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INHERITED HYPERBILIRUBINEMIAS: STATE-OF-THE-ART

Summary
In the article the current views on the etiology, pathogenesis, diagnosis and treatment of inherited hyperbilirubinemias (Gilbert, Dubin-Johnson, Rotor and Crigler-Najjar syndromes) are discussed.

Keywords
Inherited hyperbilirubinemias, diagnosis, treatment.

Inherited hyperbilirubinemias, also called hereditary pigmented hepatoses and benign (functional) hyperbilirubinemias, are a group of diseases that progress in the setting of genetically caused enzymopathies, are characterized by metabolic and bilirubin disorders and manifest in chronic or intermittent jaundice without major changes in the structure and function of liver and clinical signs of higher levels of hemolysis and cholestasis [1, 2, 5, 8].

Depending on the particular bilirubin disorder there are some types of inherited hyperbilirubinemias: Gilbert, Dubin-Johnson, Rotor and Crigler-Najjar syndromes. Pigment hepatoses include posthepatitis benign hyperbilirubinemia resulting from acute viral hepatitis being also hepaticly determinated [6, 9, 11, 14].

Classification. In ICD-10 inherited hyperbilirubinemias are presented under section E 80 – Disorders of porphyrin and bilirubin metabolism:

E 80.4 – Gilbert syndrome;

E 80.5 – Crigler-Najjar syndrome;

E 80.6 – Other disorders of bilirubin metabolism.

Gilbert syndrome (GS) is known by several names such as «intermittent juvenile icterus», «constitutional hyperbilirubinemia», «familial non-hemolytic jaundice», «benign hyperbilirubinemia» and is characterized by increased blood levels of indirect bilirubin [3, 12].

Etiology. The disease is hereditary in all cases and is transmitted by autosomal dominant type, caused by a defect in the area of S gene controlling the activity of glucuronosyltransferase. Factors contributing to its incidence are hypothermia, exhaustion, medication intake (f.e. male fern extract), intercurrent infection. The disease in 30-35% of patients progresses as a result of acute viral hepatitis and is also genetically caused – posthepatitis benign hyperbilirubinemia or Gilbert posthepatitis type [12].

Pathogenesis. GS jaundice is caused by both disorder of the uptake of free bilirubin from plasma cells of the liver and intracellular transport of pigment in hepatocytes, that was proved by examinations of bilirubin 14C; suppressed process of conjugation of bilirubin with glucuronic acid results into accumulation of free bilirubin fraction in blood.

Pathological anatomy. Laparoscopy does not demonstrate microscopic changes in liver. Histologic and histochemical studies of liver biopsy samples in some patients show no changes while in the other ones they are nonspecific: accretion of pigment in hepatocytes, obesity, nuclear glycogenesis, activation of reticuloendoteliocyti stellatum, and protein dystrophy of liver cells and fibrosis of portal areas in some cases; in this regard accretion of pigment near biliary pole of hepatocytes, mainly in central parts of slices, often combined with the activation of reticuloendoteliocyti stellatum.

The first **clinical signs** of GS are usually observed in young, adolescent or even older childhood age and very rarely in the later years of life or in early childhood. In 90% the syndrome manifests itself at the age from 11 to 30 years. The disease occurs mainly in men (75-90%). Mental labor employees prevail among adult patients.

The main symptom of the disease is jaundice in varying degrees of its intensity, but usually just apparent one. There is often scleral icterus, while icteritiousness of the sclera and skin may be observed more rarely. Mucous membranes do not manifest icteritiousness. The intensity of jaundice is unstable. It may significantly regress or even disappear for a long period, or progress after hypothermia, fatigue (mental and physical), intercurrent diseases, alcohol consumption [7, 14].

Approximately 25% of patients express no complaints except for jaundice. Other express mainly complaints of dyspeptic nature, epigastric pain in the right subcostal plane, especially during exacerbations. Dyspeptic disorders manifest themselves by nausea, belching, acid indigestion, bitterness in the mouth etc. Astheno-vegetative disorders are often observed as well.

A minor hepatomegalia occurs in about 30% of patients; it is non-sclerosal and painless. The spleen is normally not palpable.

Diagnosis. Majority of patients experience an increase in free bilirubin level, while conjugated bilirubin is either absent or increased to a much lesser extent than the free one. Even during exacerbation of the disease the concentration of bilirubin is usually less than 85-100 µmol/L. Minor or no changes in biochemical indicators of liver functioning unrelated to pigment exchange have been observed in the majority of patients suffering from GS. The increase of free bilirubin level in the blood serum of relatives of patients (15-40% of cases) is disclosed [13].

Diagnostics also includes a study of sample with partial starvation: restriction of the total daily calorie content up to 1.6 kJ (400 kcal) for patients with GS results into increase of free bilirubin in the blood serum in two or more times during the day. Radio-hepatography with Bengal rose131J demonstrated a minor disorder of absorbing and excretory function of liver; Bromsulfalein test relatively often revealed retention of contrast.

Duodenal intubation revealed cholangitis in about a 30% of patients.

The disease has long-term morbidity. It lasts for years and runs an undulating course. Exacerbations are mainly result from errors in nutrition, hypothermia, fatigue, intercurrent diseases.

Patients over time develop increased intolerance of alcohol and rich food; the frequency and severity of hepato- and splenomegaly increases; the activity of liver enzymes often increases just as well, indicating a dynamics of pathological process such as abnormalities in the hepatocytes. At different times (usually 2-5 years after incursion of disease) patients may contract chronic hepatitis, inflammation in the biliary tract that in a certain manner would influence the course of underlying disease.

Normal histological structure or minor degenerative changes therein upon decreasing activity in hepatic glucuronosyltransferase and apparent increase in indirect bilirubin in the blood is an indication of GS.

GS should be differentiated from hemolitic jaundice, especially hereditary ones. GS does not include: declination of osmotic and mechanical resistance of erythrocytes, changes in their morphology and increased excretion urobilinogen bodies. The most reliable criterion of hemolytic process is a reduced life expectancy of erythrocytes. Table 1 illustrates the main differential diagnostic signs of typical forms of inherited hyperbilirubinemias [1].

Treatment of patients with GS comes to physical and mental loads limitations, nutritional therapy (dietary menu No. 5) and medication intake such as inducers of enzyme activators of hepatocyte monooxygenase system.

In particular, the following medications are administered: a) Benzonalum 0.1 g 3 times per day for two weeks and b) Phenobarbital 0.1 g 3 times per day for 3 weeks c) Zyxorin (Flumecinol) initially 0.4 g 3 times per day (for 10 days), followed by 0.2 g 4 times per day for 7 days [4].

Patients with GS should avoid strenuous exercise, and give up smoking. Their diet, particularly during exacerbations of disease, should contain limited number of fatty meats, fried foods and dishes with a keen relish, spices, canned goods; alcohol consumption is prohibited. During remission patients preserve their performance capability; their performance decrement may occur in exacerbation of disease.

Table 1. Differential diagnostic signs of typical forms of inherited hyperbilirubinemias

Signs	Syndromes			
	Gilbert	*Crigler-Najjar*	*Dubin-Johnson*	*Rotor*
Incursion of disease	In adolescence and youth	In infancy	In adolescence and youth	Often in childhood and adolescence
Integumentary pigmentation	Mild jaundice	Severe jaundice	Moderate jaundice	Moderate jaundice
Hepatic abdominal pain	Rare	Rare	Often has contractions nature	Often has contractions nature
Increased bilirubin level in the blood serum	Mostly free	Only free	Mostly conjugated	Mostly conjugated
Bilirubinuria	Absent	Absent	Present	Present
Results of bromsulfalein test	Normal	Normal	Tardive subsequent increase of conjugated dyes concentration in the blood (after 90 min)	Increased retention of dye in the blood after 45 min
Results of X-ray studies of biliary tract	Normal	Normal	Bile ducts are not filled or have poor and tardive opacification (regardless of the method of injection of radiopaque substance)	Bile ducts are not filled after intravenous contrast substance injection
Hepatic tissue (histologically)	Normal or accretion of pigment in hepatocytes and activation of reticuloendoteliocyti stellatum	Normal or minor obesity of hepatocytes, periportal fibrosis	Large number of coarse-grained dark pigment in hepatocytes	Normal

GS **prognosis** is favorable. Progressive changes in the liver that may result into its severe malfunctioning usually do not occur, but high sensitivity of patients to different hepatotoxic poisons (alcohol, some medications, etc.) has been observed [14].

Crigler-Najjar syndrome (CNS) is an inherited nonhemolytic unconjugated hyperbilirubinemia, when a level of unconjugated (free) fraction of bilirubin in blood serum is greater than 300-340 μmol/L in the complete absence of conjugated bilirubin in relation to a lack or deficiency of the UGT1A1 enzyme [11].

This rare form of severe hyperbilirubinemia was first described in 1952 by S. Crigler and P. Najjar who discovered it in newborns, and was named for their surnames.

Etiology. It is a inherited disease with an autosomal recessive nature of the transmission of defect of absence of UGT1A1 enzyme, which is caused by mutation of the encoding gene identified in a long branch of chromosome II (locus 2937). Pronounced enzyme deficiency (type II) occurs much more frequently and is transmitted by autosomal dominant mode.

Pathogenesis. Complete absence of glucuronosyltransferase in hepatocytes, resulting into a complete liver failure to conjugate bilirubin (microsomal jaundice) accompanied by significant increases in concentration of indirect bilirubin (CNS type I). The life span of red blood cells is unchanged. Since the major route of the wash-out of pigment from the body is blocked, relatively constant and usually fairly high level of free bilirubin is set in the blood. By accumulating in the body, bilirubin toxically affects the central nervous system, causes the development of «nuclear jaundice,» particularly when its concentration in the blood serum exceeds a concentration of 257 μmol/L, but may occur at a lower concentration of a free pigment, if there are promoting factors (acidosis, lack of binding of bilirubin by blood albumin due to hypoalbuminemia or presence in the blood of substances that compete with pigment for contact with protein, etc.) [14].

Histologic study of liver reveals that hepatic tissue is unchanged or has slightly obese hepatocytes and small portal fibrosis. Electron microscopy reveals changes in vascular pole of hepatocytes - damaged membranes, their reduced number and flatness of microvilli, cell organelles outflow in Disse space.

Clinical implications of disease consist of apparent jaundice and severe neurological disorders. Jaundice appears usually in the first days or even hours after birth and persists throughout life. Lesions occur with equal frequency in boys and girls. Stool is acholic; bile shows submicrogram of bilirubin alone. In some patients with hepatomegalia, no splenomegaly is observed. Symptoms of central nervous system damage appear in childhood, sometimes in the first days of life. They are manifested in muscle hypertension, nystagmus, opisthotonos, athetosis, tonic and clonic convulsions etc. Sick children usually lag in mental and physical development [3].

Diagnosis. Hematologic parameters remain unchanged. Cholecystography findings are normal.

The most important biochemical sign of the disease is an increase of free bilirubin in the blood serum. Bilirubinemia reaches peak level: in most cases it exceeds 342 μmol/L and some patients have its concentration of 856 μmol/L. Bilirubinuria is absent. There are few urobilinoids in urine and feces. Periodic changes in indicators and other liver function tests (aspartate aminotransferase, cholesterol esterase and cholesterol esterification rate) are possible.

Majority of patients die in their first year of life as a result of nuclear jaundice or intercurrent diseases. Nuclear jaundice may also progress in later years – patients survive up to their late childhood or adolescence in some cases.

Diagnosis of CNS is based on the following specific signs: permanent or progressive jaundice caused by increased levels of free pigment in the blood is apparent and appears in the first days after birth; a slight and variable disorder of the liver function tests; poor opacification of biliary tract and gall bladder by contrast substance; dark liver pigmentation (accretion of pigment in hepatocytes), association of jaundice with neurological disorders in different periods; family medical history [7, 9].

Depression of conjugation liver function may be found when examining the patient's relatives - heterozygous carriers of the defective gene. The most accurate diagnosis is substantiated by the results of biochemical studies of liver biopsy samples (no glucuronosyltransferase activity).

CNS should be distinguished from other types of jaundice affecting the newborns and resulting from increase of free bilirubin in the blood.

An important factor in **therapeutic measures** for CNS is to reduce bilirubin in the blood to a level that does not cause damage to the central nervous system.

The most effective is phototherapy i.e. exposure of a patient to a regular blue incandescent bulb light (eye protection is required). Normal daylight or direct sunlight has almost similar effect. Treatment is permanent during life. The duration of sessions is individual (up to 15 h per day in some cases). Possible side effects are dehydration, loose stools, acute hemolysis. Given the different biological effects of light on the neuro-endocrine system, phototherapy should be resorted to only when there is actual evidence of dangerously high levels of free bilirubin in the blood serum. Duration of phototherapy treatments can be reduced by the simultaneous prescription of substances that bind bilirubin in the intestinal tract and contribute to its elimination from the body through excretions (biliginum, cholestyramine) [4].

If hyperbilirubinemia is severe (above 342 μmol/L in newborns carried to full time, and above 257 μmol/L in premature newborns) an urgent hyperhemotransfusion is needed, which gives temporary effect. Treatment with barbiturates is ineffective.

Treatment with enzyme-inducing agents, in particular with barbital, is effective for patients with CNS type II. The drug effect is mainly associated with an increase in activity of glucuronosyltransferase. Therapeutic dose is 3 mg/kg of body weight (up to 10 mg/kg in children) per day in the evening. Phenobarbital intake (onset of action is after 48 h) normalizes the level of bilirubin in the blood serum within 2-4 weeks. The withdrawal of the drug is accompanied by a gradual increase in bilirubin.

Medications binding unconjugated bilirubin in the blood serum are prescribed (Biligninum 5-10 g 3 times per day for 30-40 minutes prior to eating washed down with water; Cholestyramine 4 g 2-4 times per day, washed down with water) [1].

Prognosis. Disease (especially type I) progresses severely and is fatal as a result of nuclear jaundice or intercurrent diseases incidence.

Dubin-Johnson syndrome (DJS) is a hereditary familial idiopathic jaundice with unidentified pigment in hepatic cells and liver melanosis that was first described by T.N. Dubin and G.D. Johnson in 1954. It is a very rare disease: only 0.3% of patients with various liver diseases contract it.

Etiology. 30-35% of patients were found to have a familial nature of the disease with autosomal recessive mode of inheritance. The cause of the disease is most likely a defective gene that controls the synthesis of protein transporter of bilirubin (cMOAT-ing, canalicular Multispecific Organic Anion Transporter), responsible for the emission of conjugated bilirubin into the bile capillary.

Main link of **pathogenesis** is a partial disorder of the excretory function of hepatocytes (post-microsomal hepatocellular jaundice). Defect of this function extends to the emission from cells of bilirubin, cholecystographic agents, bromsulphalein, Bengal rose, indocyanine green and several other organic anions. Disorders are manifested by chronic increase of conjugated bilirubin in the blood serum, as well as by changes in a number of functional test indices [14].

DJS does not disturb a conjugation function of liver. Production of bilirubin in the body is not changed.

Gross examinations of a liver are primarily characterized by an unusual color with a predominance of blue, green, gray and black hues with varying intensity and shades - from blue-green to almost black, due to accretion of melanin-like pigment (melanosis).

Microscopic examinations of hepatic tissue reveal a large quantity of pigment with peribiliar nature. This together with the change of color of the liver is a more common morphological sign of DJS. Pigment inclusions are normally yellow-brown, nodular, coarse-grained and located mainly in the center of particles.

The first **clinical signs** of disease may be manifested within the period from birth up to 40 years old (up to 25 years at 90% of cases). Patients at risk of contracting DJS are mostly men.

The main symptom is a chronic or intermittent jaundice, usually with no apparent manifestation. Mild or moderate hepatomegalia is observed in majority of patients. There are light stools and dark urine from time to time. Patients often complain of fatigue, abdominal pain, nausea, decreased appetite, and as well as express complaints representative of neurosis and vegetative dystonia [7].

Diagnosis. Duodenal intubation usually results in normal findings. During cholecystography and intravenous cholegraphy a gall bladder and bile ducts demonstrate poor and tardive opacification (or no opacification at all).

Hematological factors are unchanged. The most important biochemical sign is hyperbilirubinemia. Most frequently it is stipulated by prevailing increase of the conjugated pigment with its share exceeding 50% in most cases (volatile within 25-90%). Total bilirubin is usually low amounting to 17-51 μmol/L, in some cases exceed 85 μmol/L. Bilirubinuria, increased emission of urobilinogen in the urine may be observed.

Indices of bromsulfalein test are definitive. There is normally a small retention of contrast in the blood during the first 30-45 minutes, followed by its distinctive increase caused by the excretion disorder and regurgitation of hepatocytes of conjugated bromsulfalein. Tardive subsequent increase of conjugated pigment in the blood is also observed after bilirubin load.

Diagnosis of DJS is based on the following symptoms: chronic or intermittent jaundice associated with prevailing increase in concentration of conjugated bilirubin, tardive subsequent increase of bromsulfalein in the blood after bilirubin load, a mild and inconstant liver parafunctions; no opacification or poor or tardive opacification of gall bladder and bile ducts at X-ray studies; dark pigmentation of liver due to accretion of pigment in hepatocytes [1, 10].

Treatment. Patients are recommended to avoid exerting toxic effects on the liver (alcohol consumption, etc.). Courses of hepatoprotective drugs (Essenciale-N, Livolin, Legalon and its analogs, Heptral, Citrarginine, B-group vitamins, Lipoic acid, etc.) and preventative measures of the formation of gallstones are prescribed [7].

Prognosis is favorable.

Rotor syndrome (RS) is a chronic familial benign non-hemolytic jaundice with elevated levels of conjugated (direct) bilirubin and normal histological structure of the liver (excluding unidentified pigment in hepatic cells). The combination of DJS and RS in the same families is described, but most clinicians consider identified syndromes separately.

Etiology and pathogenesis. The disease has a hereditary nature (familial nature of the disease has been established in almost one third of the described cases) with autosomal recessive mode of inheritance.

The main link of pathogenesis is the same as in

DJS – a disorder of excretory function of hepatocytes (post-microsomal hepatocellular jaundice), which exhibits less severity (lower diffusivity). It does not apply, for example, to the emission of radio-opaque substances from hepatocytes. Bromsulfalein load shows increased retardation of unconjugated substrate in the blood (without subsequent increase common to DJS). Examination of bilirubinemia dynamics after intravenous injection of pigment indicates that the withdrawal of both free and conjugated pigment from the blood is significantly lagging, reflecting the combined dysfunction of the uptake and excretion of bilirubin by hepatocytes. Generation of bilirubin is usually unchanged, as well as no decreased conjugation ability of liver is observed [1, 11].

Gross examinations of a liver show no changes. Histologic examination of hepatic tissue normally demonstrates no pathological changes as well. Electron microscopy of hepatocytes reveal pigment inclusions with 0.4 to 1 microns diameter, damages of plasma membrane of sinusoidal pole, appearance of giant mitochondria and other non-specific changes.

The first **clinical manifestations** of RS are often apparent in early childhood. The disease often affects both men and women.

Non-severe chronic jaundice stands for the main clinical symptom. Some patients have a minor hepatomegalia. There is also darkening of urine from time to time.

The subjective condition of patients is disturbed less often and less severely than of those with DJS. The most typical complaints are fatigue, pain in the right subcostal plane, dyspeptic disorders and reduced appetite [9].

Diagnosis. Hematological factors are unchanged. Duodenal intubation and oral cholecystography result in normal findings. At the same time intravenous injection of contrast agents often does not demonstrate X-ray visualization of biliary tract.

Total bilirubin concentration is higher in average than that in patients of DJS. It normally amounts to 68-103 μmol/L, but often may exceed 171 μmol/L; 30-80% (often 50% or more) bilirubin accounts for conjugated fraction. There is an incidence of bilirubinuria from time to time. Changes in other liver function test (other than noted above load tests) are uncharacteristic.

RS course is favorable. The disease lasts for years. Exacerbation is possible after exposure to the same initiating agents as those of DJS (pregnancy is an exception because of it was often observed to even reduce jaundice). Potential complication is cholelithiasis.

Diagnosis of RS is based on the following symptoms: chronic or intermittent jaundice associated with prevailing increase in concentration of conjugated bilirubin in the blood serum, mild and inconstant liver parafunctions unrelated to the bilirubin metabolism, and no visible changes of hepatic tissue in the findings of light microscopy. Some indices have negative results of intravenous cholegraphy and increased retention of bromsulfalein in the blood [1, 3, 7, 10].

Morphological study of hepatic tissue is crucial to both diagnosis and differential diagnosis.

Treatment of RS is the same as in DJS.

Prognosis is favorable; the disease has long-term morbidity. No progression of chronic hepatitis has been observed.

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СПАДКОВІ ПІГМЕНТНІ ГЕПАТОЗИ: СУЧАСНИЙ СТАН ПРОБЛЕМИ

А.С. Свінціцький

Резюме

У статті проаналізовані сучасні погляди на етіологію, патогенез, діагностику та лікування спадкових пігментних гепатозів (синдромів Жильбера, Дабіна-Джонсона, Ротора й Кріглера-Наджара).

Ключові слова: спадкові пігментні гепатози, діагностика, лікування.