48. Yang Y., Chen X., Saravelos S.H., Liu Y., Huang J., Zhang J., Li T.C. *HOXA-10* and E-cadherin expression in the endometrium of women with recurrent implantation failure and recurrent miscarriage. *Fertil. Steril.* 2017; 107(1): 136-43. e2.

49. Zheng J, Luo X, Bao J, Huang X, Jin Y, Chen L, Zheng F. Decreased Expression of *HOXA10* May Activate the Autophagic Process in Ovarian Endometriosis. *Reprod Sci.* 2018 Sep;25(9):1446-1454.

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HDV INFECTION: A PREDICTOR OF SEVERE HEPATIC FIBROSIS (LITERATURE REVIEW)

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Abstract: About a third of the world's population has serological signs of previous or current HBV infection, and 350 million people suffer from chronic hepatitis B. It is generally known that the combined damage of the liver with hepatitis B (HBV) and delta (HDV) viruses significantly increases the risk of adverse outcomes such as liver cirrhosis and hepatocellular carcinoma. However, the lack of official registration of HDV in Russia contributes to the belittling of the threat posed by it. In addition, many aspects of the pathogenesis and improvement of HDV diagnostic methods still require detailed study. The problem is of particular importance for the Republic of Sakha (Yakutia), since the share of chronic hepatitis D in the etiological structure of chronic viral hepatitis accounts for 24.5%, in some areas the number of people with antibodies to HDV infection among HBsAg-positive population reached 31% [8]. In the European part of Russia, antibodies to the HD virus were detected in 1.3-5.5% of individuals with HBsAg [3].

The aim of this study is to study the epidemiological and pathogenetic aspects of HDV infection using the example of the Republic of Sakha (Yakutia).

The rate of progression of chronic hepatitis D infection in patients is not the same, while the factors that determine the unfavorable outcome of this infection need to be clarified [14,16,28]. In addition to the genetic characteristics of the virus, the role of interferon genes in the formation of liver fibrosis was noted, due to their binding to the receptors of host cells and their influence on the process of viral reproduction within the cell. The results of clinical studies indicate their predictive effects in Asian populations (Japan, China, Taiwan). There are works indicating the influence of polymorphism (rs368234815) of the IFNL4 gene on the incidence of hepatocellular carcinoma [17]. Taking into account the above, the clinical and epidemiological situation for hepatitis D can serve as the subject of studying the influence of the virus genotype and polymorphisms of candidate genes on the formation of HDV-associated hepatocellular carcinoma, as well as on the likelihood of achieving a stable virological response and / or spontaneous clearance in patients with different rates of liver disease progression.

Keywords: Hepatitis D virus, hepatitis B virus, chronic hepatitis, epidemiology, predictors, gene polymorphism, INFL 3, INFL 4, liver cirrhosis, hepatocellular carcinoma.

Introduction. Despite some progress in studying the characteristics of the epidemiology of hepatitis D, the risk of its progressive course remains high. Chronic hepatitis D is a severe form of liver disease characterized by an aggressive course and leading to the rapid development of liver cirrhosis and hepatocarcinoma [3, 6, 7].

Due to the lack of an official registration of this disease in the Russian Federation, the epidemiological situation is assessed fragmentarily by based on the available results of selected scientific studies. In hepatitis B, super-infection with the delta virus causes progression of the disease and leads to a more rapid development of liver cirrhosis than mono-infection of hepatitis B. [1, 2, 12].

Purpose of the study: is to study the epidemiological and pathogenetic aspects of HDV infection using the example of the Republic of Sakha (Yakutia).

Research results: The Republic of Sakha (Yakutia) is one of the disadvantaged territories of the Russian Federation in terms of the prevalence of parenteral viral hepatitis [9]. According to the Rospotrebnadzor Administration for the Republic of Sakha (Yakutia), the incidence of chronic viral hepatitis in 2018 amounted to 67.8 people / 100 thousand people, which is higher than the incidence rates in the Far Eastern Federal District (48.1 people / 100 thousand people) and the Russian Federation (42.2 people / 100 thousand people. The frequency of detection of antibodies to hepatitis D virus according to scientific research in Yakutia is heterogeneous, ranging from 17.2% to 31.7% [8]. In the federal register "Chronic viral hepatitis in the Republic of Sakha (Y)", only 15,068 people were registered, of which the share of chronic hepatitis D accounted for 15.5%. Chronic viral hepatitis D is detected more often in men of working age and is characterized by a progressive course, with the development of cirrhosis of the liver (LC) and hepatocellular carcinoma (HCC). In the etiology of all cirrhosis, the proportion of delta infection is 38.4%, and in HCC - 28.5%, among all deaths from viral hepatitis in Yakutia in 2019, 43% suffered from chronic viral hepatitis D. According to the analysis cases of detection of hepatocellular carcinoma in the Republic of Sakha (Yakutia), this pathology exceeds the average incidence in the country, and the incidence of malignant neoplasms of the liver is ten times higher than the average in the Russian Federation both among men and women [5, 9, 11].

A feature of the hepatitis D virus is its ability to replicate in the human body in the presence of hepatitis B virus [4, 25]. The causative agent of HDV infection was first identified by Italian scientists in 1977 when analyzing 83 liver biomaterials in HBsAg carriers [20, 21]. The

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antigen found in liver cells was initially mistaken for a new HBV marker, but further research led to the discovery of the defective hepatitis D virus [22]. The virus particle is formed from the nucleocapsid, which is represented by the only virus protein with an envelope coated with the surface proteins of the hepatitis B virus [5]. The genetic material, in the form of genomic HDV RNA, has a size of 1700 nt and is located inside the nucleocapsid. [24].

The rate of progression of chronic hepatitis D in patients is not the same, and the factors that determine the unfavorable outcome of this infection need to be clarified [25]. It is customary to distinguish 8 main genotypes of the hepatitis D virus, based on the polymorphism of the nucleotide sequences of genomic RNA, the geography of distribution of which is extensive and diverse [18, 26, 27, 28].

The most common variation - genotype 1, covers all continents and is characterized by variety of clinical course. Genotypes 2, 4 are more common in East Asian countries, including the Far East, and have a milder and slower course of the disease than genotype 1. Genotype 3 is common in the more northern countries of South America, such as Peru, Ecuador, Venezuela, Colombia; genotype 3 is often characterized by a fulminant course with the rapid development of cirrhotic changes. Genotypes 5,6 and 7 are poorly studied, found in the countries of Central and West Africa (Table 1) [3,6].

Based on genotyping of blood serum samples from patients with HDV infection living in the Republic of Sakha (Yakutia) and subsequent phylogenetic analysis of hepatitis D virus isolates, the prevalence of hepatitis D virus genotypes 1 and 2 was revealed. Among the indigenous population of the republic, both genotypes were equal in frequency of occurrence, but in the non-indigenous population genotype 1 was found somewhat more often (11.4%) (Table 2). The incidence of liver cirrhosis in both groups is almost the same, 37.1% and 36.6%, respectively. With the 1st genotype, chronic hepatitis in 54.3% of cases proceeded with an active cytolytic reaction, with the 2nd genotype it was slightly less - 36.6%. The proportion of patients in the stage of cirrhosis prevailed in genotype 2 (46%), HCC was observed in patients with only HDV genotype 1 (5.7%) [10].

There are data from the analysis of partial or complete HDV sequences isolated in certain regions of the world [4, 23], including in Russia [8], however, ideas about the evolution of HDV and the relationship of different variants of the virus with the progression of the disease and molecular evolution of HDV are fragmentary character. As a result of the analysis of HDV sequences obtained in dynamics by the Sanger sequencing method, the existence of positive selection in the domains located in the T- and B-cell epitopes of HDAg was shown, as well as a return to the original sequence, i.e. a tendency towards "reverse evolution" of HDV. Apparently, this indicates the selection of more replicatively successful and, possibly, more pathogenic variants, as well as the evasion of the virus from the immune response [22].

From a clinical point of view, in the prospective observation of patients, an association of high levels of viral load was noted HDV with disease progression [1], as well as reactivation in advanced liver disease of HB-virus replication, usually suppressed by HDV [13]. There are also studies of host genetics, especially variants of genes that control immune and inflammatory response pathways. The role of interferon genes is due to binding to cell receptors and participation in the process of viral reproduction inside the cell. N. Ma et al. [19] in their work investigated 3128 people, a homogeneous (Chinese) population, for the possibility of infection with HBV and a number of gene polymorphisms (14 loci) of interferons. The most significant gene variants - IFN associated with HBV elimination were genes IFNAR2, IFNLR1, and the polymorphic variant rs4649203 of the IFNLR1 gene was associated with persistent virological effect (SVR). In addition, the authors point out the connection between the formation of HCC and the polymorphisms of the IFNA1, IFNA2, IFNL4 genes. In the studied groups with cirrhosis and liver cancer, genotypes rs12971396 G, rs8113007 T and rs7248668 A of the IFNL 4 gene, which are associated with a worsening of the course of viral hepatitis B. In addition, the development of liver cancer in polymorphic variants of the IFNA1-rs1831583 and IFNA2-rs649053 genes is indicated. The polymorphic variant rs4649203 of the IFNLR1 gene is designated as a predictor of virus elimination, and the polymorphisms rs1051393, rs12233338 of the IFNAR2 gene as a candidate gene for infection in the studied population [19]. There are studies indicating the relationship between the development of HCC and the polymorphism (rs368234815) of the IFNL4 gene [17, 18]. The IFNL3 gene

Table 1

Distribution of HDV genotypes in world

HDV genotype	Distribution	Pathogenity
1	All around the world, predominantly North America, Middle East, Europe, incl. Russia (Tuwa, Yakutia)	Variable
2	Eastern and Northern Asia (Japan, Taiwan, Yakutia)	Mild
3	Northern part of South America (Brazil, Peru, Columbia, Venezuela, Ecuador)	Severe
4	Japan, Taiwan, China	Mild
5-7	Western and Central Africa	No data
8	Western and Central Africa, Brazil	No data

Table 2

Indicator	Genotype	
	I (n = 36)	II (n = 29)
Mean age (yr)	42±12,4	41,2±8,9
M:F ratio	1 : 1.6	1.3 : 1
Indigenous population share, %	88.6	96.7
LC formation frequency, %	37.1	36.6
Hepatitis activity grade, %: - Chronic hepatitis without activity - Chronic hepatitis with cytolytic activity	 8.6 54.3	 6.6 36.7
- HDV-цирроз	40.0	46.7
- HDV- liver cancer	5,7	-

polymorphism (rs8105790) is associated with spontaneous clearance of hepatitis B [16].

Conclusion: The course of chronic hepatitis D is characterized by its aggressive nature and rapid development of complications such as cirrhosis and liver cancer. The clinical and epidemiological situation for viral hepatitis D in the Republic of Sakha (Yakutia) can serve as an example for studying the influence of candidate genes and their polymorphic variants on the formation of HDV-associated hepatocellular carcinoma or probability of obtaining a stable virological response, spontaneous clearance in patients with different rates of liver disease progression and different activity of the disease. The results obtained will expand the understanding of the course of HDV infection and can be used to form priority groups for the appointment of antiviral therapy and develop a personalized approach to the management of people with HDV infection. To objectively assess the situation with HDV infection and improve the effectiveness of preventive measures, it is recommended to introduce official registration of HDV infection.

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Литература

1. Абдурахманов Д. Т. Хронический гепатит В и D / Т.Д. Абдурахманов. - М.: ГЭОТАР-Медиа, 2010. – 288 с. [Abdurahmanov, D. T. Chronic hepatitis B and D. M.: GEOTAR-Media, 2010; 288].
2. Блохина Н. П. Хронический вирусный гепатит дельта (клиника, диагностика, лечение): Автореф. дисс. …д-ра мед. наук. - М., 1989. – 48 с. [Blohina, N.P. Chronic virus hepatitis delta (clinics, diagnostics, treatment): Abstract.diss. … doct. med.sciences. M. 1989; 48].
3. Вирусные гепатиты: клиника, диагностика, лечение / Н. Д. Ющук, Е. А. Климова, О. О. Знойко [и др.]; под общ. ред. Н. Д. Ющук. - 3-е изд., перераб. и доп. – М.: ГЭОТАР-Медиа, 2018. - 368 с.[Yushchuk ND, Klimova EA, Znoiko OO et al. Viral hepatitis: clinic, diagnosis, treatment. 3rd ed., reprint. and add. - M.: GEOTAR-Media, 2018; 368].
4. Есмембетов К. И. Современные представления о патогенезе, естественном течении и лечении гепатита дельта (35 лет с момента открытия) / К. И. Есмембетов, Д. Т. Абдурахманов, А. В. Одинцов, Н. А. Мухин // Клиническая медицина. - 2013. - № 1. - С. 22-26. [Esmembetov KI, Abdurakhmanov DT, Odintsov AV, Mukhin NA. Contemporary conceps about pathogenesis, natural course and treatment of hepatitis delta (35 years since the discovery). *Klinicheskaya medisina [Clinical medicine]*. 2013; 1: 22-26].
5. Жданов К.В. Вирусные гепатиты / К. В. Жданов, Ю. В. Лобзин, Д. А. Гусев, К. В. Козлов. - СПб.: Фолиант, 2015. – 304 с. [Zhdanov KV, Lobzin YuV, Gusev DA, Kozlov KV. Viral hepatitis. St. Petersburg: Folio, 2015; 304].
6. Исаева О.В. Вирусный гепатит дельта: недооцененная угроза / О. В. Исаева, К. К. Кюрегян // Инфекционные болезни: новости, мнения, обучение. - 2019. - Т. 8. - № 2. - С.72-79. DOI: 10.24411/2305-3496-2019-12010. [Isayeva OV, Kyuregyan KK. Viral hepatitis delta: an underestimated threat. Infekcionnye bolezni: novosti, mneniya, obuchenie [*Infectious diseases: news, opinions, training]*. 2019; 8(2): 72-79]. DOI: 10.24411/2305-3496-2019-12010.
7. Кожанова Т.В. Вирусный гепатит дельта: существует ли в Российской Федерации проблема дельта-инфекции? / Т. В. Кожанова, Л. Ю. Ильченко, М. И. Михайлов // Экспериментальная и клиническая гастроэнтерология. - 2014. - Т. 112, № 12. – С. 4-12. [Kozhanova TV, Ilchenko LY, Mikhailov MI. Viral hepatitis Delta: is there the problem of Delta-infection in the Russian Federation,? *Eksperimental'naya i klinicheskaya gastroenterologiya* [*Experimental and clinical gastroenterology]*. 2014; 112 (12): 4-12].
8. Михайлов М.И. Гепатит В и гепаднавирусы: автореф. дисс. … д-ра мед. наук / М.И. Михайлов. – М., 1988. – 43 с. Mikhailov M. I. Hepatitis B and hepadnaviruses: abstr. diss. ... Doctor of medical sciences. M; 1988: 43].
9. Молекулярно-генетический анализ изолятов вируса гепатита дельта, циркулирующих в Республике Саха (Якутия) / С. С. Слепцова, О. В. Исаева, А. А. Карлсен [и др.] // Вирусные гепатиты – достижения и новые перспективы: материалы XII Всероссийской научно-практической конференции с международным участием, Москва, 19-20 сентября 2019 г. – М.: ООО «Гепатит-инфо», 2019. - С. 40. [Sleptsova SS, Isaeva OV, Carlsen AA et al. Molecular genetic analysis of isolates of the hepatitis Delta circulating in the Republic of Sakha (Yakutia). *Virusny gepatit [Viral hepatitis]. Achievements and new perspectives: proceedings of the XII all-Russian scientific-practical conference with international partic*ipation. Moscow, 19-20 September 2019. M.: OOO "Hepatitis-info", 2019: 40].
10. Структура вируса гепатита дельта в Республике Саха (Якутия) / С. И. Семенов, М. М. Писарева, А. В. Фадеев [и др.] // Журнал инфектологии. – 2020. - Т. 12, № 2. - С. 112-113. [Semenov SI, Pisarev MM, Fadeev AV et al. Structure of the hepatitis Delta in the Republic of Sakha (Yakutia). *ZHurnal infektologii* [*Journal Infectology*]. – 2020; 12 (2): 112-113.
11. Слепцова С.С. Парентеральные вирусные гепатиты и их исходы в Республике Саха (Якутия) / С.С. Слепцова. - М., 2017. – 208 с. [Sleptsova S. S. Parenteral viral hepatitis and its outcomes in the Republic of Sakha (Yakutia). M., 2017; 208.
12. Andernach I. E., Leiss L. V., Zekiba S. T. Characterization of Hepatitis Delta Virus in Sub-Saharan Africa. *J. Clin. Microbiol*. 2014; 52: 1629-1636. DOI: 10.1128/JCM.02297-13
13. Gonzales-van Horn S. R., Farrar J. D. Interferon at the crossroads of allergy and viral infections. *Journal of Leukocyte Biology*. 2015; Aug; 98(2): 185-194. DOI: 10.1189/jlb.3ru0315-099r.
14. Ivaniushina V., Radjef N., Alexeeva M. Hepatitis delta virus genotypes I and II cocirculate in an endemic area of Yakutia. *Russia J. Gen. Virol*. 2001; 82: 2709-2718. DOI: 10.1099/0022-1317-82-11-2709.
15. Karatayli S. C., Bozdayi M., Karatayli E., et al. Interleukin-28 gene polymorphisms may contribute to HBsAg persistence and the development of HBeAg-negative chronic hepatitis. *Liver Int.* 2015; 35 (3): 846-853. DOI:10.1111/liv.12595
16. Lee M. H., Yang H. I., Lu S. N. et al. Polymorphisms near the IFNL3 Gene Associated with HCV RNA Spontaneous Clearance and Hepatocellular Carcinoma Risk. *Sci Rep*. 2015; 5: 17030. DOI:10.1038/srep17030
17. Liao B., Zhang F., Lin S., He H., Liu Y., Zhang J., Xu Y., Yi J., Chen Y., Liu H., Wang Z., Cai W. Epidemiological, clinical and histological characteristics of HBV/HDV co-infection: a retrospective cross-sectional study in Guangdong, China. *PLoS One*. 2014; Dec 22; 9 (12): 115888. doi: 10.1371/journal.pone.0115888.
18. Ma N., Zhang X., Yang L., Zhou J., Liu W., Gao X., Yu F., Zheng W., Ding S., Gao P., Yuan M., Liu D. Role of Functional IFNL4, IFN-LR1, IFNA, IFNAR2 Polymorphisms in Hepatitis B virus-related liver disease in Han Chinese population. *J. Viral. Hepat.* 2018; 25. 3 : 306-313. DOI: 10.1111/jvh.12817.
19. Pascarella S., Negro F., Hepatitis D virus: an update. *Liver Int.* 2011; 31 : 7-21.
20. Rizzetto M., Canese M., Aricoo S. et al. Immunofluorescence detection of new antigen-antibody system (delta/anti-delta) associated to hepatitis B virus in liver and in serum of HBsAg carriers. *Gut.* 1977; 18 : 997-1003.
21. Rizzetto M. Hepaitis D: thirty years after. *J. Hepatol*. 2009; 50 : 1043-1050.
22. Rizetto M., Alessia C. Epidemiology of Hepatitis D. *Semin. Liver*. Dis. 2012 ; 32 : 211-219.
23. Rizetto M. The adventure of delta. *Liver Int.* 2016; 36 : 135-140.
24. Romeo R., Perbellini R. Hepatitis delta virus: Making the point from virus isolation up to 2014. *World J. Hepatol*. - 2015; 7 (22) : 2389-2395. DOI: 10.4254/wjh.v7.i22.2389
25. Shirvani-Dastgerdi E., Amini-Bavil-Olyaee S., Alavian S.M., Trautwein C., Tacke F. Comprehensive analysis of mutations in the hepatitis delta virus genome based on full-length sequencing in a nationwide cohort study and evolutionary pattern during disease progression. *Clin. Microbiol. Infect.* 2015; 21.: 510. http://dx.doi.org/10.1016/j.cmi.2014.12.008
26. Watanabe H., Nagayama K., Enomoto N. Chronic hepatitis delta virus infection with genotype IIb variant is correlated with progressive liver disease. *J. Gen Virol*. 2003; 84: 3275-3289. https://doi.org/10.1099/vir.0.19499-0
27. Wranke A., Lourdes M. Pinheiro B., et al. Clinical and virological heterogeneity of hepatitis delta in different regions world-wide: The Hepatitis Delta International Network (HDIN). *Liver Int.* 2018; 38: 842-850. DOI: 10.1111/liv.13604