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Chronic Liver Diseases in Children

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Annotation: The following article presents the most up-to-date information from the literature regarding the prevalence, structure, development mechanisms, and progression of chronic liver diseases in children, as well as the distinctive features of their clinical manifestations, classification, and prognosis.

Keywords: Liver cirrhosis, cholestasis, acute hepatitis, chronic hepatitis, liver cancer.

Chronic liver diseases (CLD) hold a significant place in the structure of pediatric diseases, characterized by their numerous clinical forms, often progressive course complicated by liver cirrhosis (LC), and the disability of patients (V.A. Tabolin, 2000; A.A. Baranin, 2002; M. Jonas, 2000). Chronic viral hepatitis (CVH) is one of the pressing issues in modern hepatology. The prevalence of this pathology is determined by its widespread occurrence (S.I. Sorinson, 1998; M.M. Mikhaylov, 1999; G.G. Onishenko, 2001; V.V. Serov, 2004) and also by its occurrence in childhood (Baranov A.A., 2002; Kaganov, 1991; Lok A.S., 2002; Sh. Sheriok, 1999; Yu. Mayer, 1999; N.I. Nisevich, 2001; Uchaykin V.V., 2003). In adults, it can lead to complications such as liver cirrhosis and hepatocellular carcinoma (Stertfey M., Lenion, 2000; Caballena L., 2001), with an unpleasant progression of the disease.

Chronic viral hepatitis (CVH) is widespread across the globe. According to various criteria, the number of hepatitis B (HBV) carriers worldwide is between 300-400 million. Nearly 2 million people die annually from HBV-related diseases. Over half a billion people worldwide are infected with hepatitis C (HCV). In Russia, the number of those infected is close to 5 million [Bobrov I.A. et al., 2007]. The prevalence of HCV varies: in Canada, it ranges from 0.6%, in Japan and the USA from 1.5%, and in African countries, it ranges from 8-12%. HCV is relatively less common among children: 0.2-0.4% in the USA and 0.3-0.7% in Russia. In the structure of CVH, hepatitis B (HBV) accounts for 29.2%, hepatitis C (HCV) 33.3%, hepatitis B+C 16.7%, hepatitis B+D 4.1%, and hepatitis of unknown etiology [Denisov M.F., Berezenko B.S., 2004] accounts for 16.7%.

One of the most severe consequences of acute viral hepatitis is the development of chronic liver damage, which can lead to liver cirrhosis and hepatocellular carcinoma. Research has shown that currently, 2-10% of adults with hepatitis B (HBV) develop a chronic course starting from an acute phase of the disease. In children with HBV infection, the likelihood of developing chronic liver damage depends on the child's age and the timing of the infection. If the infection occurs at 1 year of age, the chance of progressing to a chronic form is 70-90%; at 2-3 years old, it is 40-70%; at 4-6 years old, 10-40%; and for those older than 7 years, it is 6-10% [Kaganov B.S., 1998].

In Uzbekistan, if in 2000 the incidence of hepatitis B was 61.9 per 100,000 people, by 2002, there were 215 reported cases of hepatitis C, though these reliable figures may have been significantly higher [Tilyaeva G.Y., 2004].

The assessment of acute and chronic, especially viral hepatitis, remains one of the pressing issues in modern hepatology [Aprosin Z.G., 1996; Maleev B.B., 2000; Shamirzayev N.X., 2002; Berke G., 1997; Tilyaeva G.Y., 2004]. The high frequency of hepatitis cases, the risk of liver cirrhosis and liver cancer due to chronic processes, the numerous aspects of pathogenesis that are not yet fully

understood, and the low effectiveness of treatment have increased interest in research on these diseases.

Data from molecular and cellular biology have significantly expanded our understanding of the pathogenesis of both acute and chronic viral hepatitis. Recent studies [Bueverov A.O. et al., 2000; Dmitrieva E.V., Moskaleva E.Yu., Bueverov A.O. et al., 2002; Dmitrieva E.V., Moskaleva E.Yu., Severin E., 2003; Nogaller A.M., 2002] have provided evidence of the replication of hepatitis B and C viruses not only in the liver but also in mononuclear cells and polymorphonuclear leukocytes in peripheral blood, explaining various extrahepatic manifestations of these infections [Abdurakhmanov D.T., Russkikh A.V., 2003; Nogaller A.M., 2002]. Additionally, the mechanism of hepatocyte damage is largely dependent on the impact of the damaging agent. However, the virus remains incompletely understood.

According to Lopatkin T.N. (1997) and Minushkin (2002), the damaging factors do not attract significant interest from researchers, as the virus falls into the toxicological (and also medicinal) and immunological categories.

Liver damage can vary in form depending on the nature, dose, duration, and other factors related to toxic substances. Hepatotoxins can cause direct damage or indirect damage through their metabolic byproducts [Toporkov A.S., 2004]. Additionally, substances introduced into the body through the gastrointestinal tract can have damaging effects on the liver via the portal vein. Approximately 75% of these substances reach the liver [O.M. Ipatova].

Liver damage can be classified into four main clinical-pathological syndromes:

1. **Cytolysis Syndrome:** This involves necrosis of liver cells, caused by the disruption of hepatocyte and organelle membrane permeability, leading to the leakage of intracellular contents into the intercellular space and eventually into the bloodstream. Indicators of cytolysis include increased activity of liver cell necrosis enzymes in the blood (such as ALT, AST, aldolase, glutamate dehydrogenase, LDH), as well as elevated levels of bilirubin, vitamin B12, and iron.
2. **Cholestasis Syndrome:** This results from damage to very small bile ducts and disruption in the formation of bile micelles, leading to impaired bile secretion by liver cells. Morphologically, cholestasis is typically associated with disruption of the hepatocyte cytoskeleton, which causes loss of microvilli on the apical surface of the cells, decreased contractility of canalicular membranes, and retrograde flow of bile fluid into the sinusoids due to impaired intercellular tight junctions [Trauner M., Fickert P., Zollner G., 2001]. Another possibility for the cholestasis mechanism is related to the state of the hepatocyte cytoskeleton, which can lead to intracellular vesicular transport disruptions. Cholestasis syndrome is characterized by increased activity of alkaline phosphatase, leucine aminopeptidase, gamma-glutamyl transferase, and 5-nucleotidase; hypercholesterolemia; increased levels of bile acids and phospholipids; and hyperbilirubinemia.
3. **Hepatic Failure Syndrome:** This reflects changes in the liver's primary synthetic and metabolic functions. Hepatic failure includes hyperazotemia, impaired liver synthetic function, and decreased activity of cholinesterases in the blood serum.
4. **Immunoinflammatory Syndrome:** The cause of this syndrome is the activation of the reticuloendothelial system and sensitization of immune competent cells. This is characterized by increased levels of β- and γ-globulins; total protein in the blood serum; immunoglobulins A, G, M; the presence of non-specific antibodies, as well as antibodies to DNA, smooth muscle fibers, and mitochondrial proteins; changes in the quantity and ratio of lymphocyte subpopulations (helper, suppressor).

The classification of chronic hepatitis remains complex, contentious, and subject to periodic debate. The difficulty in creating a classification for liver diseases arises from the fact that the main features (etiological, pathogenetic, clinical-morphological) are intrinsically “linked” in different forms of liver

damage. Previous classifications have proposed using either etiological, morphological data, or clinical symptom characteristics as a basis [Inoyatov F.I., Abdumadjidova Sh.U., 2006].

To date, various classifications of chronic hepatitis are used in the literature. According to Siprich B. et al. (1981), the classification is incorrect in all its criteria, and while chronic hepatitis is considered for clinical comparative diagnosis, morphological and etiological factors are not comprehensively covered.

Volkov A.A. (1982) proposed a classification of chronic hepatitis with two forms, plus an additional third clinical variant for children: cholestatic hepatitis, which occurs in approximately 0.5-1% of chronic liver disease cases in children. The author recommended the following working classification for chronic hepatitis in children:

- ✓ **Disease Forms:** Persistent; active and aggressive; cholestatic.
- ✓ **HBsAg Type:** Seropositive and seronegative.
- ✓ **Disease Phases:** Active (I-II-III degrees of activity); inactive.
- ✓ **Liver Functional State:** Compensated (PN0), decompensated (PN1, PN2, PN3).
- ✓ **Disease Course:** Progressive (continuous slow; continuous fast; relapsing); stable; latent; regressive.

At the European Congress of Gastroenterologists held in Rome (1988), a classification of chronic viral hepatitis based on the presence or absence of viral replication in the liver was proposed. According to this classification, chronic hepatitis B is divided into three forms:

1. **Chronic Hepatitis with Positive HBeAg:** Active viral replication.
2. **Chronic Hepatitis with Negative HBeAg:** Hepatitis with normal aminotransferase levels in the serum.
3. **Chronic Hepatitis with Negative HBeAg and Elevated Transaminases:** According to Riss E.A. et al. (1991), the first form of chronic hepatitis is characterized by a strong clinical-laboratory manifestation of active inflammation in the liver. Clinically, it corresponds to active chronic hepatitis caused by the B virus. The second form is understood as chronic persistent hepatitis. The third form differs in its diversity. This includes cases with co-infection with the D virus, liver damage due to medications, metabolic pathology, and even changes associated with malignant hepatomas.

For a long time (until the late 1960s and early 1990s), the classification of chronic hepatitis accepted by the International Council and the European Association of Hepatologists was considered a working classification. This classification was based on morphological principles, distinguishing two main forms: chronic persistent (non-aggressive) hepatitis (CPH) and chronic active (aggressive) hepatitis (CAH).

The division of chronic hepatitis as mentioned is based on the main diagnostic features (morphological), but it does not provide information about the etiology, clinical signs of different forms, or their progression characteristics [Inoyatov F.I., Abdumadjidova Sh.U., 2006].

It was later found that not all cases of chronic hepatitis were covered by these forms. In some instances, the morphological appearance of CPH and CAH could change in the same patient. Consequently, the terms CPH and CAH reflect the degree of activity and stages of the process but do not address the disease forms.

As a result, contemporary views on chronic hepatitis consider it as an independent disease with its own clinical, morphological, and etiological characteristics and pathogenesis features, utilizing various classification principles. Podimov S.D. (1993) proposed a new classification that includes etiology, morphology, clinical features, disease activity, and the functional state of the liver.

In hepatological practice, highly sensitive and specific methods such as ImmunoFluorescence Assay (IFA) have been introduced, and Polymerase Chain Reaction (PCR) has made significant progress in elucidating the etiology of chronic viral hepatitis and identifying different variants of autoimmune hepatitis. Significant achievements have been made in the treatment of chronic hepatitis considering etiopathogenetic factors [Chistov L.V., 1997].

At the International Congress of Gastroenterologists held in Los Angeles (USA) in 1994, an international expert group adopted a classification that remains relevant today. Its significant feature is the non-morphological, non-limitative approach, similar to previous principles (chronic persistent hepatitis and chronic active hepatitis), with etiological factors, activity level, and stages of the pathological process: replicative and integrative. This classification is based on virological, biochemical, and morphological data [Desmet V.J. et al., 1994]. It considers morphological criteria in diagnosis and provides important additional information about the process stage and activity. The agreed classification divides chronic viral hepatitis into groups B, C, D, and G. These groups include drug-induced, cryptogenic, and autoimmune hepatitis.

In children, the natural course of chronic hepatitis B (CHB) differs significantly from that in adults, especially in younger children. The disease often proceeds asymptomatically. However, the clearance of HBeAg may extend up to 40 years of age [Zaysev I.A., Zaplotnaya A.A., 2006]. In chronic hepatitis C (CHC), the disease progresses to a chronic form in 70-90% of patients who initially present with an acute form. Many authors acknowledge that the spontaneous clearance rate of chronic hepatitis C (CHC) in adults is low (ranging from 8% to 20%), and it can progress to liver cirrhosis in 8-24% of cases and to hepatocellular carcinoma in 0.7-1.3% of cases [Guido M., Rugge M., Jara P., 1998; Lebensztein D.M., Skiba E., Kaczmarski M. et al., 2003].

Currently, it is believed that the natural course of chronic hepatitis C (CHC) in most children is relatively mild and persistent compared to infection, with the condition typically developing later in life. Children infected through previous parenteral interventions or blood transfusions exhibit spontaneous clearance in 20-45% of cases, but they remain at higher risk for the development of cirrhosis. According to literature, the risk of developing liver cirrhosis in children with CHC can reach 8% between the ages of 3 and 7 years after infection [Denisov M.F., Berezenko V.S., 2004].

The clinical progression of chronic hepatitis has distinct features. Chronic viral hepatitis B and C in children often present with subclinical progression, characterized by predominantly asthenovegetative symptoms, slight hepatomegaly, and normal or slightly elevated levels of transaminases in the blood. The natural progression of chronic viral hepatitis B depends on the clinical form of the disease (HBeAg-positive or HBeAg-negative) and the age at which the infection occurred [Abdukadirov M.A., 2002; Kamilov F.X., 2000].

In children with chronic viral hepatitis B and HBeAg-positive variants, the immunotolerant phase may last from 10 to 30 years. During this phase, the amount of HBV DNA in the blood is high, and the transaminase levels are close to or within the normal range. Spontaneous seroconversion to anti-HBeAg is very rare [Abduraxmanov D.T., 2001].

Children with chronic viral hepatitis B, particularly those who were infected at an older age, often exhibit a more severe course of the disease. The manifestation of the disease typically occurs in patients aged 30-40 years. Spontaneous seroconversion occurs in 8-15% of patients. The higher the level of alanine aminotransferase (AlAT), the more likely spontaneous seroconversion is to occur [Kadirov B.A., 1994].

In younger children, chronic hepatitis occurs similarly to how it does in children older than 3 years. The clinical manifestation of chronic hepatitis varies in severity, and corresponding biochemical indicators may be moderately or minimally altered [Baranov A.A., Kaganov B.S., Uchaykin V.F., et al., 2004].

Nearly all children with chronic hepatitis exhibit asthenic symptoms such as fatigue, weakness, and a lack of energy, along with rapid exhaustion and emotional instability. Often, after viral hepatitis,

various forms of dyspeptic syndrome can be observed at different times. Symptoms include reduced appetite, discomfort in the epigastric region after physical exertion, belching, nausea, and occasionally vomiting. Some children report diarrhea or constipation, while others complain of abdominal distension [Uchaykin V.F., 1998; Cherednichenko T.V., Moskovskaya M.A., 2003].

Consequences: Chronic viral hepatitis can have a long-term persistence with active pathological processes. Chronic hepatitis B typically shows a decrease in disease activity over 5-10 years; 10% of patients develop antibodies against surface antigens (anti-HBs) and clear the virus, leading to a stable normalization of AST and ALT levels and recovery. In 1-1.5% of cases, cirrhosis may develop, while 89% of cases result in long-term remission with HBsAg carrier status. Chronic hepatitis D often has a poor outcome, with 20-25% of cases progressing to liver cirrhosis, and elimination of the pathogen does not occur. Chronic hepatitis C usually has a prolonged, "mild" course with periodic increases in transaminase activity, persistent viremia over many years, and a high tendency for fibrosis [Aprosin Z.G., 1993; Kotovich M.M., 2003; Kupershteyn A.P., Kim A.A., 2000].

Despite significant progress in studying chronic liver diseases, many aspects of this pathology remain poorly studied or even unexplored. Currently, the prevalence of chronic liver diseases among children is not well determined, and the etiological factors and structure affecting the development and progression of chronic processes in practice are not fully investigated. Furthermore, there is a lack of reliable studies on the use of hepatotropic drugs for treating chronic viral hepatitis in children. Difficulties arise in the investigation and application of these drugs for the treatment of chronic viral hepatitis in children.

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