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ТИББИЁТДА ЯНГИ КУН

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IMMUNOLOGICAL PARAMETERS OF CHANGES OBSERVED IN THE LIVER IN HDV INFECTION

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✓ ***Resume***

Viral hepatitis remains the most urgent problem of global public health. Every year, infectious diseases are the cause of death in more than 4 million people, about 1 million people die from hepatitis B (HBV) and C (HCV) in the world every year, and even more people infected with these viruses lose their ability to work. Losses associated with viral hepatitis account for a significant share of the economic damage from the most common infectious diseases. Against the background of rapid progress in the treatment of viral hepatitis C, the role of insufficiently studied and difficult to treat mixed hepatitis B infection with delta agent is currently increasing.

Keywords: hepatitis D, hepatitis B, epidemiology, cirrhosis of the liver

HDV ИНФЕКЦИЯСИДА ЖИГАРДА КУЗАТИЛАДИГАН ЎЗГАРИШЛАРНИНГ ИММУНОЛОГИК МЕЪЗОНЛАРИ

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✓ ***Резюме***

Вирусли гепатит глобал соғлиқни сақлашнинг энг долзарб муаммоси бўлиб қолмоқда. Ҳар йили юқумли касалликлар 4 миллиондан ортиқ одамнинг ўлимига сабаб бўлади, дунёда ҳар йили 1 миллионга яқин одам гепатит В (ҲБВ) ва С (ҲСВ) дан вафот этади ва ҳатто бу вируслар билан касалланган одамлар ҳам ўз қобилиятини йўқотади. Вирусли гепатит билан боғлиқ йўқотишлар энг кўп тарқалган юқумли касалликлардан келиб чиқадиган иқтисодий зарарнинг катта қисмини ташкил қилади. Вирусли гепатит С ни даволашда жадал ривожланиш фонида ҳозирги вақтда delta агенти билан аралаш гепатит В инфекциясини етарли даражада ўрганилмаган ва даволаш қийин бўлган роли ортиб бормоқда.

Калит сўзлар: гепатит D, гепатит B, эпидемиология, жигар цирроз

ИММУНОЛОГИЧЕСКИЕ ПАРАМЕТРЫ ИЗМЕНЕНИЙ ПЕЧЕНИ ПРИ ИНФЕКЦИИ HDV

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✓ ***Резюме***

Вирусные гепатиты остаются актуальнейшей проблемой мирового общественного здравоохранения. Ежегодно инфекционные болезни являются причиной смерти более чем у 4 млн. человек, от гепатитов В (ВГВ) и С (ВГС) в мире каждый год погибает около 1 млн. человек, ещё большее количество инфицированных этими вирусами людей теряет трудоспособность. Потери, связанные с вирусными гепатитами, составляют значительную долю экономического ущерба от наиболее распространенных инфекционных заболеваний. На фоне стремительного прогресса в лечении вирусного гепатита С, в настоящее время, нарастает роль недостаточно изученной и трудно поддающейся терапии микст-инфекции гепатита В с дельта агентом.

Ключевые слова: гепатит D, гепатит B, эпидемиология, жигар циррози

Relevance

In the world, there are more than 350 million people infected with the hepatitis B virus, of which 15-25% (750 thousand) die each year due to the development of complications of liver cirrhosis and hepatocellular carcinoma [1]. The proportion of patients with HBV who have a concomitant delta agent that dramatically complicates its natural course varies from less than 1% to more than 10% in different populations. Worldwide, 20 million people may be infected with hepatitis delta virus [2].

An indicator of the prevalence of chronic hepatitis D is the frequency of detection of anti-HDV antibodies. Based on the prevalence of delta infection among patients with hepatitis B, regions can be conditionally classified into one of four zones: zones of high endemicity - the frequency of anti-HDV antibodies is over 60%; zones of moderate endemicity - the frequency of anti-HDV antibodies is 30–60%; areas of low endemicity - the frequency of anti-HDV antibodies ranges from 10 to 30%; zones of very low endemicity - the frequency of antiHDV antibodies does not exceed 10%.

In general, in developed countries, IOP is rare; in Europe and the USA it ranges from 0.2% to 1.0%. The regions of maximum distribution of anti-HDV are the Mediterranean countries, especially Southern Italy and Greece, as well as Romania, a number of countries in Southeast Asia, the Middle East, Africa and South America vary from 15.0 to 20.0%. In Russia, the prevalence reaches an average of 7.0%. In the post-Soviet space, the most affected regions are Russia, Central Asia, Moldova and Kazakhstan [3,5].

According to expert estimates in the Republic of Uzbekistan, screening studies in risk groups in 2014 revealed the presence of HBsAg in 2.3% of the population. Among pregnant women and blood donors, the prevalence of HBV is 1.3% in 2021 and 1.2% in 2022, respectively.

Given the fact that HDV RNA cannot replicate without infection by HBsAg, the endemicity of HDV should directly depend on the prevalence of HBV in the country. However, according to current epidemiological studies, this relationship is not natural and the areas of circulation of the delta agent do not correspond to the prevalence of HBV. Thus, in most of South Asia (Taiwan, China), where the incidence of HBV is extremely high, infection with the delta agent is rare. Probably the main factors influencing the prevalence of the delta agent are the processes of globalization and population migration [5,6,10]. Based on polymorphism of nucleotide sequences of genomic HDV (differences between genotypes from 19 to 38%), currently 8 genotypes of the virus. The wide genotypic profile is probably due to the ability to mutate. HDV genotype 1 is widespread throughout the world, predominant in Europe and the Mediterranean countries, Iran, Turkey, and North America. Genotype 2 predominantly circulates in East and North Asia. In the northern part of South America (Brazil, Colombia, Venezuela, Peru, Ecuador) - genotype 3; in Japan, Taiwan and China - genotype 4. In Western and Central Africa, genotypes 5 to 8 are common [10]. The route of transmission of the delta agent is the same as that of HBV; therefore, the risk group includes patients with a rich parenteral history - recipients of donor blood, hematological patients, injection drug users. Infection through non-medical invasive procedures (manicure, pedicure, tattooing, piercing) is quite widespread. Unfortunately, The hospital route is still relevant, so among medical organizations the leaders are: surgical, tuberculosis departments, dental clinics, chronic hemodialysis centers. Data on the activity of sexual transmission of the delta agent are at the stage of accumulation. An increased frequency of detection of anti-HDV antibodies is known among homosexuals and commercial sex workers [6]. The vertical variant from mother to fetus also exists, but epidemiologically its role is minimal due to the

specific clinical course. Chronic hepatitis B with the delta agent is a severe and rapidly progressive form of viral hepatitis, leading to cirrhosis in 70% of cases within 5–10 years. In 15% of patients, cirrhosis can develop within 1 to 2 years from the onset of acute hepatitis. The risk of developing liver cirrhosis is three times higher in HDV-infected patients compared with those who have HBV mono-infection only [1,8,11]. The causative agent of HDV, a virion with a single-stranded RNA molecule, is defective due to the low content of genetic material, and therefore is not capable of independent reproduction. The HDV RNA supercapsid includes significant amounts of HBsAg antigen, so delta infection replicates only in the presence of HBV.

HDV replication begins only after HBV infects hepatocytes and HBsAg synthesis is initiated. Anti-HDV IgG occurs in both acute and chronic delta infections and is detected in more than 90% of cases within 3–8 weeks after infection. As a result of the complex interaction between the two viruses, the clinical manifestations of co-infection of hepatitis B with the delta agent vary from mild to severe, in some cases, fulminant hepatitis. It is still unclear what determines the outcome of the disease: the massiveness of viral invasion, the nature of the specific immune response, the genotype of the virus, genetic drift of the surface immunodominant epitopes of the virus, allowing it to partially escape the host's immune surveillance, finally, the set of expressed HLA antigens or other, still unknown reasons [9].

A higher rate of growth of liver fibrosis was established in Kazakhs of the study group, a correlation between TNF-alpha and the rate of growth of liver fibrosis, which allows us to consider tumor necrosis factor-alpha as a genetic marker of the risk of developing viral cirrhosis of the liver. A high correlation coefficient of ALT/IL-1beta was revealed, which allows us to consider the IL-1beta indicator as a genetic marker of the activity of viral liver inflammation.

The universal mechanism for the development of inflammation in the liver during viral infections, including co-infection of hepatitis B with the delta agent, is the synthesis of specific chemokines by hepatocytes in response to the introduction of the virus, causing the migration of T-lymphocytes, which through cytokines lead to liver damage [15,16]. Currently, there is an opinion that when the delta virus is attached, the synthesis of HBeAg stops. According to Wu JC, et al (1996), HDV RNA superinfection can accelerate the process of selection of the mutant form of hepatitis B. Treatment options: PEG-IFN-α was introduced into HBV therapy with a delta agent in 2006. The HIDIT-1 study showed significant antiviral effectiveness of PEG -IFN-2α against HDV RNA in more than 40% of patients, with 25% achieving SVR at 48 weeks of treatment. In June 2009 The second study evaluating the effectiveness of PEG-IFN-2α in combination with Tenofovir (HIDIT II) has started and is scheduled for completion in May 2017. Patients with chronic HBV with a delta agent (70 people) will receive PEG-IFN-2α (180 μg) in combination with Tenofovir (245 mg), and the comparison group - PEG-IFN-2α (180 μg) in combination with placebo. In the Republic of Kazakhstan, treatment with interferons is provided within the framework of the guaranteed volume of medical care; the effectiveness cannot be considered sufficient (about 30%) and requires further study.

A new direction in the treatment of IOP is the development of drugs that inhibit the binding of the delta agent and the hepatitis B virus (Mircludex B), the proposed mechanism of action of which is the ability to firmly bind to specific (however, still not fully studied) receptors for HBV located on the surface hepatocytes, which does not allow viral particles to penetrate into the cell. In addition, a group of drugs that affect the processes of post-translational modification of delta agent antigens, in particular the processes of prenylation, i.e. modification of the cysteine residue at the C-terminus of the L-HDVAg molecule, which enhances the lipophilic properties and ensures a stable connection of the HDV RNA nucleocapsid with the virus envelope (HBsAg) [9]. Nucleose(t)ide analogues are ineffective in inhibiting HDV RNA replication. However, this therapy should be considered in patients with active HBV DNA replication (HBV DNA greater than 2000 IU/ml) [8]. IOP is currently poorly understood, but it is the most dangerous and virulent hepatotropic virus, leading to rapid progression and development of liver cirrhosis. However, pairing the delta agent with HBV gives it the same status of a "preventable infection" as that of viral hepatitis B.

Conclusion

In the Republic of Uzbekistan, the distribution is quite heterogeneous in different regions and requires further study. Vaccination against hepatitis B still remains the only available method of preventing infection with the delta agent

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