an open-chain tetrapyrrole exhibiting extensive internal hydrogen bonding which engenders a highly involuted conformation rendering the pigment totally insoluble in water. In the plasma, BR is firmly bound to albumin which carries it to the liver and transfers it to hepatocytes. In the liver cells' endoplasmic reticulum, BR is esterified with one or two molecules of glucuronic acid, a reaction catalyzed by the microsomal enzyme BR UDP-glucuronosyl transferase. This so-called conjugation breaks the pigment's internal hydrogen bonding which renders the glucuronide-conjugated BR watersoluble and excretable in bile (and urine).

Bilirubin in plasma is easily quantitated colorimetrically using van den Bergh's diazo reagent which reacts directly with conjugated pigment because both are w ater-soluble (direct diazo reaction). On the other hand, unconjugated, involute d BR is non-reactive unless ethanol is added to the reaction mixture (indirect diazo reaction). Meansuring both pigment types is clinically useful because it permits to distinguish cholestatic jaundice from those forms of hyperbilirubinemi a in which conjugation of BR with glucuronic acid is impaired. In healthy individuals, total plasma BR concentration ranges up to 1.2 mg/dL, of which approximately one-third is direct-reacting pigment.

In Gilbert's syndrome, unconjugated indirect-reacting plasma bilirubin is raised to levels raging from 1.3 to 5 mg/dL. There is no evidence of overt hemolysis and individuals with this clinical anomaly enjoy excellent health and have an uneventful prognosis. Plasma bilirubin concentrations commonly exhibit spontaneous fluctuations, at times falling to levels below the upper limit of normal. Fasting, exercise, stress, intercurrent illness, menstruation or large blood extravasations tend to raise unconjugated pigment levels two to four times above normal, whereas certain drugs, such as phenobarbital, reduce it. Although long in doubt, the pathogenesis of Gilbert's syndrome now has been shown to consist of a number of different genomic mutations which result in reduced expression or in functional defects of the BR-conjugating enzyme UDP-glucuronosyl transferase in the liver. Such genetic anomalies have been detected in various ethnically different population groups with surprising frequency, far in excess of the incidence of clinically recognizable Gilbert's syndrome which generally ranges from five to twelve percent. In individuals exhibiting normal plasma BR concentration despite the presence of a genetic mutation in the hepatic BR UDP-glucuronosyl transferase gene, deliberate fasting or stress frequently raises the plasma bile pigment level transiently above normal. Crigle-Najjar disease type Ⅰ and Ⅱ are rare forms of severe unconjugated hyperbilirubinemia caused by inherited defects of hepatic BR UDP-glucuronosyl transferase. In type Ⅰ, no BR conjugating activity is detectable in the live nor is BR glucuronide present in bile. Plasma unconjugated BR levels commonly range from 25 to 40 mg/dL, and patients uniformly die from BR encephalopathy in childhood or adolescence. Liver transplantation, performed before the appearance of neurological lesions, is the treatment of choice. Several different structural mutations of the gene encoding BR UDP-glucuronosyl transferase have been reported, for which afflicted patients are homozygous. Blood-related family members with "Gilbert's syndrome" have been shown to be heterozygous for one of these mutations. Type Ⅱ is a less severe form of the disease, with unconjugated hyperbilirubinemia intermediate between type Ⅰ and Gilbert's syndrome. Residual BR UDP-glucuronosyl transferase activity is present in the liver, and bile contains some conjugated BR, most of it being BR monoglucuronide. BR encephalopathy is rare in Type Ⅱ disease and induction of hepatic BR UDP-glucuronosyl transferase with drugs, such as phenobarbital, substantially reduces the plasma BR level. Structural mutations of the gene encoding the BR conjugating enzyme have been described, but the mode of inheritance remains unclear. Type Ⅱ patients do not require treatment and their long-term prognosis is good. Low doses of phenobarbital or comparable enzyme inducers may be used for cosmetic reasons.

In Dubin-Johnson and Rotor's syndromes, the genetic defects cause impaired hepatic excretion of BR glucuronides, resulting in their accumulation in plasma and excretion in urine. Levels of plasma BR usually range from 2 to 6 mg/dL but are fluctuating and occasionally may rise to 20 mg/dL; at least half of the bile pigment is BR glucuronide. Patients with these benign conditions usually are asymptomatic, and except for mild icterus and bilirubinuria, abnormal physical findings are lacking and conventional liver

function tests yield normal results. Pruritus is absent as plasma bile acid concentrations are normal. The mode of inheritance in both conditions is autosomal recessive but the molecular mechanisms of the hepatic excretory defects are unknown.

In Dubin-Johnson syndrome, hepatic transport of organic anions, such as BR, sulfobromophthalein (BSP) and indocyanine green is severely impaired. After intravenous bolus injection, their initial plasma disappearance rate is normal, but after a delay, conjugated BR and BSP are reappearing in the circulation, reflecting hepatic regurgitation. The liver exhibits normal histology except for a unique black color caused by dark melanin-ike pigment stored in the hepatocytes' lysosomes. Urinary excretion of coproporphyrin is quantitatively normal but as compared to controls, the ratio of coproporphyrin isomers Ⅰ and Ⅲ is revers ed which is characteristic for Dubin-Johnson syndrome and allows identification of heterozygous carriers of the trait. The mechanism underlying this unique pat tern of coproporphyrin excretion is unknown.

Rotor's syndrome resembles Dubin-Johnson syndrome in that patients are asymptomatic, abnormal physical findings are lacking except for mild icterus, and with the exception of hyperbilirubinemia, conventional laboratory tests yield normal results. The liver exhibits normal histology without pigmentation. Total urinary coproporphyrin excretion is substantially increased with a modest excess of isomer Ⅰ, as is seen commonly in other hepatobiliary disorders. Kinetics of the transport of organic anions in the liver differ from those of Dubin-Johnson syndrome in that after bolus injection, their removal from plasma is greatly delayed. However, their overall hepatic transport is only moderately impaired though calculated hepatic storage capacity is very low. In individuals heterozygous for the trait, values for urinary coproporphyrin and hepatic anion transport are intermediate between those of homozygous patients and healthy controls.

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