

Parenteral viral hepatitis (B, C, D) in the Sakha Republic (Yakutia)

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Abstract. This research had the task of estimating the epidemiological situation of viral hepatitis B in the Sakha Republic (Yakutia). The Republican Rospotrebnadzor data (form 1) and the results of immunoenzyme research of viral hepatitis markers (HBsAg, a-HBcor IgG, a-HDV, a-HCV) among 17 districts in the republic were studied. The accomplished analysis has manifested the tendency of reduction of morbidity to acute and chronic hepatitis B. The immunoenzyme study over the Yakutia territory has shown the distribution of markers of viral hepatitis among the population, which corresponds to the criteria of moderate (intermediate) intensity, meanwhile viral hepatitis D corresponds to the high intensity. The morbidity of hepatitis C is considerably higher in five times, than in the Russian Federation.

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Introduction

Viral hepatitis with parenteral pass of pathogens (hepatitis B, C, D and G) is the gravest challenge of domestic public health. The total number of hepatitis B carrier in Russia exceeds 3 million. About 90% of neonates from mothers-carriers of HBeAg are infected during pregnancy. The hepatitis B of the neonates acquires a chronic evolution after infection at the first year of life in 50%, among adults it exceeds 5-10% [1].

Yakutia is an extremely vast territory with the population under one million; a considerable part is in the permafrost zone. Separate groups of researchers have studied various aspects of viral hepatitis on the territory of Yakutia so far [2]. The studies have manifested that the incidence of HBS-antigenemia in the indicator groups of healthy population (blood donors and pregnant women) in Yakutsk amounts to 3.6%; it is not higher than among the same groups in the European part of Russia.

The official statistics of morbidity of viral hepatitis B and C of Russian and Yakut Rospotrebnadzor shows common reduction of hepatitis B morbidity, including the virus carriers due to the active vaccination against the hepatitis B. Nevertheless, the morbidity of chronic hepatitis B in the Sakha Republic (Yakutia) is two times higher than in Russia: 33.2 and 14.0 per 100,000 people, respectively. The level of HBsAg carriers in Yakutia considerably exceeds the average European level, and sometimes exceeded the average Russian in three

times. Also we can underline two periods in Yakutia. A high virus carriage was registered between 1995 and 1999 alongside with distinct indicator growth from 213.8 per 100,000 people in 1995 to 322.1 in 1999 (the maximum indicator). A significant reduction of indicators has been registered in 2000; it is worthwhile to note that it has begun in Yakutia one year earlier than in Russian Federation. Since 2007 it has reduced over five times in the Sakha Republic (Yakutia) and has amounted to 55.8 per 100,000 people exceeding the average level in Russia in 1.3 times. The studies have been conducted in different Russian areas and have established the fluctuation range of HBsAg from 1.2% to 9-11% [3,4]. It is worth to mention that the hepatitis B is most often registered in a number of regions of Russia; one of them is the Sakha Republic (Yakutia) [5]. There is no information about the genotypic variety of viral hepatitis B, or about the likely features of the disease clinical evolution, induced by the infection.

The viral hepatitis B (VHB) is one of the most changeable DNA-containing viruses: it is due to the complex replication cycle comprising the stage of reverse transcription of the RNA-gene precursor [6]. At present the acute hepatitis is studied for mutant VHB strains intensively worldwide, in other words, the virus variants that are different in the nucleotide DNA sequences from prototype strains. Since the VHB genotype is determined by the genome nucleotide sequence, the genotyping is most suitable to explore the VHB geographic incidence and epidemiology. At present time, no relation has been

revealed between definite HBsAg subtypes nor any VHB genotypes and the severity of hepatitis B acute or chronic evolution [7]. At the same time, according to A. Kramvis and M.C. Kew believe [8] the specific features of VHB genotypes, which are now vary as 8 from A to H, can cause the clinical outcome of the infection and a response to the antiviral therapy in different populations. The clinical and molecular biological differences between B and C genotypes of the viral hepatitis B have been reported by E. Orito et al. [9]. They have discovered a double mutation in the main core promoter validly more frequent among the patients with the C genotype. These patients have manifested more frequent progressing disease evolution.

The acute need of these studies is dictated by the fact that the actions of different selective factors in the population, the VHB strains, so called elusive factors, become manifested and secured. The first to report the VHB mutant capable to evade the vaccine-induced response, were W.F. Carman et al. [10]. B. Weber [11] has summarized the results of many researchers and noted that the particular importance belongs to the discovery of appeared and secured in the population VHB mutants, as the effect of external selection factors, such as vaccine prophylaxis and treatment with interferon and antiviral preparations. The accomplished study have resulted the description of numerous mutations of all VHB genes. In West Europe and USA the mutant VHB strains have been revealed primarily among patients after liver transplantation and among infected children born from HBeAg positive mothers notwithstanding repeated vaccination [12]. Today the data about a large number of mutations in the VHB S-gene have been published already and among them three (G145R, K141E and T131I) dislocate the HbsAg antigenic structure considerably; it affects the diagnostics of enzyme-linked immunospot test-systems [13].

To our opinion these studies are most worthwhile when conducted in the regions with a high VHB incidence level and other factors (multinational population, intensive migration, and others). These factors influence the epidemic process, including the Sakha Republic (Yakutia).

Materials and expiatory techniques

The incidence of viral hepatitis has been analyzed by the official data registered by the Tsentropotrebnadzor of the Sakha Republic (Yakutia) (form 1 of the Data on infectious and parasite diseases in 1999-2011). The enzyme-linked immunosorbent diagnostics was conducted using the district clinical and diagnostic laboratories during the expedition to the sites observing all sanitary and

epidemiological rules and norms (R.I. Chemezova, head of the clinical and immunological laboratory of the Institute of public health, A.R. Ignatjeva, laboratory assistant). The test-systems of the Vector stock Co. (Novosibirsk) were used. The positive results were confirmed with the imported test-systems: the HbsAg tested with the test-systems "HbsAg UniForm II" (Organon Teknika), a-HCV tested with the "Monolisa anti-HCV Plus" Version 2 (Bio Rad), a-HDV tested with the ImBio and Vector-Best (by the results of two applications). In addition, the "Hepaxan HbsAg", "Hepascreen" test-systems were used, and the experimental series of test-systems for detection of antibodies to hepatitis enzymes manufactured by Bioservice Closed Stock Co, Moscow, "Vectorgene D – antibody-strip" manufactured by Vector-Brest Closed Stock Co, Novosibirsk, "Anti-HBc EIA" Cobas Core, Hoffman La Roche (Germany). Total 22 villages from 17 districts from the Republic were examined. All in all, enzyme-linked immunosorbent studies were conducted covering 26,204 persons, among them 16,570 persons were examined for the presence of HbsAg in the blood serum, totally 3, 398 for HBc, 5,464 for HCV, 772 for a-HDV. The study covered persons between 7 to 60 years old and more.

The molecular and biological studies (polymerase chain reaction, genotyping of viruses B) were conducted at the laboratory of molecular microbiology and genetic engineering (M.P. Grudin, head of the laboratory) of the Influenza Research Institute of the Russian Academy of Medical Science in Saint Petersburg (professor O.I. Kiselev, director, doctor of biology), at the laboratory of chronic viral infections (S.N. Kuzin, director, doctor of medicine) of the O.G. Andzhaparidze Research Institute of Viral Medications of the Russian Academy of Medical Science, Moscow (V.V. Zverev, director, doctor of medicine, Academician of the Russian Academy of Medical Science).

Exploration results and their discussion

The level of hepatitis morbidity in the Russian Federation during the last years tends to reduce considerably due to measures to prevent infections with the hepatitis virus B. Some authors attribute the Sakha Republic (Yakutia) to the regions of high morbidity with the viral hepatitis B.

The official statistic data shows that the level of morbidity with the acute hepatitis B in Yakutia has reduced over 24 times during the last thirteen years (1999-2011). For instance, beginning from 1999, when the indicators of morbidity with acute hepatitis were in the Sakha Republic (Yakutia) at the maximum (24.3 per 100 thousand of people), a

gradual morbidity reduction was registered to 0.9 per 100 thousand of people in 2011.

Yakutia has not manifested from 1999 to 2011 any considerable rise of morbidity with acute hepatitis, unlike many areas of the RF in 1999 -2001. During this period, the morbidity indicators in Russia exceeded considerably the morbidity in Yakutia reaching the maximum in 1999 year (43.8 per 100 thousand of people), at the same time the prevalence in Yakutia was 24.3 (Table 1).

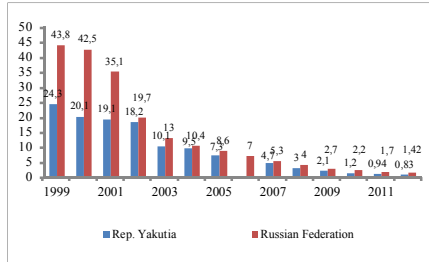


Table 1. Multiyear dynamics of acute hepatitis prevalence in Yakutia and Russian Federation (indicators per 100 thousand people)

The main reason of VH morbidity growth in Russia during 1999-2001 was a broad distribution of drug addiction among young generation; earlier this way of VH spreading in Yakutia was not so prevalent. Since 2002, the AVH morbidity in the RF and Yakutia were actually the same and amounted to 19.7-18.2 per 100 thousand of people reaching the maximum in 2011– 1.7 per 100 thousand people in the RF and 0.94 in Yakutia.

Thus, the AVH morbidity indicators in Yakutia in the taken period were lower (substantially in certain period) than the average European indicators. The recent years (2006-2011) are characterized by a stable reduction of AVH morbidity due to the implementation of vaccination from hepatitis B. It should be remembered that the official statistics do not reflect the genuine VH morbidity level since they are based on data of symptomatic jaundice forms of CVH. The jaundice-free and AVH subclinical patients are ignored by doctors and remain unregistered mainly.

Notwithstanding the distinct reduction of morbidity with acute hepatitis, high level morbidity with chronic hepatitis B is observed in Yakutia. Exactly the patients with chronic hepatitis are well remarked, at present, are the source of 90% infections of acute hepatitis. Table 2 shows the comparative

dynamics of chronic hepatitis B morbidity in Yakutia and RF.

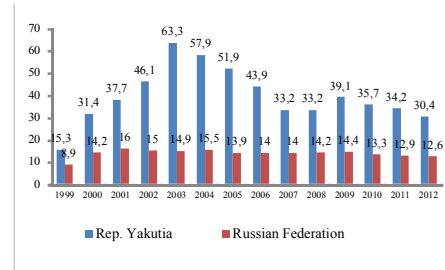


Table 2. Chronic hepatitis prevalence in Yakutia and Russian Federation during 1999 to 2012 (indicators per 100 thousand people)

It is worth to mention that, since 1999 until the year of CHV official registration, the morbidity in Yakutia was almost two times higher than in the RF – 15.3 and 8.9 per 100 thousand people, respectively. Till 2001, an insignificant rise of morbidity was remarked in Russia (to 16.0 per 100 thousand people), and then a gradual reduction occurred to 12.9 in 2011. The rapid growth of morbidity has reached maximum in 2003 – 63.3 per 100 thousand people in Yakutia, exceeding the average Russian level in 4.2 times. Afterwards, a considerable morbidity reduction occurred to 34.3 per 100 thousand people in 2011. Despite the tendency of reduction, in 2011 the CHV morbidity in Yakutia was two times higher than in the RF.

The accomplished analysis enables to state that, in the Republic of Sakha (Yakutia), there is tendency of reduction of morbidity with various hepatitis B. It is noteworthy that, when the AVH morbidity was lower than in the RF, the CHV in Yakutia exceed the general Russian index in two times.

Since 2002 the Research Institute of Health has intensively been identifying the patients and carriers of viral hepatitis in the republic. Special medical team expeditions were arranged equipped with necessary equipment to conduct enzyme-linked immunosorbent essays. Total 22 villages from 17 districts from the Republic were examined. All in all, enzyme-linked immunosorbent studies were conducted covering 26,204 persons, among them 16,570 persons were examined for the presence of HbsAg in the blood serum, totally 3, 398 for HBc, 5,464 for HCV, 772 for a-HDV. The study covered persons between 7 to 60 years old and more.

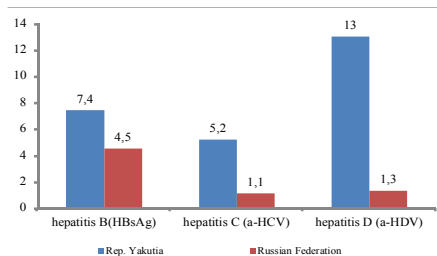


Table 3. Distribution of markers of viral hepatitis B, C and D in the Sakha Republic (Yakutia) and RF (Shakhgildyan I.V. and co-authors, 2003) (indicators in per cent)

The broad of dissemination of markers of hepatitis B among the population on the territory of the Sakha Republic (Yakutia) correlates the criteria for moderate (intermediate) intensity, whereas hepatitis D is high. Morbidity of hepatitis C is considerably higher in 5 times, than in RF.

Genotype viral hepatitis B was determined in blood serum of 29 samples from patients in Yakutia and of 172 samples from patients in Saint Petersburg with CHV. Genotyping of VHB was performed with the PCR and RFLP at the Influenza Research Institute of the RAMS (Saint Petersburg). It was established that there were three genotypes of viral hepatitis B among patients from Yakutia (Table 4).

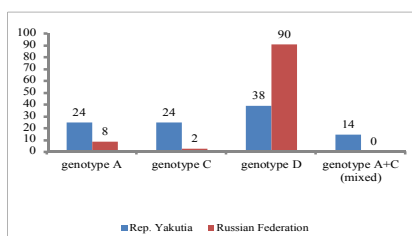


Table 4. Structure of genotypes of viral hepatitis B circulating in the Sakha Republic (Yakutia) and in Saint Petersburg

Patients have revealed the genotype D in 38%, the genotypes A and C have been identified in equal proportions of 24%. In the remaining cases, the mixed forms of chronic hepatitis B have been identified with genotypes A and C (14%). At the same time, the accomplished study of VHB genotypes among CHV patients from Karelia and Saint Petersburg has revealed the prevalence of

genotype D determined in 90% cases. The genotype A (8%) has been identified among individual patients in the European part of Russia.

Conclusions

1.) The morbidity with chronic viral hepatitis B in the city of Yakutsk, against the background of reduction, was somewhat higher than in the republic. During seven years (2002-2008) the prevalence of acute hepatitis B reduced almost from 67.1% to 22.0% from all who fell sick, the chronic hepatitis - in two times from 29.9% to 15.2%. compared with the average republican indicators (55.8 per 100,000 people), the level of virus carrying was stable and two times higher (102 per 100,000 people). The general reduction of the registered hepatitis B was due to the recent vaccination against hepatitis B.

2) The most specific gravity in the etiological structure of acute and chronic hepatitis, according to the Yakutsk department of viral hepatitis, belongs to hepatitis D+B and C, which has the shares of general hepatitis (HDV+HBV-co-infection) 40%, CHD (HDV+HBV-superinfections) 41.2% and ACC 26%, CHC 40.7%. Considering the gravity of hepatitis D and C, the extremely unfavorable prediction, fast hepatic cirrhosis evolution, hepatocellular carcinoma development, frequent lethal outcomes - this situation should be recognized as highly alarming.

3.) The phylogenetic analysis of nucleotide sequences of virus B strains separated from chronically infected persons has revealed three variants - genotype A (44%), genotype C (12%) and genotype D (44%) in the structure of circulating genotypes VHB on the territory of Yakutia.

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