Juvenile Hyperbilirubinemia

Juvenile hyperbilirubinemia is an etiologically heterogeneous group of diseases that primarily affects the adolescent population. The prevalence is relatively high, 2-6% in the adolescent population, with a predominance of boys. The onset or exacerbation of hyperbilirubinemia in adolescence is probably related to an increased load on hepatocytes (asymptomatic EBV infection, hormonal contraception, alcohol abuse or experimentation with drugs). Adolescents with newly detected hyperbilirubinemia often present with symptoms of increased fatigue, non-specific digestive problems, accumulation of infections or intolerance to heavy loads during sports training.[1]

Differential diagnosis of unconjugated hyperbilirubinemia

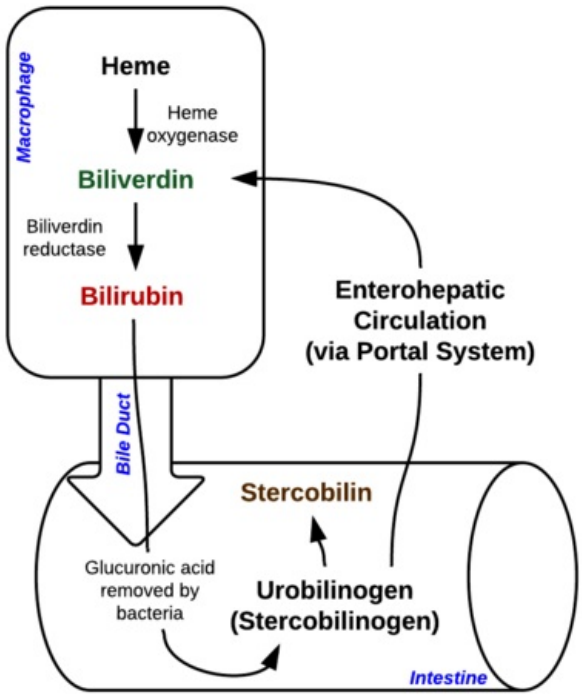
- Gilbert syndrome – a benign, relatively common AR hereditary disease; decreased UGT1A1 activity;
- Crigler-Najjar syndrome – rare AR inherited disease; very low UGT1A1 activity;
- hemolysis;
- Wilson's disease – AR hereditary degenerative disease with abnormal accumulation of copper in the liver, brain, cornea and other organs;
- Alpha 1-antitrypsin deficiency – a genetically determined protease inhibitor defect; liver disease and pulmonary emphysema.

Differential diagnosis of conjugated hyperbilirubinemia

- Dubin-johnson syndrome – benign AR hereditary disease; hepatocellular disorder of conjugated bilirubin secretion into bile;
- Rotor syndrome – benign AR hereditary disease; impaired excretion of conjugated bilirubin into the bile.

Bilirubin

- Bilirubin is the final degradation product of ***hemoglobin***. The main source is erythrocytes removed from the circulation and destroyed by the reticuloendothelial system.
- Bilirubin (unconjugated, indirect) is bound to *albumin* in the blood (if its binding capacity is not exceeded), is soluble in fats (→ settles in adipose tissues and CNS) → absorbed by the liver → conjugated with 2 molecules of *glucuronic acid* in the endoplasmic reticulum of hepatocytes, conjugation is catalyzed by uridine diphosphoglucuronosyltransferase (UGT1A1) → conjugated, direct bilirubin, soluble in water, is transported back into the cytosol → from the biliary pole of the hepatocyte, it is excreted into the bile using a canalicular transporter.[2]



Heme metabolism.

Gilbert syndrome

🔎 *For more information see Gilbert syndrome.*

- autosomal recessive, benign hyperbilirubinemia;
- a total of 9 different gene disorders were identified;
- most often caused by the insertion of TA nucleotides in the TATA box of the gene for uridine diphosphoglucuronosyltransferase (UGT1A1) – the frequency of this allele of the UGT1A1 gene is 35–40% in the Indo-European population, i.e. in our population, 11–16% are homozygotes for the extended TATA box, but only a fraction of them have hyperbilirubinemia;
- mutation in the promoter region of the gene → impaired transcription initiation → reduced UGT1A1 activity by 30%;
- some also have a shortened survival time of erythrocytes, thus potentially higher production of bilirubin;
- about a third of patients show a disorder in the transport of all organic anions in the hepatocyte, which manifests itself in reduced absorption of bilirubin;
- manifestation sometimes already in the newborn age by protracted neonatal icterus, which sometimes impresses like jaundice of breast-fed babies;
- **typical clinical manifestation**: mild isolated unconjugated hyperbilirubinemia, usually up to 80 µmol/l, rarely up to 100 µmol/l, without manifest hemolysis and without signs of other liver function disorders (except glucuronidation), without macro- or microscopic changes in the liver parenchyma;
- historical diagnostic tests: the so-called starvation trial (fasting), tests with phenobarbital or nicotinic acid - non-specific.[1]

Crigler–Najjar syndrome

- a rare autosomal recessive disease – various mutations in the structural part of the UGT1A1 gene that cause a severe disorder of bilirubin glucuronidation with residual UGT1A1 activity;
- marked unconjugated hyperbilirubinemia (bilirubin 100–300 μmol/l);
- hyperbilirubinemia can be reduced with enzyme inducers (phenobarbital) and phototherapy.[1]

Hemolysis

- isolated unconjugated hyperbilirubinemia;
- decrease in erythrocytes and hemoglobin in the blood count; increased amount of reticulocytes;
- a decrease in haptoglobin indicates an increased level of free hemoglobin in the blood.[1]

Wilson's disease

- AR hereditary degenerative disease - large number of mutations;
- abnormal **accumulation of copper** in the liver, brain, cornea and other organs;
- a gene defect that is important for the incorporation of copper into ceruloplasmin (or apoceruloplasmin) and for the excretion of excess copper into the bile;
- copper is **toxic** to hepatocyte organelles – causes cell necrosis → liver steatosis → chronic active hepatitis → liver cirrhosis;
- during hepatocyte necrosis, unbound copper is released into the circulation and has a toxic effect on erythrocytes and the brain (basal ganglia), eye tissues, kidneys, bones, etc.
- initially asymptomatic course - only accumulation of copper in the liver and histological changes;
- manifestations usually only after 12 years of age, but also significantly later: fatigue, loss of appetite, abdominal pain with hepatomegaly, subicterus to icterus;
- later symptoms from cirrhotic remodeling: portal hypertension, splenomegaly, ascites, bleeding from esophageal varices, spider nevi, coagulation disorders;
- neurological symptoms: lack of concentration, slight tremor, dysarthria, dystonia, hyperkinesia, increased salivation, rigidity;
- ocular manifestations: greenish-brown ***Kayser-Fleischer ring*** on the edge of the cornea on the back of Descemet's membrane;
- rarely occurs under the guise of fulminant liver failure: massive necrosis in the liver, a large amount of copper in the circulation, Coombs negative hemolytic anemia with hemoglobinuria and multiorgan failure;
- **diagnosis**: low to trace level of ceruloplasmin, increased aminotransferases and bilirubin, increased waste of copper in urine, molecular genetic examination, liver biopsy (quantitative determination of copper);
- **treatment**: chelation effect of D-penicillamine with pyridoxine (penicillamine leads to pyridoxine deficiency), liver transplantation;
- untreated Wilson's disease is progressive and fatal.[3]

Alpha1-antitrypsin deficiency

- genetically determined defect of the protease inhibitor ***α_1-antitrypsin***;
- different phenotypes; the most clinically significant is the PiZZ mutation, which causes pulmonary emphysema and liver disease (cirrhosis, hepatoma);
- the proteolytic activity of neutrophil elastase in the lung epithelium is not hindered (+ smoking, air pollution → COPD already in the 3rd decade);
- cholestatic icterus with acholic stools, pruritus and hepatosplenomegaly may appear already in the newborn age;
- liver disease is usually benign;
- **diagnosis**: decreased serum level of α 1 -antitrypsin; electrophoresis of serum proteins - reduced α-fraction;
- **treatment** in adults with COPD: substitution with recombinant synthetic α 1 -antitrypsin (bronchial or IV); in fulminant liver disease - liver transplantation;
- the most common genetically determined liver disease of childhood.[4]

Posthepatic hyperbilirubinemia

- in most cases of acute inflammation of the liver without transition to chronicity, all liver tests normalize.
- in the case of chronic hepatitis, the leading basic laboratory manifestation is the elevation of aminotransferases and hyperbilirubinemia is absent or very mild.
- in severe liver diseases, the so-called shunt mechanism of the formation of unconjugated hyperbilirubin is assumed: shunts between the arterial and venous channels without blood flow in the "cleaning" part of the liver parenchyma can cause an increase in unconjugated bilirubin in the serum.[1]

Dubin-johnson syndrome

- benign AR hereditary disease;
- hepatocellular disorder of conjugated bilirubin secretion into bile;
- diagnosed usually around age 10;
- fluctuating hyperbilirubinemia (34-136 μmol/l) with a 30-60% proportion of the conjugated component;
- in case of acute deterioration: temperature, nausea, vomiting, abdominal pain, dark urine, colored stool, hepatomegaly;
- **diagnosis**: conjugated hyperbilirubinemia, pathological excretion of dyes that must pass through the bile ducts (bromosulfophthalein), negative cholecystography, liver histology with accumulation of brown to red pigment in lysosomes;

- **treatment**: only symptomatic in case of acute deterioration, prognosis is good.[4]

Rotor syndrome

- benign AR hereditary disease;
- impaired excretion of conjugated bilirubin into the bile;
- clinical picture same as in Dubin-Johnson syndrome, but abdominal pain is absent;
- **diagnosis**: conjugated hyperbilirubinemia, pathological excretion of dyes that must pass through the bile ducts (bromosulfophthalein), positive cholecystography, liver histology without accumulation of pigment in lysosomes ;
- **treatment**: only symptomatic in case of acute deterioration, prognosis is good. [4]

Laboratory examination

- blood count + differential + reticulocytes (3×)
- haptoglobin (decreased in hemolysis)
- liver function tests (AST, ALT, ALP, GMT), total and conjugated bilirubin
- Quick's test, APTT
- cholinesterase, prealbumin
- ceruloplasmin (Wilson's disease), alpha;$_1$-antitrypsin (deficiency)
- infectious hepatitis A, B, C
- EBV, CMV, HSV
- toxoplasmosis
- immunoglobulins, CIK, ANAb

The normal level of serum bilirubin is **17–20 µmol/L**.

- at a value of 20–30 µmol/l, monitoring of liver tests is indicated
- above 30 µmol/l, a more detailed examination is appropriate
- proof of hemolysis – there are 3x more reticulocytes in the blood than usual (the norm is up to 10%)
- unconjugated hyperbilirubinemia means that the conjugated fraction must be represented up to 15%.[5]

Links

Related articles

- Jaundice • Hyperbilirubinemia of newborns and infants • Icterus • Differential diagnosis of jaundice

References

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