Table 6

The estimation of BMI in men and women with CHD aged 60 and older (n=354)

BMI, kg/m2	Gender				X^2	p
	men (n=187)		women (n=167)			
	abs.	rel., %	abs.	rel., %		
18.5–24.9	84	44.9	69	41.3	0.33	>0.10
25.0–29.9	78	41.7	55	32.9	2.54	>0.10
30.0 and more	25	13.4	43	25.7	7.93	<0.005

Note: X^2=9,11; p=0,011.

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SEROLOGICAL AND MOLECULAR-BIOLOGICAL VERIFICATION OF VIRAL HEPATITIS B, C, D AND E IN VARIOUS POPULATIONS OF THE REPUBLIC SAKHA (YAKUTIA)

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ABSTRACT

The **purpose** of the study is the serological and molecular-biological monitoring of the latitude of viral hepatitis B, C, D and E in the Republic of Sakha (Yakutia).

Materials and methods. Used official statistics and annual reports. The analysis of the incidence of acute and chronic viral hepatitis B and C, hepatitis carriers for the period from 1999 to 2016, as well as serological and molecular biological monitoring of the latitude of viral hepatitis B, C, D and E in the Republic of Sakha (Yakutia).

Results and discussion. In the dynamics of the incidence of AVG B, the carriage of VGV and VG C in Yakutia, there is no existence of any of their own laws that are not inherent in many regions of Russia. In general, based on the level and dynamics of the incidence of chronic viral hepatitis In the country, it is possible to characterize the overall epidemiological situation as unfavorable, even despite a noticeable decrease in the incidence. The unstable undulating nature of the incidence and their increase in recent years indicate the persistence of epidemiological tension with respect to viral hepatitis B. A distinctive feature of the structure of chronic viral hepatitis in the Republic of Sakha (Yakutia) is the high incidence of chronic viral hepatitis B and the steady growth of chronic viral hepatitis C. The infection of the population of the Republic with hepatitis B and C viruses can be determined as high. This situation, given the high frequency and severity of the adverse effects of HBV, HCV infections, as well as the endemicity of HDV infection, poses a threat to public health. According to the results of serological, molecular biological studies, a high incidence and infection rate of the population of the republic with all known hepatitis viruses was stated. An increased circulation of hepatitis E virus, previously considered a tropical infection, was also detected in the Arctic zone of Russia.

Conclusion. In general, an epidemiological analysis of the incidence of acute and chronic viral hepatitis showed that in the Republic of Sakha (Yakutia) a highly endemic area with respect to viral hepatitis C, B, D and E, and such a tense epidemiological situation requires urgent appropriate measures. Studies of the genetic heterogeneity of the identified hepatitis viruses and the pathogenetic mechanisms of the development of the disease among the indigenous people of the Russian North are also required.

Keywords: acute hepatitis B and C, chronic hepatitis B and C, hepatitis D, hepatitis E, HBsAg, HBV DNA, a-HCV, HCV RNA, a-HDV, a-HEV.

Introduction. In recent years, the epidemic process of parenteral viral hepatitis B, C and D in the world and Russia is changing. There is a sharp decline in the prevalence of acute forms of viral hepatitis B and D, which is associated with the widespread use of vaccine prevention of viral hepatitis B. However, the proportion of chronic hepatitis B in the overall structure of chronic viral hepatitis in Russia, in particular, in the Republic of Sakha (Yakutia) remains [1, 19]. Against the background of a decrease in the incidence of viral hepatitis B, the prevalence of the incidence of chronic viral hepatitis C is commonly observed [21, 9, 3]. It is especially relevant for Yakutia to study the patterns of the spread of infection caused by viral hepatitis D. Earlier studies have shown an extremely high frequency of detection of antibodies to the hepatitis D virus in different regions of the country [17, 7, 5].

Hepatitis E is an important public health problem throughout the world and by some estimates, one third of the world's population is infected with HEV infection [18]. Studies show the widespread prevalence of viral hepatitis E. Mainly it manifests itself in an outbreak of acute hepatitis in tropical, subtropical countries [2, 4, 8]. In many European countries, the detectability of serological markers of viral hepatitis E among donors varies from 1.3% in Italy to 52% in France, and in risk groups among farmers and hunters this range varies from 1.3% to 52 % [12,15].

Russia is considered a non-endemic region for hepatitis E, especially the northern territories. Often, HEV infection is found in immunosuppressed patients who may have a delay or absence of a pronounced humoral immune response to the infection [6]. Recent studies have shown that viral hepatitis E is not only an anthroponotic disease, as previously thought, but may also be zooanthroponotic [13]. Moreover, genotypes 1 and 2 cause disease in humans, and genotypes 3, 4 - in various wild and domestic animals (pigs, cows, horses, deer, dogs, ducks) [20, 11, 14, 10, 15].

The aim of the study is the serological and molecular-biological monitoring of the latitude of viral hepatitis B, C, D and E in the Republic of Sakha (Yakutia).

Methods and materials of the research. To study the incidence of acute and chronic viral hepatitis B and C in the Republic of Sakha (Yakutia), data of official statistics, annual reports of the Republican Center of Rospotrebnadzor were used. The analysis of the incidence of acute and chronic viral hepatitis B and C, and the carriage rates of hepatitis B from 1999 to 2016 have been carried out.

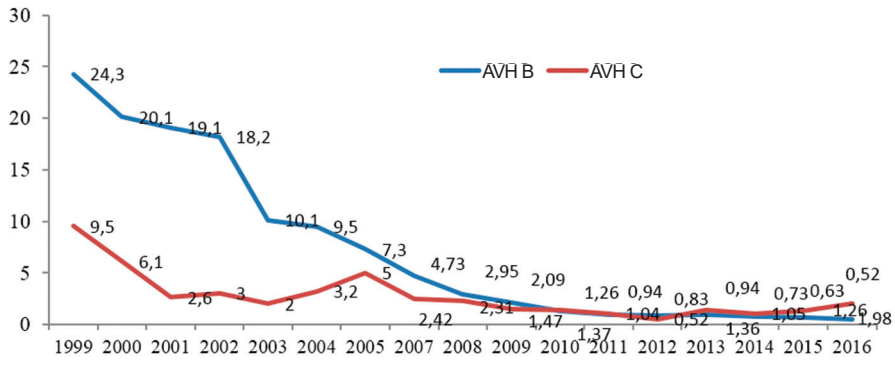

Fig.1. Dynamics of the incidence of acute forms of viral hepatitis B and C in the period from 1999 to 2016 (figures per 100,000 population)

Serological and molecular biological studies were carried out in two groups of the population of the Republic. The first group consisted of "conditionally healthy" people in the amount of 71 people, of whom 13 were men (18.3%) and 58 were women (81.7%). The average age of the subjects was 41.6 years (the median of the age of the conditionally healthy was 42 years, the range was 12-65 years, the interquartile range was 35-53 years), while the median age of men was 39 years old with an interquartile range of 32-45 years women - 43.5 and 32-53, respectively; no statistically significant age differences were found by sex (Z = 0.85; p = 0.39). The second group (group II) included 78 patients with various etiological forms of viral hepatitis (B, C and D), among whom there were 24 men (30.7%) people, women - 54 (69.3%). The average age of patients was 50.3 years (the median age of patients was 52 years, the range was 28-83 years, the interquartile range was 43.5-59 years), the median age of men was 49 years old with an interquartile range of 41-58 years, women - 53 and 45-60 respectively; in this group of subjects, there were also no statistically significant differences in age by gender (Z = 0.92; p = 0.36).

By ELISA studies were performed for the presence of HBsAg, a-HBsAg (mU / ml), a-HBc-total, a-HBs IgM, a-HBeAg, a-HBe IgG, a-HDV, a-HDV-IgM, a-HCV , a-HEV-IgG. For detection of viral hepatitis markers, Gepascan HBsAg and Gepascrin test systems were used, manufactured by Bioservice, Moscow, Vektogep D - antibodies-strip, manufactured by Vector-Best, Novosibirsk, Anti -HBc EIA »Cobas Core, Hoffmann La Roche (Switzerland). Anti-HBs were quantified using the anti-HBs Quant EIA II Roche ELISA test system on a Cobas Core II automatic analyzer from Hoffmann La Roche (Switzerland). HCV-quantitative RNA was isolated by PCR, followed by HCV genotyping, HBV-quantitative DNA, HDV-qualitative RNA. Statistical analysis of laboratory results was performed using Statistica 8.0 statistical software package.

Results and discussion. In the Republic of Sakha (Yakutia), the epidemiological situation regarding acute viral hepatitis has now improved significantly (Fig. 1). The incidence of acute hepatitis B from 1999 to 2002 was characterized by a gradual decrease in indicators from 24.3 per 100 thousand to 18.2, then there was a sharp decline in 2003 to 10.1 per 100 thousand people, followed by a gradual decrease in up to 0.53 per 100 thousand population. In 2014, only 7 cases of acute hepatitis B were registered in the republic, in 2015 and in 2016, 6 and 5 cases, respectively.

In the dynamics of hepatitis B virus infection, there is a markedly noticeable trend of a sharp decrease in infection of the population with the hepatitis B virus (Fig. 2). This is due to the implementation of preventive work against hepatitis B. The level of virus-carrying indicators in 1999 was 322.1 per 100 thousand population, which was significantly higher than the average level of the all-Russian indicator. This exceptionally high level exceeded the average Russian figure by about 3 times. In 1999, the virus infection rate in the Russian Federation was 88.0 per 100 thousand people. A decrease in virus infection rates of more than 19 times in 17 years (from 322.1 to 16.91 per 100 thousand people) indicates a significant breakthrough effect of preventive work and a high efficacy of hepatitis B vaccination, especially with the introduction of hepatitis B vaccination The national calendar of prophylactic vaccinations in 2002, which pledges three-time vaccination of newborns against hepatitis B according to the scheme 0-6-12 (the first 12 hours of life - 6 months - 12 months).

The incidence rate of acute hepatitis C in 1999 was 9.5 per 100 thousand people (Fig. 1). In subsequent years, there was a decline in indicators to 2.0 per 100

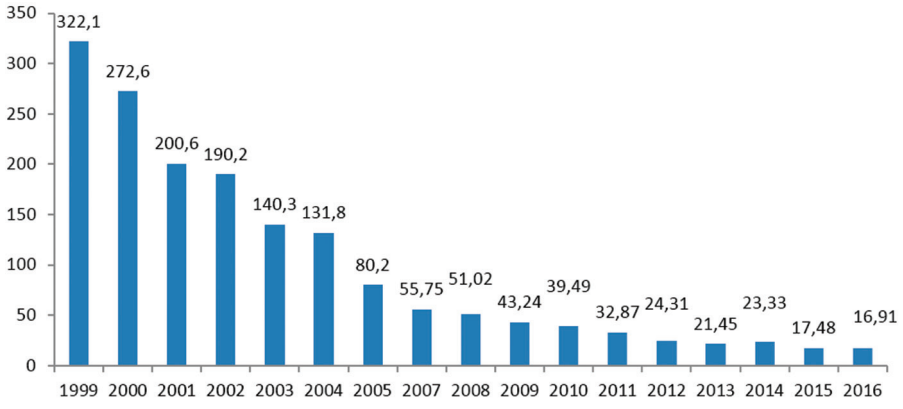

Fig.2. The long-term dynamics of the decrease in the carriage of hepatitis B (figures per 100,000 population)

thousand population in 2003 and a slight increase in indicators to 5.0 in 2005.

Since 2007, there has been a gradual steady decline in the incidence of acute viral hepatitis to 0.52 per 100 thousand people in 2012. Moreover, in 2008-2012, the incidence rates of acute viral hepatitis B and C were compared and amounted to 1.0-2.0 per 100 thousand people. Since 2013, there has been a change in the epidemiological situation with respect to acute viral hepatitis B and C. The incidence of acute viral hepatitis B continues to decline gradually, reaching 0.52 per 100 thousand people in 2016. At the same time, the incidence of acute viral hepatitis C gradually, steadily increases from 1.36 in 2013 to 1.98 per 100 thousand people in 2016. It should be noted that in recent years an unfavorable situation has been created for viral hepatitis C, there is a tendency to an increase in the incidence rate, prevailing over acute hepatitis B.

Thus, in the dynamics of the incidence of AVH B, the carriage of VGV and VG C in Yakutia, there is no existence of any own patterns that are not inherent in many regions of Russia.

The dynamics and incidence of chronic forms of viral hepatitis B and C are significantly different from acute forms. From 1999 to 2013, the incidence rates of chronic hepatitis B rose steadily, and significantly, due to improved diagnostics and the widespread introduction of immunological laboratories in health care facilities, mandatory testing for the first time applied for a viral hepatitis marker - HbsAg. The epidemiological situation in relation to chronic hepatitis B is the same as in acute hepatitis B: with the maintenance of hepatitis B vaccination in the national immunization schedule since 2003, a decrease in incidence has been observed.

The decrease in the incidence of chronic hepatitis B was undulating. The maximum incidence rates of chronic hepatitis B were at 63.3 per 100 thousand population in 2003, the minimum decrease to 33.13 in 2007. In recent years, there has been a trend of a moderate steady increase from 27.83 per 100 thousand people in 2013 to 37.15 per 100 thousand people in 2016.

In general, based on the level and dynamics of the incidence of chronic viral hepatitis B in the country, it is possible to characterize the overall epidemiological situation as unfavorable, even despite a marked decrease in the incidence. The unstable undulating nature of the incidence and their increase in recent years indicate the persistence of epidemiological tension with respect to viral hepatitis B. Against the background of a general decrease in the incidence of hepatitis B, the incidence of viral hepatitis C increases. 13 per 100 thousand population for chronic hepatitis C versus 37.15 chronic hepatitis B in 2016). This tendency is observed everywhere, since there is no specific prophylaxis for viral hepatitis C (Fig. 3).

In order to detect infection of the population with hepatitis B, C, D, and E viruses, selected groups studied serological and molecular biological markers with the aim of etiological verification, as well as determining the virological activity of the pathological process. The total results of the studies in both selected groups for the study are shown in Table 1.

Analysis of the results of detection of markers of viral hepatitis B, C, D and E according to serological studies showed a high intensity of the course of the epidemic process of viral hepatitis among various population groups of the Republic of Sakha (Yakutia). Analysis of the presented studies found that among the population of the republic there is a high proportion of seropositive individuals for all viral hepatitis with the highest rates of hepatitis C in the group of patients (I group) up to 71.8%, hepatitis B up to 24.3% and hepatitis E up to 23, 0% of cases. High infection of HBsAg-positive individuals with hepatitis D virus markers (a-HDV — 42.1%) was particularly alarming.

For the purpose of diagnostic verification in the group of patients with viral hepatitis, he was examined for hepatitis B virus markers (Table 1). The main marker of viral hepatitis B HBsAg was detected in a quarter of patients (24.3%). At the same time, out of 19 HBsAg-positive patients, HBV DNA was detected in 13 patients, which was 68.4%, which indicates an increased replicative activity of virus B. Moreover, a quantitative analysis of HBV DNA showed an average viral load of 2.6 × 10 4 copies / ml the maximum indicators 3.1 * 102, with the minimum - 1.7 * 104. These patients require long-term systematic treatment, regular follow-up, taking into account clinical manifestations, biochemical and serological indicators.

In group I, HBsAg was detected in 9.8% of the subjects. Of 7 HBsAg-positive people, HBV DNA was detected in 5 (71.4%). Moreover, the viral load of HBV DNA was higher than in the group of patients, and the rates ranged from 1.9x102 to 3.0x102. Hepatitis B markers, such as a-HBeAg IgG and a-HBcor-cumulative, were found in 21.1 and 28.1% of cases, respectively, which are now estimated to be a sign of chronic latent HBV infection.

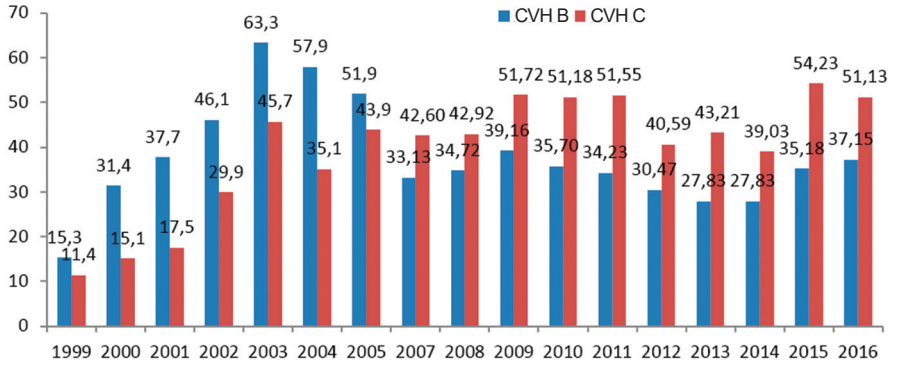

Fig.3. Dynamics of incidence rates of the registered forms of chronic viral hepatitis B and C in the Republic of Sakha (Yakutia) in the period from 1999 to 2016

The significantly high detection rate of a-HBc IgG in both groups of patients also indicates a history of acute hepatitis B, the presence of chronic hepatitis B, and the carriage of HbsAg.

One of the aspects of HbsAg-positive viral hepatitis, which cause worsening of the disease and a high degree of chronicity, is the addition of HDV infection. In the group of patients, the proportion of a-HDV among HBsAg positive was 42.1%, and the marker of replicative activity, showing active viral replication, a-HDV IgM was detected in 10.5% of the studied (Table 1). The identified indicators of the presence of hepatitis D virus markers in the structure of chronic viral hepatitis are unprecedentedly high in the Republic of Sakha (Yakutia). Usually HDV infection is registered in 5-7% of cases in the European part of Russia.

Of particular concern is the fact that the hepatitis D virus causes, as a rule, very severe forms of chronic hepatitis, which in a short time lead to cirrhosis of the liver. It is necessary to note the alarmingly high proportion of HDV infection in the structure of chronic viral hepatitis 42.1%, which indicates an obvious increase in the intensity of the epidemic process in recent years of viral hepatitis B in the territory of Yakutia.

In Yakutia, as well as throughout the country, the proportion of the incidence of viral hepatitis C is increasing and prevailing over the incidence of viral hepatitis B. In the study of the breadth of prevalence in patients with chronic hepatitis and healthy individuals, the serological markers of viral hepatitis C (a-HCV) were detected in most patients and accounted for 71.8%. Among conditionally healthy individuals, this indicator was 12.6%, while HBsAg in this group was detected in only 9.8% of cases. The wide distribution of a-HCV and the core, NS3, NS4, NS5 spectrum among patients and the high proportion of hepatitis C virus (HCV RNA) detected in seropositive individuals among patients and conditionally healthy 67.8% and 77.7%, respectively, indicates a significant intensity Hepatitis C epidemic process among the population of the republic. (Table 1). The group of conditionally healthy individuals consisted of the studied, not belonging to the groups at high risk of infection with viruses of parenteral hepatitis. The detection of up to 71.4% of HBV DNA and 77.7% of HCV RNA in seropositive, conditionally healthy subjects indicates a high activity of viral B and C infections in the studied population.

Thus, the infection of the population of the republic with hepatitis viruses B and C can be defined as high. This situation, given the high frequency and severity of the adverse effects of HBV, HCV infections, as well as the endemicity of HDV infection, poses a threat to public health.

The viral hepatitis E endemic to tropical countries in the republic was not subject to testing for patients with hepatitis, as well as during monitoring studies. Our studies showed a high circulation of the E virus among conditionally healthy and sick VH - 25.3% and 23.0%, respectively. In addition, patients with acute viral hepatitis with unclear etiology may have cases of acute viral hepatitis E, which is currently not routinely diagnosed in Russia in routine practice.

In connection with the detection of serological markers of hepatitis E in domestic and wild animals, which can be food of the population, these animals can be a source of infection of acute hepatitis E, which can be especially dangerous for pregnant women.

Our further studies have shown that the serological and molecular biological characteristics of chronic hepatitis B and C in the country are distinguished by an increased replicative activity of viruses in more than 3/4 of patients and a high degree of infection by 2, 3, and even 4 other viruses. hepatitis at the same time (mixt infection). So among 19 patients with chronic hepatitis B, hepatitis C markers were found in 31.5% of cases, while the virus (HCV RNA) was detected in 21.0% of cases. Anti HEV IgG was detected in 21.0% (4 of 19). A similar situation occurs in patients with chronic viral hepatitis C. Among 68 patients with chronic hepatitis C, markers of hepatitis B (HBsAg), hepatitis D, and hepatitis E are often detected (in fact, a fourfold infection (HCV + HBV + HDV + HEV) in 11.7% , 4.4% and 25% of cases, respectively (table 2).

Thus, according to the results of serological, molecular-biological studies, a high incidence and infection of the population of the republic with all known hepatitis viruses was stated. An increased circulation of hepatitis E virus, previously considered a tropical infection, was also detected in the Arctic zone of Russia.

Table 1

Serological and molecular biological markers of viral hepatitis B. C. D. E among various population groups (n-149)

VG markers	Number of examinations	Sick		Number of examinations	Conditionally healthy		Chi-apt.	p
		n	%		n	%		
Markers of viral hepatitis B								
HBsAg	78	19	24.3	71	7	9.8	5.4	0.02
a-HBsAg*		21	26.9		35	49.2	7.9	
a-HDcor-суммарные		42	53.8		20	28.1	10.1	0.002
HBeAg		0	-		0	-		
a-HBeAg IgG		34	43.5		15	21.1	8.5	0.004
ДНК HBV**	Of 19 HBsAg positive	13	68.4		5	7.0	6.7	0.01
Markers of viral hepatitis D								
a-HDV IgM	Of 19-HBsAg positive	2	10.5	Of 19-HBsAg positive	0	-		
a-HDV		8	42.1		0	-		
Markers of viral hepatitis C								
a-HCV	78	56	71.8	71	9	12.6	52.8	<0.001
core	Of 56 HCV positive	12	21.4	Of 9 HCV positive	1	1.4	10.0	0.002
NS3		10	17.8		0	-		
NS4		7	12.5		0	-		
NS5		6	10.7		0	-		
PHK HCV***		38	48.7		7	77.7		
Markers of viral hepatitis E								
a-HEV IgG	78	18	23.0	71	14	25.3	0.3	0.6

Note: a-HBsAg * - quantitative analysis on average 122.09 MU / ml. maximum indicators -> 263.9 MU / ml. minimum - 12.7 MU / ml
HBV ** DNA - quantitative analysis of an average of 2.6 * 10 ^ 4. the maximum of 3.1 * 10 ^ 2. the minimum - 1.7 * 10 ^ 4
HCV *** RNA - quantitative analysis of an average of 2.6 * 10 ^ 4. the maximum performance of 7.0 * 10 ^ 4. the minimum - 5.4 * 10 ^ 2

Table 2

4-fold infection (HBV + HCV + HDV + HEV) among patients with chronic hepatitis B (n-19) and C (n-68). in%

Patients	HBsAg	a-HBcor amounts	a-HBe IgG	DNA HBV	a-HDV	a-HCV	PHK HCV	a-HEV IgG
Hepatitis B	84.2	100.0	68.4	57.8	1.4	31.5	21.0	21.0
Hepatitis C	11.7	45.5	35.3	7.3	4.4	97.0	57.3	25.0

Conclusion

In general, an epidemiological analysis of the incidence of acute and chronic viral hepatitis showed that in the Republic of Sakha (Yakutia) a highly endemic area with respect to viral hepatitis C, B, D and E, and such a tense epidemiological situation requires urgent appropriate measures. Studies of the genetic heterogeneity of the identified hepatitis viruses and the pathogenetic mechanisms of the development of the disease among the indigenous people of the Russian North are also required.

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