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MODERN METHODS OF DIAGNOSIS AND THERAPY OF CHRONIC HEPATITIS DELTA

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Abstract: Hepatitis D occupies one of the leading places in infectious pathology, which is characterized by global spread and a high degree of chronicity, with subsequent development of liver cirrhosis and hepatocellular carcinoma. The article is focused on the theoretical basis of virology, modern methods of diagnostics, and treatment of viral hepatitis Delta.

Keywords: Hepatitis D, diagnosis, etiotropic treatment, pathogenetic treatment.

Introduction. Chronic hepatitis D is a long-term infection with a relatively high propensity to develop liver cirrhosis (LC) and progression to serious liver-related complications, which are more common in patients with persistently replicating HDV or HBV [21]. Globally, the World Health Organization (WHO) has estimated that approximately 5% of people with chronic HBV infection are also infected with HDV, meaning that a total of 15-20 million people is infected with hepatitis D worldwide. Adherence of HDV to HBV is known to increase the severity of progression to LC and hepatocellular carcinoma (HCC) [20].

High morbidity affected people of working age, a variety of clinical forms, with a high frequency of chronification and/or malignization of the process, the possibility of developing LC, as well as the huge damage caused by viral hepatitis to

the economy as a whole—all these factors determine the wide interest of researchers in the diagnosis and therapy of viral hepatitis D [7].

The article aim: To provide a comprehensive overview of the current state of the art on modern methods of diagnosis and treatment of chronic hepatitis D, which will facilitate early diagnosis and timely treatment to reduce the risk of complications from the disease.

Considering recent evidence that the global disease burden may be higher than previously thought, screening of all HBsAg-positive patients for anti-HDV is necessary. This strategy will not only allow a more accurate determination of the prevalence of HDV infection but will also lead to early therapeutic interventions that reduce the burden of disease complications.

Materials and methods: *Clinical methods* include the determination of a general blood test and urine test. Assessment of liver disease severity should include biochemical markers, such as ALT, AST, GGT, alkaline phosphatase, bilirubin, serum albumin, globulins, blood coagulation, and creatinine.

Serological and molecular biological methods.

The tests are performed by enzyme-linked immunosorbent assay (ELISA) and polymerase chain reaction (PCR). HDV infection is diagnosed by detecting antibodies to HDV - immunoglobulin G (IgG) and immunoglobulin M (IgM) - and confirmed by detecting HDV RNA in serum. Total antibodies against HDV are currently used as the first screening method for detecting HDV infection. Serum HDAg is only detectable in the initial phase of HDV infection [28]. In cases where HDV RNA quantification is not possible, HBsAg quantification is an appropriate marker for monitoring response to treatment. Decreasing HBsAg titer often indicates the disappearance of surface antigen and clearance of HDV, although the disappearance of surface antigen is rare in treatment-resistant HDV infection. Confirmation of infection is based on the detection of HDV RNA by RT-PCR and positive anti-HDV [12].

The first step is an anti-HDV screening followed by an HDV RNA test. In cases of HDV coinfection, HBsAg, HBeAg, and HBV DNA appear in the serum during the incubation period. IgM anti-HBc shows the onset of disease symptoms and indicates acute co-infection. HDV markers, IgM anti-HDV, and HDAg appear in serum subsequently. HDAg appears in serum earlier but for a short time except in immunocompromised patients. All markers disappear within a few months after recovery, while total anti-HBc and anti-HDV IgG persist [8]. In the acute phase of HDV superinfection, high titers of anti-HDV IgM and IgG are observed. Determination of HDV RNA viral load is recommended to assess the efficacy of antiviral treatment [23]. Patients with elevated transaminase but undetectable HBV DNA and negative HDV serology should be tested for HDV RNA to exclude seronegative hepatitis D [13]. The amount of HDAg decreases with the progression of fibrosis, almost undetectable in the last stage of the disease [24]. PCR can be used to detect HDV RNA in both HDV coinfection and HDV superinfection, as the aim is to quantify circulating virus in the blood (real-time PCR) and to determine genotype [29]. If HDV RNA is negative, it is recommended to repeat the PCR and/or, if necessary, to use other diagnostic methods such as immunohistology (liver biopsies) and biochemical methods [17].

Instrumental research methods: Liver, spleen, gallbladder ultrasound, MRI - as indicated, Liver biopsy/elastography. Serum HDAg can be detected by radioimmunoassay, which is not commonly used in a clinical setting. It is also unable to detect antigens that form a complex with anti-HD, and therefore immunoblot tests are required [9]. Immunohistochemistry of biopsy specimens for HDAg has been proposed as the gold standard for diagnosis. However, up to 50% of all biopsy specimens from chronically infected patients are negative. Liver biopsy is an important tool for clarifying the diagnosis in more than 20% of patients with unknown causes of cirrhosis [22].

Therapy. Currently, there are no standards of treatment for hepatitis D. Interferon alfa (Peg-IFNα) is the only method to control and treat chronic hepatitis

delta. In the past, Peg-IFNα has been evaluated as a treatment for HDV with limited success [26]. Peg-IFN is administered for longer than one year to improve the efficacy of therapy. However, the efficacy of long-term therapy is controversial. Virological response within 24 weeks of treatment is the most widely used surrogate marker of treatment efficacy but does not represent an indicator of sustained virological response [31]. Nucleoside and nucleotide analogs (NAs) are considered ineffective in the treatment of HDV because they do not prevent HDV replication in the short term. HAs therapy may be effective in cases where HBV, not HDV, is the dominant virus. Longer courses of HA treatment may have some effect on reducing HDV RNA, but the exact results remain uncertain [15]. The combination preparations of standard or pegylated interferon with lamivudine [11], adefovir [27], tenofovir [26], and entecavir [1] have been studied but were disappointing as they did not result in improved viral response rates compared to IFN monotherapy for HD.

New treatment options include the prenylation inhibitor lonafarnib [30], nucleic acid polymers, and the HBV penetration inhibitor *myrcludex B* [6] and interferon lambda [16], which are currently in clinical trials. The drugs are being studied individually and in combination with pegylated interferon. The results of clinical trials with *Mircludex B* fulfill expectations for combination therapy of HDV infection in the future. Currently, a drug is being studied - *lonafarnib*, which affects the processes of post-translational modification of antigens of the delta agent, in particular, the processes of prenylation at the C - the end of the L-HDVAg molecule, which ensures the binding of the HDV RNA nucleocapsid with the HBsAg of the virus.

Ritonavir, a CYP3A4 inhibitor, provides higher serum concentrations of lonafarnib, a greater reduction in viral load, and better gastrointestinal tolerability (as a result of a lower administered dose). The combination of lonafarnib+ritonavir with Peg-IFNa achieves the greatest antiviral response.

Nucleic acid polymers (NAPs) are broad-spectrum antiviral agents whose antiviral activity in hepatitis B virus (HBV) infection is due to their ability to block

the release of hepatitis B virus surface antigen (HBsAg), block the replenishment of HBsAg in the circulation, and ensure clearance. The antiviral effects of NAPs are negatively charged molecules that interfere with the initial non-specific adsorption of viruses on the surface of the cell [25].

The mechanism of the therapeutic effect of *REP 2139* in CHD is not fully understood. Various NAPs have been shown to inhibit the entry of HDV into human hepatocyte cells by preventing the virus from attaching to glycosaminoglycans on the cell surface [4]. The search for drugs for the treatment of HDV continues.

Pathogenetic drug therapy.

Detoxification therapy. Infusion therapy is used for a limited time, mainly at the height of intoxication. For this purpose, intravenous drip infusions of 5% glucose solution, and 0.9% saline are used.

Detoxification agents: Ornithine-L-aspartate (Hepa-Merz) reduces the level of ammonia in the body, in particular in the brain, participates in the ornithine cycle of urea formation from ammonia, promotes insulin production, and improves protein metabolism. It should be prescribed 20-40 ml per day in the presence of signs of encephalopathy.

Glutathione (Neomarin) is a tripeptide whose molecule contains cysteine, glutamic acid, and glycine. The detoxification properties are largely due to the presence in its molecule of the SH group belonging to the cysteine residue. Oxidized by the SH group, glutathione enters into processes associated with detoxification and excretion of absorbed heavy metals, metabolic products, drugs, carcinogens, and other toxic compounds of both exogenous and endogenous origin [3]. It also contains sulfur-containing groups that are able to "attract" toxins, free radicals, and harmful chemical compounds, and then quickly remove them from the body. *Antioxidants:* glutathione plays a key role in protecting cells from oxidative stress, and it is implemented in three ways at once. Firstly, glutathione is a cofactor of the enzyme glutathione peroxidase - the most important component of the body's antioxidant defense, which neutralizes inorganic and organic peroxides. Secondly, due to the

presence of a thiol group, glutathione itself is able to capture and destroy free radicals. functions of other antioxidants — vitamins A, C, and E [2]. Glutathione is synthesized in the human body from amino acids that form a tripeptide molecule. Under the influence of adverse external factors, psychological stress, infections, radiation, and poor ecology, as well as a result of the use of medications, the amount of glutathione synthesized in the human body decreases. With a long-term lack of glutathione, the process of premature aging of all tissues begins, liver and kidney diseases develop, and neoplasms may appear. The antioxidant effect of glutathione has been confirmed in many clinical studies, which have shown that taking L-glutathione helps to increase the endogenous antioxidant defense of the body, reduce the level of total cholesterol and high-density lipoproteins, and improve the condition of blood vessels [10]. Another study showed an improvement in the indicators of redox status and an increase in the levels of vitamins A, C, and E in all participants experiment [5,10]

Hepatoprotectors – preparations of betaine glucuronate, ursodeoxycholic acid, glutatine, thinitric acid salts.

Anti-fibrotic - To prevent LC, it is necessary to start treatment immediately after detection of liver fibrosis. Disturbance of liver cellular organizations gives grounds for the use of antifibrotic drugs from the group of hepatoprotectors. One of such drugs is liverrin [18]. A drug with antifibrotic activity must have the following properties: suppression of profibrotic activity and maintenance of antifibrotic activity in stellate cells (reduction of matrix synthesis and enhancement of its decay, suppression of Ito cell proliferation); and influence on collagen secretion by liver stellate cells. Cytoprotective, antioxidant, anti-inflammatory, immunomodulatory, membrane-stabilising, and antifibrotic properties of oxymatrine have been revealed and continue to be studied [19]. According to Chinese researchers, oxymatrine suppresses the activation, replication, and proliferation of stellate cells, thereby reducing collagen synthesis by Ito cells. It also suppresses the expression of proliferation, growth, and fibroblast growth factors β (TGF β) [32].

Correction of metabolic disorders: cocarboxylase, thiotriazolin, vitamins B6, PP, K, E, folic acid, potassium, calcium, magnesium, zinc.

*Choleretic drugs (*Preference is given to ursodeoxycholic acid preparations).

Sorbents are natural or artificially synthesized substances capable of absorbing and removing toxic substances and harmful compounds from the digestive tract (cholestyramine, bilignin, activated carbon, filtrum, smecta).

Antispasmodic drugs (Duspatalin, No-Shpa, Papaverine).

Glucocorticoids: Low transcortin content explains the lack of effect of endogenous and exogenic hormones in severe viral hepatitis. In this regard, the content of glucocorticoid hormones in the blood and saliva increases [14].

If necessary: *coagulopathy correction* (vitamin K, plasma, aminocaproic acid, vikasol). Enzyme preparations that do not contain salts of bile acids (Creon, Chilak forte, Mezim forte, etc.).

To monitor the effectiveness of therapy is necessary:

- Determination of blood biochemical parameters, every 1-3 months during the first 6 months of treatment, and then every 6 months.

-Clinical blood analysis once every 2 weeks in the first month of treatment and monthly thereafter.

Dynamic study of relevant serological markers.

Findings:

1. Screening all HBsAg-positive patients for anti-HDV. This strategy will not only allow a more accurate determination of the prevalence of HDV infection but will also result in a reduced burden of disease complications.
2. If the anti-HDV test is positive, a test for HDV RNA should be performed.
3. Patients with elevated transaminase but undetectable HBV DNA and negative HDV serology should be tested for HDV RNA to rule out seronegative hepatitis D.
4. There are currently no standards of care for the treatment of hepatitis D. Interferon alfa (Peg-IFNα) is the only method of control and treatment for chronic hepatitis delta.

5. Given the low efficacy of etiological treatment, the use of pathogenetic therapy using detoxification, antioxidative, anti-apoptotic, and antifibrotic agents is indicated.

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