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DIFFERENTIAL DIAGNOSIS OF DIRECT HYPERBILIRUBINEMIA IN CHILDREN: A LITERATURE REVIEW

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ANNOTATION

The article discusses various causes of direct hyperbilirubinemia in young children. Earlier in issue 3 for 2021 in this journal, we published an article on familial progressive intrahepatic cholestasis, as one of the causes of cholestatic jaundice. In this article, we present others, including more frequent (such as biliary atresia) and rarer and rarer pathologies. The proposed review may be useful in the differential diagnosis of direct hyperbilirubinemia syndrome in children of early age.

Key words: direct hyperbilirubinemia, cholestatic jaundice, young children.

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ДИФФЕРЕНЦИАЛЬНАЯ ДИАГНОСТИКА ПРЯМОЙ ГИПЕРБИЛИРУБИНЕМИИ В ДЕТСКОМ ВОЗРАСТЕ: ОБЗОР ЛИТЕРАТУРЫ

АННОТАЦИЯ

В статье рассмотрены разнообразные причины прямой гипербилирубинемии у детей раннего возраста. Ранее в номере 3 за 2021 год в данном журнале нами публиковалась статья о семейном прогрессирующем внутрипечёночном холестазе, как о одной из причин холестатических желтух. В настоящаящей статье мы представляем другие в том числе более частые (такие как билиарная атрезия) и более редкие и редчайшие патологии. Предлагаемый обзор может быть полезен при провежении дифференциальной диагностики синдрома прямой гипербилирубинемии у детей раннего возаста.

Ключевые слова: прямая гипербилирубинемия, холестатическая желтуха, дети раннего возраста.

An increase in the level of direct (conjugated) bilirubin in children of the first six months of life is much less common than an increase in the level of unconjugated pigment, but more often reflects the presence of a severe pathology and often represents a diagnostic puzzle. A formal criterion for direct hyperbilirubinemia can be considered an increase in the level of conjugated bilirubin of more than 17.1 μmol/l with a level of total bilirubin below 85.5 μmol/l. If the level of the total pigment does not reach the specified value, then a rise in direct bilirubin of more than 20% of the total level should be considered as a criterion. An increase in the level of conjugated bilirubin often accompanies indirect hyperbilirubinemia, which may be associated with secondary cholestasis, in particular with bile thickening syndrome, and can also be observed against the background of parenchymal lesions. Mild mixed jaundice with cholestasis is more common. In these cases, cholestatic lesion is superimposed on physiological and conjugative jaundice. Prematurity, birth asphyxia, intrauterine hypoxia, parenteral nutrition, drug stress act as additional risk factors, and therefore, the true cause of cholestasis may not be recognized. Neonatal jaundice should be considered protracted if it persists for more than 6 weeks, however, the presence of a direct component requires immediate active diagnostic actions. The complexity of differential diagnosis and the multiplicity of causes and risk factors justify the use of the term "transient neonatal cholestasis" in such situations, the frequency of which in full-term newborns can reach up to 8.5%. Cholestasis develops by the end of the first week of life and can last up to 3-4 months; in some cases, deviation of liver tests, hepatomegaly can last up to a year. A special place in this group is occupied by cholestasis in children born before the 35th week of gestation. In the case of persistence or progression of direct hyperbilirubinemia, the syndromic diagnosis can be formulated as "cholestatic neonatal liver disease" [1]. Most often, severe conjugated jaundice in newborns and children in the first six months of life is associated with biliary obstruction. About 45% of cases are due to biliary atresia, up to 17% - to Alagille syndrome. The most common non-obstructive cause of severe cholestasis is progressive familial intrahepatic cholestasis (PSIC), which accounts for at least 13% of cases in various forms, which exceeds the total frequency of such causes as alpha-1 antitrypsin deficiency, galactosemia, tyrosinemia, cystic fibrosis, and also neonatal hepatitis and biliary cirrhosis of various and unspecified etiologies. Various studies have shown an unequal structure of the causes of direct hyperbilirubinemia in newborns, which can be associated with the inclusion in the study of patients with different severity, level of examination, and possibly with regional and ethnic characteristics. According to Arora N.K. et al. (2001) among children with neonatal cholestasis, biliary atresia occurs in 25% of cases, neonatal hepatitis with an established cause - in 45.5%, idiopathic neonatal hepatitis - in 19.7% [2]. According to Gottesman L.E. et al. (2015) from a survey of 1692 newborns, idiopathic neonatal hepatitis accounted for 26%, for biliary atresia - 25.9%, for infectious causes - 11.5% (of which 31.5% - for CMV), for chole- stasis associated with parenteral nutrition - 6.4%, α-antitrypsin deficiency - 4.1% [3]. Infectious hepatitis is the most expected cause of hyperbilirubinemia in combination with elevated transaminase levels. As a rule, a serological and PCR test for the main hepatotropic viruses is the first diagnostic step. Cytomegalovirus (giant cell) hepatitis is the most well-studied and common (more than half of cases) cause of neonatal hepatitis. In newborns with biliary atresia and other cholestatic diseases, active CMV infection is not uncommon, which should not stop the diagnostic search. A wide range of infections are considered as causes of neonatal cholestatic liver damage: parvovirus, hepatitis B, adenovirus, enterovirus, Ebstein-Baar virus and herpes simplex virus, HIV. In HbsAg positive mothers, transmission of the virus to the fetus occurs in 70% of cases, and clinical manifestation usually occurs within 12 weeks. Gottesman L. E. et al. (2015) noted the following infectious causes as the most common causes of cholestatic hepatitis: CMV 33.5%, sepsis 24.7%, congenital syphilis 10.8%, pyelonephritis 9.8%, rubella 6.2% , toxoplasmosis 3.6% and only 1.6% hepatitis B [4]. Iatrogenic causes of cholestatic disease of the newborn are drug-induced hepatitis and cholestasis with parenteral nutrition. The development of clinically significant cholestasis can be expected with total parenteral nutrition in newborns for more than 2 weeks or more.

Bile thickening syndrome can be detected in 1.4-6.5% of newborns and children in the first months of life with an increased level of direct bilirubin. Risk factors for bile slugging are, first of all, prematurity and parenteral nutrition, as well as low weight, prescription of diuretics, ceftriaxone, hemolysis, sepsis, blood transfusions. However, sludge-related cholestasis can develop in the absence of these factors. Thickening syndrome may accompany other liver diseases and thus complicate their diagnosis [5, 6].

Biliary atresia is the most common cause of severe direct hyperbilirubinemia in newborns and, at the same time, the main cause of liver cirrhosis in children. Its frequency ranges from 5 to 32 per 100,000 live births, reaching a maximum in the Pacific region. The syndromic form of biliary atresia is less than 1/10 of all cases and is characterized by the presence of other anomalies (polysplenia or asplenia, transposition of internal organs, anomalies of the vena cava and portal veins, incomplete bowel rotation). Diagnosis of biliary atresia using imaging methods, as a rule, is not difficult. About 25% of children with biliary atresia have intrahepatic cysts. It should be noted that the increase in the level of transaminases may not be pronounced, an increase in the size of the liver may occur by the end of the first month of life, hemorrhagic syndrome and impaired weight gain may also be absent at this time, in some patients at 1-2 weeks of life there may be some decrease in the level of bilirubin, which can slow down the diagnosis. A permanent symptom is discolored feces.

Alagille syndrome (Alagille syndrome, hypoplastic bile duct syndrome) is a rarer cause of neonatal cholestasis (1:70,000–1:100,000 live births). This is an autosomal dominant disease, in 90% of cases the mutation is localized in the JAG1 gene (20p12), less often a mutation in NOTCH2 is detected [7]. The diagnosis is not difficult when a newborn has a combination of progressive cholestasis and characteristic

developmental anomalies, including facial dysmorphism and anomalies in the development of the pulmonary artery, eyes (embryotoxon), skeleton (splitting of the vertebral bodies in the form of a "butterfly") and urinary system [8]. Approximately 30% of patients have a subclinical course of the disease with a decrease in the level of bilirubin in the second half of the year. In some cases, neonatal jaundice and hepatomegaly may not be expressed or even absent. The cause of cholestatic jaundice can also be non-syndromic forms of bile duct hypoplasia, which can only be diagnosed by morphological examination [9].

The last 2 decades have been marked by significant progress in the study of cholestatic diseases. Largely due to the development of genetic diagnostic methods from direct single gene sequencing to panel sequencing, from exome sequencing to whole genome sequencing, a number of new cholestatic hepatopathy have been discovered [10–14]. Today, at least three more phenotypically similar types of PSVH are distinguished, which have an autosomal recessive mode of inheritance [15].

Violation of the synthesis of the “tight junction” protein (ZO proteins - Zonula occludens), caused by a mutation in the TJP2 gene (9q21.11), causes cholestatic syndrome without an increase in γ-GTP. This is the so-called type IV PVH, characterized by manifestation in the first years of life and a high risk of cirrhosis [16].

Several patients with neonatal manifestation of the disease and rapid development of cirrhosis were also described, who had a mutation in the NR1H4 (12q23) gene encoding the farnesoid X nuclear receptor (FXR), which affects the ABCB11 and ABCB4 genes and thereby regulates bile acid metabolism. This type of disease claims to be called PSVH-5. The presence of K-independent coagulopathy, a low level of γ-GTP, and a high level of AFP are described as its features. It is possible that this mutation is responsible for some cases of cholestatic diseases with late manifestation (drug-induced and gestational cholestasis) [17, 18].

Mutation of the MYO5B gene (18q21.1), encoding the synthesis of type Vb myosin, has been described in children with atrophy of the microvilli of the small intestine and severe chronic diarrhea, and is also associated with cholestasis with low γ-GGT. In these infants, cholestasis often manifested during parenteral nutrition. Subsequently, mutations in this MYO5B gene were described in patients with different severity and age of disease manifestation, including those in the second half of life without rapid progression, as well as in the absence of diarrhea. Similar biochemical changes and the presence of diarrhea make it possible to differentiate this syndrome from PSVH-1 [19, 20].

Violation of the synthesis of primary bile acids (BASD) is a group of very rare (from 0.6 to 2 per 1 million newborns) autosomal recessive diseases with neonatal manifestations, manifested by cholestatic syndrome. For the first time the case of BASD was described by P. Clayton et al. in 1987 in children with fetal hepatitis, coagulopathy, and deficiency of fat-soluble vitamins, born in consanguineous marriage to parents from Saudi Arabia [21]. The features of this group are the absence of itching, the normal level of γ-GTP and the absence of proliferative changes in the biliary ducts. To date, at least 6 variants of BASD have been described [22, 23].

A mutation in the CYP27A1 (2q35) gene encoding sterol-27-hydroxylase causes a disease known as cerebrotendin xanthomatosis or juvenile xanthogranuloma, characterized by neonatal cholestasis. At school age, the appearance of tendon xanthomas is noted, subsequently cataracts and neurological disorders (dementia, ataxia, spasticity, peripheral neuropathy), endocrine disorders, and chronic diarrhea develop. The clinical picture is characterized by a variety of age manifestations and symptoms.

The most common cause of BASD is a mutation in the HSD3B7 (16p11.2-12) gene that causes a deficiency of 3-β-hydroxy-δ-5-C27-steroid oxidoreductase, characterized by a polymorphic clinic in terms of severity and duration of manifestation. Mutation AKR1D1 (7q32-q33) causing deficiency of δ-4-oxosteroid-5-β-reductase is characterized by rapid progression of cirrhosis. A mutation in the CYP7A1 gene (8q12.1), causing deficiency of cholesterol-7-α-hydroxylase (known as cytochrome P450), was detected in newborns with cholelithiasis and hypercholesterolemia.

The cause of direct hyperbilirubinemia may be α1-antitrypsin deficiency, a well-studied disease associated with a mutation in the SERPINA1 gene (14q32.13). It is one of the most common hereditary diseases (in the European population 1 in 1500 - 3500 people) involving the liver and lungs. α1-antitrypsin deficiency is characterized by wide clinical variability. Usually there is an isolated transient cholestasis in the neonatal period, the general condition of the child is usually not disturbed. In rare cases, a manifestation with severe manifestations (increasing liver failure, hepatosplenomegaly and coagulopathy) is possible. Pulmonary symptoms develop much later. The diagnosis is confirmed by a low level of α-1-antitrypsin in the blood.

The development of neonatal cholestasis is characteristic of Niemann-Pick type C disease. Other symptoms are mild psychomotor retardation and splenomegaly, less often hepatomegaly. The diagnosis is confirmed by a genetic study or a study of cellular cholesterol esterification in skin fibroblasts [24].

Cystic fibrosis is a well-known cause of cholestatic liver disease at any age and is now well diagnosed by neonatal screening. The frequency of cystic fibrosis-associated hepatobiliary pathology is about 37.9%, and cirrhosis of the liver develops in 5-10% of patients by the age of 10 years. It should be noted that in some patients, liver damage may be a manifest and predominant syndrome. The severity of liver damage depends not only on the type of mutation in the CFTR gene, but also on the action of modifier genes, for example, the Z allele of the SERPINA1 gene and the A allele of VNTR in the eNOS4 gene [25].

Galactosemia is a rare (1 in 18,000 - 180,000 live births) autosomal recessive disease characterized by polysystemic stormy manifestation from the first days of life, which can be diagnosed by neonatal screening, and therefore can rarely be a problem in the differential diagnosis of cholestatic lesions. . Direct hyperbilirubinemia with galactosemia develops already in the first hours or days after birth. Cholestasis may be preceded by symptoms such as diarrhea, vomiting, and weight loss. Neurological symptoms develop rapidly - manifestations of intracranial hypertension, cataracts, tubulopathy with the development of hyperchloremic acidosis, albuminuria and aminoaciduria. While maintaining the intake of galactose with food at the age of 3-6 months, cirrhosis of the liver may form.

Classical polycystic diseases (autosomal recessive and autosomal dominant polycystic kidney disease - ARPKD, ADPP) are often accompanied by dilated hepatic ducts with cholestasis (Caroli syndrome). Liver damage usually develops later than renal, but polycystic diseases have a pronounced phenotypic polymorphism. Many children with subsequently diagnosed cystic diseases had prolonged mixed or direct hyperbilirubinemia at neonatal age [26–28].

Congenital liver fibrosis is also a phenotype of Caroli syndrome in most cases, and patients have a mutation in the PKHD1 gene (6p21.1-p12), which is responsible for the synthesis of the fibrocystin/polyductin protein complex and the corresponding ARPKD. Fibrocystin is a protein that forms primary cilia, which makes it possible to consider fibrocystic diseases as ciliopathies. In patients with ARPKD, fibrosis in the liver can be detected even in the absence of a clinical and laboratory picture of hepatopathy. It should be noted that in most cases complex heterozygotes with two different mutations are detected [29, 30].

Cysts of the common bile duct (choledochus) in most cases are combined with biliary atresia, but in some cases it can be isolated, and in this case, complete or partial obstruction can also be observed. The incidence of choledochus cysts is 1 in 13,000 newborns. With incomplete obstruction, clinical manifestation may occur later.

Type I tyrosinemia is one of the typical causes of an increase in the level of conjugated bilirubin in children during the first months of life, while icteric and cytolytic syndromes are moderately expressed, and the severity of the condition is due to severe liver failure [31]. Tyrosinemia I is also characterized by hypoglycemia, coagulopathy, encephalopathy, ascites, and sometimes hyperinsulinism. The diagnosis can be confirmed by the detection of sulfur-containing amino acids in the plasma, and succinylacetone in the urine. A high level of alkaline phosphatase and γ-GTP is characteristic, even with moderate hyperbilirubinemia.

Hepatopathy in the infantile form of Wolman's disease (deficiency of lysosomal acid lipase) in some cases can manifest itself as a

cholestatic lesion against the background of hepatosplenomegaly, while in the first weeks of life a severe manifestation is characteristic with vomiting, diarrhea, damage to the adrenal glands, development of dynamic intestinal obstruction and neurological symptoms. A laboratory study reveals hyperlipidemia, an increase in the level of LDH, ferritin and transaminases.

Mitochondrial diseases (MD) that occur with the syndrome of mitochondrial DNA depletion (depletion) and are caused by defects in the genes encoding the factors of stability and replication of mitochondrial DNA often occur in the form of encephalohepatopathy in early childhood [32]. MBs are characterized by pronounced clinical polymorphism and a wide range of age of manifestation, which makes diagnosis extremely difficult. Certain information can be given by the detection of a high level of lactate, pyruvate, CPK. However, patients with severe liver damage and other severe disorders, such as hypoxia, sepsis, may have hyperlactatemia, and the presence of encephalopathy may be of both mitochondrial and hepatic origin. New, more informative, markers of mitochondrial disorders have been proposed: plasma protein FGF-21 (fibroblast growth factor 21); GDF15 (growth differentiation factor 15) [33-38].

A mutation in the GFM1 gene (G elongation factor mitochondrial 1, EFG1) associated with a combined deficiency of oxidative phosphorylation may be one of the causes of encephalohepatopathy with lactic acidosis, microcephaly, developmental delay, and seizures [39].

Mutations in the POLG gene, encoding the mDNA replication enzyme γ-polymerase, are associated with various phenotypes, including infantile Alpers-Hattenlocher syndrome (Aplers-Huttenlocher, AHS), which includes epilepsy, hepatopathy, and neuropsychiatric developmental disorders.

Mitochondrial DNA depletion syndrome with nDNA MVP17 hepatopathy - Navajo neurohepatopathy (Navajo, NNH), affecting children of the same Indian tribe and manifested by hepatopathy, developmental delay, lactic acidosis, hypoglycemia and neurological symptoms. A mutation in the mitochondrial transcription factor (TFAM) gene is also associated with mitochondrial DNA wasting syndrome.

With a mutation in the BCS1L gene encoding the chapiron protein, which is ultimately responsible for the assembly of the respiratory chain, in addition to Leigh (Lee) syndrome, it is also associated with the GRACILE syndrome (or Fellman's Finnish neonatal syndrome), which includes developmental delay, aminaciduria, cholestasis , excess iron, lactic acidosis and leads to early death.

Also known causes of mitochondrial encephalohepatopathy are MB associated with mutations in the FBXL4, SUCLG1 and 2, ANT1 and AGK genes (in combination with encephalomyopathy with cardiomyopathy); RRM2B (associated with encephalomyopathy and tubulopathy); nDNA COX as-sembly factors (SCO), nDNA DGU

Type 2 citrullinemia is a rare autosomal recessive disease caused by a mutation in the SLC25A13 (7q21.3) gene encoding the liver mitochondrial aspartate-glutamate carrier (AGC) citrine, which is involved in the neutralization of ammonia. The disease occurs predominantly in the Japanese population (1 case per 100–230 thousand inhabitants) and manifests itself as a progressive lesion of the nervous system in adults. However, it has been noted that about 10% of patients in the neonatal period had intrahepatic cholestasis, and some patients develop chronic liver failure by the second half of life [40-43].

A very rare cause of direct hyperbilirubinemia are diseases characterized by a violation of the secretion of already conjugated bilirubin into the bile ducts or "overcapture". These are Rotor syndrome (mutations SLCO1B1 (OATP1B1) / SLCO1B3 (OATP1B3) and Dubin-Johnson syndrome (mutation of the gene encoding the synthesis of ABCC2 / MRP2 transport protein), which are characterized by the deposition of black pigment in the liver, are not accompanied by an increase in the level of transaminases, have a benign course and do not require treatment.Usually, the first manifestations of Dubin-Johnson syndrome are observed at an older age, but cases of early manifestation have been described.44 Rotor syndrome has been described in both newborns and older children and in in adults Diagnosis of Rotor syndrome can be aided by the detection of a 2- to 5-fold elevated level of coproporphyrin in the urine, with coproporphyrin I accounting for 65% [44].

Neonatal ichthyosis syndrome with sclerosing cholangitis (NISCH), caused by a mutation in the CLDN1 gene encoding the synthesis of claudin-1 (tight junction protein), is another rare (1 in 1,000,000) genetic cause of cholestatic neonatal syndrome. Hypotrichosis with cicatricial alopecia and dysplasia of tooth enamel are also noted. Cases of neonatal sclerosing cholangitis in combination with nephronophthisis and hearing loss associated with a mutation in the DCDC2 gene encoding the synthesis of a doublecortin-domain-containing protein responsible for the functioning of cilia (cileopathy) are described. Many cases of neonatal sclerosing cholangitis remain genetically undeciphered [45].

Hemochromatosis of newborns is another rare pathology characterized by iron deposition in various organs (in the liver, pancreas, brain, myocardium, bone marrow), manifested by severe early progressive liver damage with cholestatic jaundice, hypoglycemia, coagulopathy , cardiopathy and encephalopathy, hypoproteinemia and edema. Acute liver failure can develop in the first hours of life. The diagnosis is confirmed by the detection of high levels of serum iron and ferritin. The level of transaminases rises moderately. A gestational alloimmune lesion is considered as the cause of the pathology, a woman often has anti-nuclear antibodies, the disease can recur in subsequent pregnancies [46].

Cerebrohepatorenal syndrome (Zelweiger's syndrome), described in 1964 by a group of American doctors, is the rarest (1:50,000 - 500,000 newborns, and in one of the districts of Quebec - 1:12,000) autosomal recessive pathology associated with mutations in one of 13 PEX genes. This most severe variant of peroxisome biogenesis disorder is defined by characteristic craniofacial dysmorphism, enlarged large fontanelle, muscular hypotension, feeding difficulties, neonatal convulsions, and hepatic dysfunction with the development of cholestatic jaundice and coagulopathy. Also, patients have skeletal anomalies, renal cysts, progressive ophthalmopathy, sensorineural hearing loss. Most babies die within the first year of life.

Cholestatic syndrome without an increase in γ-GTP can be observed in the fatal syndrome of arthrogrypposis - tubulopathy - cholestasis (ARC) associated with mutations in the VPS33B and VIPAR genes encoding vesicular transport proteins. Most cases have been described in Saudi Arabia and Pakistan. Newborns may present with ichthyosis, agenesis of the corpus callosum, platelet abnormalities, and tubular acidosis [47].

Deficiency of the pentose phosphate pathway enzyme transaldolase with TALDO1 mutation was described by Verhoe et al. in 2001 causes cholestatic liver damage with the development of fibrosis in combination with facial dysmorphism, hepatosplenomegaly, thrombocytopenia and coagulopathy. In the urine, a high concentration of polyon can be detected.

The causes of cholestatic neonatal syndrome are not limited to the listed diseases. There are descriptions of the development of conjugated hyperbilirubinemia in children during the first months of life with autoinflammatory diseases, in particular with hyperimmunoglobulinemia D [48], protoporphyrinuria, neonatal lupus, annular pancreas, hemophagocytic lymphohisteocytosis, portal vein thrombosis, with spontaneous perforation of the common bile duct, stenosis of the choledochojejunal junction, kleidocranial dysostosis, tubular acidosis, right ventricular heart failur.

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