

PECULIARITIES OF VIRUS HEPATITIS IN UZBEKISTAN

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✓ *Resume,*

The results of studies have shown that 1a and 1b genotypes that are more pronounced necrotic-inflammatory process in hepatocytes. This fact proves the more aggressive of the antigenic and pathogenic properties of 1a and 1b genotypes compared with 2a, 3a and 1b +3a genotypes HCV.

Keywords. Clinical and laboratory features, viral hepatitis B, genotypes of viral hepatitis C

ОСОБЕННОСТИ ВИРУСНОГО ГЕПАТИТА В УЗБЕКИСТАНЕ

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✓ *Резюме,*

Полученные результаты исследований показали, что 1b и 1a генотипы вызывают более выраженный некротически-воспалительный процесс в гепатоцитах. Данный факт доказывают о более агрессивных антигенных и патогенных свойствах 1b и 1a генотипов по сравнению с 2a, 3a и 1b+3a генотипами HCV.

Ключевые слова. Клинико - лабораторные особенности, вирусный гепатит В, генотипы вирусного гепатита С.

ЎЗБЕКИСТОНДА ВИРУСЛИ ГЕПАТИТНИНГ ХУСУСИЯТЛАРИ

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✓ *Резюме,*

Олинган тадқиқот натижалари шуни кўрсатдики, 1b ва 1a генотиплар гепатоцитларда некротик-яллиғлашиш жараёни кўпроқ намоён бўлади. Ушбу ҳолат HCVнинг 2a, 3a ва 1b+3a генотипларига нисбатан 1c ва 1a генотиплари янада агрессив антиген ва патогенлик хусусиятларидан далолат беради.

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Relevance

Virus hepatitis with hemocontact transfer of agents HBV and HCV are serious medical and social problems. By its prevalence, morbidity level, severity course, frequency of chronic forms and economic damage the virus hepatitis HBV and HCV take one of the leading parts in the infectious pathology of the man [4, 5, 6]. The high level of morbidity with virus hepatitis all over the world, difficulties of early diagnostics, different clinical variants of disease, absence effective measures of therapy and prophylaxis, serious consequences of disease, attract attention of many researchers to many-sided study problem of hemocontact hepatitis [1, 2, 3]. Morbidity with virus hepatitis in Uzbekistan has the tendency to considerable reduce especially in children less than 14 years old last years. In spite of it the frequency and level of virus hepatitis continue to have the high specific gravity among the infectious diseases [1,3]. Today the specific gravity of virus hepatitis in general structure of infectious morbidity is 3,3%, and, it takes the third place after acute respirators virus infection (ARVI), acute diarrhea infection (ADI) [3, 5, 6].

High birth rate in the Republic of Uzbekistan and carriage of virus hepatitis B is from 8 to 12% that causes the high level of morbidity from virus hepatitis B among the children.

The aim of study: To research prevalence of virus hepatitis with hemocontact transfer mechanism, and, to determine genotypic and scope of hepatitis HBV and HCV on the territory Republic of Uzbekistan with the intensive circulation of this infection.

Materials and ways

According to the aim of study we researched the longstanding morbidity dynamics with vims hepatitis B in different age groups from 1981 to 2003 by the data in the Republic of Uzbekistan. During the retrospective analysis etiologic decoding structure of virus hepatitis on the base of markers' detection hepatitis HAV (anti-HAV Ig M), hepatitis HBV (HBsAg, anti-HBc IgM, anti-HBc IgG), hepatitis HCV (anti-HCV), hepatitis HDV (anti-HDV) and hepatitis HEV (anti- HEV IgM) were taken with the help of modem high sensitive immune fermentative test systems of production by the firms "Ortho" (USA) and "Diagnostic system" (Ni- jniy Novgorod, Russia). Circulation and determination DNA HBV and RNA HCV were studied by the way PCR. Molecular genetic part of work was taken in information and molecular medicine laboratory at medicine department of University Nagoya city, Japan (head of laboratory professor Masashi Mikosami), in laboratory molecular genetics at research institute of immunology (director professor T.U.Aripova)

and in research institute of virology (director professor E.I. Musabaev).

Results and discussion

At deep study of longstanding HBV morbidity dynamics in 1981-2003, cyclic vibrations were marked, but on the whole the line of straightforward tendency is characterized by reduce of epidemic process. The general index of HBV morbidity leveled different tendencies in separating groups of population in the republic. At analysis of HBV morbidity dynamics we determined 3 periods of epidemic process in the republic; those were essentially differed by the intensity of the disease. In this connection the character of age morbidity HBV was estimated at the period of growth, high state of level and reduces of HBV-infection.

In the Republic of Uzbekistan the highest HBV morbidity indices were registered in children under 14 years old, so in our studding period of morbidity growth in 1981 to the specific gravity of this age group was $62,9 \pm 0,2\%$, and morbidity indices were in terms $162,3 \pm 0,8\%$. The analysis of indices in the period of high morbidity height from 1985 to 1995 showed, that specific gravity of HBV in this age group, was $67,5 \pm 0,1\%$, and, indices of morbidity reached $263,0 \pm 0,5\%$. At analysis of period, when reduce of HBV morbidity from 1996 to 2003, the specific gravity was $54,4 \pm 0,3\%$. Data on HBV morbidity this age group were reduced at the end of observation period in 3,4 times $47,5 \pm 0,3\%$ in 1996 to 2003, and $162,3 \pm 0,8\%$ in 1985-1995 accordingly at $P < 0,001$. It is necessary to notice, that even at marked morbidity reduce, the index in children less than 14 years old in epidemic process at HBV are the main mass of sick people $54,4 \pm 0,3\%$ from general number of patients.

The indices in age group of children from 0 to 2 years old during morbidity growth from 1981 to 1984 and at period of high morbidity growth from 1985 to 1995 in gienage group were $40,2 \pm 0,3\%$ and $40,2 \pm 0,1\%$ accordingly. In this age group the specific gravity HBV exceeded the indices of special gravity HBV of children from 3 to 6 years and 7-14 years old in 3,2 and 4,0 times accordingly, the difference was statistically significant at $P < 0,001$. Data analysis showed reduces of morbidity in this age group at the period from 1996 to 2003. These years the specific gravity was reduced in 1,7 times and was $24,0 \pm 0,3\%$, and indices of morbidity were reduced in 6 times $677,1 \pm 1,8\%$ in 1985 to 1995 and $112,8 \pm 0,6\%$ in 1996 to 2003 at $P < 0,001$. But in spite of this fact in this age group till now the highest morbidity indices are saved among all age groups of population in the republic. These indices in 1,9,5,7,3,4 times exceed the indices of age groups 3-6 years, 7-14 and 15 years and older accordingly, the difference statistically was true at $P < 0,001$. From presented data it is seen that the ratio of indices and HBV morbidity dynamics in age group 3-6 years were noticeable changed. On the whole the specific gravity of morbidity in 1996- 2003 in comparison with 1981-1984 was raised in 1,4 times at $P < 0,001$, and indices of morbidity were $114,3 \pm 1,2\%$ in the period 1981-1984 and $58,5 \pm 0,6\%$ was reduced in 1,9 times, the difference was statistically significant. But this age group takes the second place by morbidity indices among all age groups of population in the republic.

The specific gravity of HBV among age group 7-14 years for the period of observation from 1981 to 2003 was practically on one level $10,1 \pm 0,1\%$ at the beginning of

observation and $12,2 \pm 0,3\%$ at the end of study. But reduce of morbidity indices were marked at the end of observation in 2,8 times ($54,6 \pm 0,7\%$ in 1981- 1984 and $19,6 \pm 0,2\%$ in 1996-2003 at $P < 0,001$).

In age group 15 years and older as in age group 3-6 years the raise of specific gravity of virus hepatitis B morbidity was observed at the end of study was in 1,2 times in 1981-1984 $37,1 \pm 0,3\%$ and $47,5 \pm 0,3\%$ in 1996-2003 at $P < 0,001$. But it was also marked the positive tendency reduce of virus hepatitis HBV morbidity in this age group. At the end of observation period and given part of time for morbidity indices was $23,7 \pm 0,1\%$ in 1996-2003 and $60,8 \pm 0,4\%$ in 1981-1984 at $P < 0,001$.

Thus, the age structure of HBV on the whole gives us Imagination on essential changes of epidemic process intensity, taking place in different age groups of population for the last 8 years. The taken indices correlations of age morbidity were coincided with epidemiologic regularities peculiar to all infectious diseases with the intensive circulation of agent. Naturally, in these cases, in epidemic process, first of all, the most sensitive contingent of children was included. With the age the immune layer of population is raised, and morbidity in older age group of population is reduced. To formation of intra yearly morbidity dynamics, on the whole, the essential influence makes its peculiarities in different age groups. The most expressed season vibrations of morbidity in the republic were observed in children under 14 years old. In the older age groups of population this 15 year old older, monthly distribution was looked smoothly, though non-expressed season elevations of HBV were marked. It is necessary to notice that revealing mixed hepatitis has the tendency to increase. For autumn and winter seasons the most influence made intra yearly morbidity dynamics of age groups less than 14 years. Maximum morbidity indices in this age groups were observed in November and it was $12,0 \pm 0,4\%$, December $21,2 \pm 0,5\%$, January $10,7 \pm 0,1\%$, when the registration of HBV exceeded intensive minimum morbidity, the index of summer period raised to 2,7 times, the difference was statistically true at $P < 0,001$. in age group older 14 years this index was higher only in 1,2 times and it was $6,0 \pm 0,2\%$, in November $4,7 \pm 0,02\%$ July the difference of indices were also statistically significant.

Thus, the analysis of hepatitis HBV seasonality in different age groups in the Republic of Uzbekistan revealed the next main tendencies: presence of true autumn- winter morbidity elevation, raise of sickness rate in junior age group of population. To the development of epidemic process in these age groups, first of all, make the natural ways of agent transfer. With the raise of age the immune layer of population raise, that can defend organism from small doses of agent, introduction at action of natural ways of invasion. Because of entering more massive doses of virus hepatitis B at hemocontact the adult population response with the development of infectious process for the first months. By that the incubation period of infectious process is reduced. One may suppose that in older age groups mainly the parenteral way of agent for hepatitis B and C.

Decoding of etiologic structure virus hepatitis (VH) in the examined patients and data of official registration had some differences. The part of virus hepatitis HBV in general sum of morbidity with virus hepatitis according to average longstanding data 23 years in the Republic on

the whole were 15,4%, HAV were 84,4%, HCV was marked in 0,9% patients, and, HEV was only in 0,2%.

The analysis of our study showed that only in 34,1±1,4% was registered virus hepatitis HAV, the part of virus hepatitis HBV was 29,0±1,4%, virus hepatitis HCV was diagnosed in 5,9±0,7%, and, virus hepatitis HEV was in 0,9±0,2%. In 19,8±1,2% simultaneously were revealed markers of active reproduction several virus hepatitis. Thus, in 15, 4±1,1% in blood serum HBsAg and anti-HAV IgM were revealed, and in 5 people simultaneously markers of three virus hepatitis were determined HAV+HBV+HCV. As the mechanism and ways of transfer virus hepatitis HAV and agents of HBV and HCV are absolutely different, the indices of simultaneously revealing the markers of these virus reproductions in patients reflect in definite measure the frequency of "carriage" HBsAg and anti-HCV in healthy population of the Republic of Uzbekistan. The frequency of carriage HBsAg in adult persons, not referring to risk groups, are 8-12%, anti-HCV in healthy persons were revealed in 0,9% (Niyazmatov B.I., 2004). In 4,3 ±0,6% simultaneously were determined HBsAg and anti-HCV. The existence of patients with presence of markers virus hepatitis HBV and HCV in blood serum witness: firstly, on generality of transfer ways for agents HBV and HCV; secondly, on presence of definite population groups with high risk of invasion with two viruses simultaneously, or consecutively.

The quite high specific gravity among all patients were 54,7±1,5% that were infected by the agents of hemocontact virus hepatitis. In 10,3±0,9% with clinical biochemical signs of acute virus hepatitis (AVH) no one of determining markers were not revealed, that didn't allow to specify the etiological diagnose of the disease.

Etiological structure of HAV in different age groups had definite peculiarities. In children from 1 to 3 years HAV exceeded, the part of that by 2 times was higher than HBV, the difference was statistically true at $P<0,001$, and in age group of children under 12 months old, on the contrary, exceeded HBV, it's part was by 12, 4 times higher than HAV (65, 8±7, 7% and 5, 3±3, 6%) accordingly at $P<0,001$. In age group of children from 4 to 6 and 7 to 14 years, also HAV exceeded over HBV, that was by 2,8 3,5 times registered more often (48,2±3,6% and 52,2±5,4%, 16,9±2,7% and 14,9±2,8% accordingly at $P<0,001$). And in age groups from 15 to 19 years. 20 to 29 years, 30 to 39 years and 40 to 49 years exceeded specific gravity HBV over HAV from 2 to 5.7 times that with the age of patients it is gradually reduced. It should be marked, that in the teen ages of 15 to 19 years old and the adults from 20 to 29 years, 30 to 39 old and 40 to 49 years old in difference from other age groups in etiological structure of HBV the considerable place took HCV and mixed infection (HBV+HCV). The specific gravity of these forms were 14,3±5,9%, 14,7±2,9%, 28,3±4,9%, 23,8±6,6% and 8,6±4,7%, 12,6±2,7%, 9,4±3,2%, 11,9±5,0% accordingly.

It takes attention age group under 14 years old, where in 21,9±1,5% cases HBsAg was revealed in patients with virus hepatitis HAV. This position witness on intensive virus hepatitis B circulation and considerable prevalence of infection chronic forms in children's population. In age groups from 0 to 12 months, 15-19 years and 40-49 years more often than in other age groups virus hepatitis of undecoding etiology 18,4±6,2%, 22,8±7,1% and 14,3±5,4% accordingly were marked. It is necessary to notice that the part of patients who simultaneously were

revealed markers of virus hepatitis HAV and HBV were the highest among children's population, particular in the age group from 1 to 3 years, 4-6 years and 7-14 years (22,2±2,2%, 23±3,1% and 19,9±3,1%), that in 1,7-5,8 times raised the following indices in age groups from 15 to 19 years, from 20-29 years (11,4±5,4% and 4,0±1,6%) the difference is statistically true at $P<0,001$.

Thus, if to sum up clinical displays HCV infections in its different combinations it's turn out that the part of HCV in the etiological structure of acute virus hepatitis among all patient at present time is too considerable and it is 10,3±0,9%.

The part of virus hepatitis HBV in the etiological structure of acute virus hepatitis is quite considerable and the displays of this infection in its different combinations with other hepatitis are 48, 7±1,5%.

So, continuous serological study of all patients with virus hepatitis on the markers of hepatitis is essentially changed up mind on etiological structure of acute virus hepatitis in the Republic of Uzbekistan. The specific gravity of hepatitis HAV and hepatitis HBV is considerable differ from the data, taking on the base of generally accepted clinical epidemiological approaches to their diagnostics, and, mixed infection without serological study in general, can't be identified. Hepatitis HAV is not absolutely and constantly dominating type of virus hepatitis in children. At the average specific gravity equal to 34, 1±1, 4%, in children's age groups HAV are less than half of all mass of patients with virus hepatitis 46,8±2,7% and 48,2±3,6%.

Virus hepatitis HAV and hepatitis HBV have the course as combined infection and they compose 15,4±1,1% from all acute virus hepatitis and have the course of two main variants, the true mixed infection, being marked in 10,5±0,9% and HAV on the background of asymptomatic carriage HBsAg in patients 4,9±0,7%.

Analysis of literature data showed that researches of genotypes hepatitis HCV and HBV in the Republic of Uzbekistan were not practically taken

In this connection we considered purposefully to study genotypic landscape of HBV and HCV in the examined patients, to estimate the interconnection of clinical laboratory displays virus hepatitis (VH) in the adult patients with different genotypes and in fluency of genotypes on formation chronic virus hepatitis. The study on determination genotypes HBV in 37, HCV in 30 patients was taken. As the control group of comparison 40 donors from blood transfusion station at Republican Research Center of Surgery by academician V.V. Vahidov, whom HBV and HCV were determined at planned study.

Complex study of patients with HBV infection revealed that 64,9% revealed virus hepatitis of minimum and low, but 35,1% revealed moderate and expressed activity. In HBV DNA positive patients were taken determination of virus genotype. The genotypic landscape revealed the following: in 73% patients revealed detection D-genotype HBV, in 13,5% A-genotype, in 10,8% C- genotype and, in 2,7% G-genotype HBV- infection. By that in all patients, being infected C-genotype HBV; activity degree of pathological process in the liver was expressed. It is necessary to notice, that in 18,9% examined patients we determined HBeAg-negative status at presence DNA HBV in the blood.

Thus, the taken results showed that the most widespread genotype B in the Republic Uzbekistan is D-genotype HBV, genotype C, A and G occurred relatively less. In 18,9% patients with minimum and low activity we

determined HBeAg-negative status HBV, that in its turn, it can say about infecting "mutant" HBV strain.

The following analysis of genotypes HCV in the above-mentioned groups showed, that in the groups of patients with HCV the most often I genotype was revealed in 15 (50,0%) patients. Further, approximately with equal frequency the genotypes I+III were revealed in 3 (10,0%) patients and genotype III in 5 (16,7%) patients. In 2 cases (6,7%) genotypes I+IV were revealed. The presence of combined genotypes I+III, I+IV witness on repeated infection of such patients. It should be marked that in 2 patients with HCV occur genotype IV very seldom for our region. This type, as a rule, occurs in Arabic countries: Egypt, Iraq, Kuwait, Yemen and so on. Infection possibility with give genotype was connected with activation last decade the tourist business in the republic.

In the donors group the more often were revealed: genotype I in 13 (32,5%) cases, genotype III in 9 (22,5%) cases, genotype II in 4 (10,0%) cases, I+II genotypes were in 2 (5,0%) examined, that also witnesses on repeated infection. The genotypes analysis in this group of examined patients showed that genotype I (32,5%) was pre dominant, less widespread was genotype III (22,5%) and II (10,0%).

As it is seen from these data in the group of patients genotype II was not revealed, and in donors group it was genotype IV. In 5 cases (16,7%) in the group of patients, suffering from HCV, and, in 12 cases (30,0%) in the group of donors the serologic probes PCR were negative.

Thus, in patients, suffering HCV I genotype was revealed in 66,7% and 37,5% in persons with asymptomatic course. Further by the revealing frequency was type III from 26,7% in patients suffering from HCV to 22,5% in the donors. And genotype II was determined in donors group in 15% cases, and, it wasn't revealed in the group of patients suffering from HCV, but genotype, IV was determined in 6, 7% cases in the group of patients, suffering from HCV, and it wasn't determined in the group of donors.

In 5 cases (16, 7%) in groups suffering from HBV and in 12 cases (30, 0%) in group of donors seroprobes PCR were negative. Combined revealing I+II genotypes HCV in 5, 0% cases were revealed in group of donors, but they were not revealed in group of patients suffering HBV. I+III and I+IV genotypes were revealed in group of patients, suffering HBV in 10,0% and 6,7% cases accordingly.

Thus, in our republic I, II, III, IV genotypes HCV are circulating. The most widespread are I and III genotypes to 66, 7% and 26, 7% accordingly. II genotype HCV was determined in 15, 0% cases. Combined revealing of genotypes occurred to 10,0% - I+III, 6,7% - I+IV, 5,0% to I+II.

From epidemiologic anamnesis we revealed that I genotype HCV more often are transferred at medical parenteral interference, and for genotype HCV 3 the more typical transfer agent were at intravenous introduction of narcotic drugs. Analysis results of clinical and laboratory study of patients and donors, depending on genotypes HCV showed that presence I, II, IV genotypes in patients cause mainly manifested forms HCV infection, but at the same time, it doesn't exclude presence and asymptomatic course. For II genotype the presence of asymptomatic course of HCV infection

The aggravation of disease is more often connected with the blood circulation of I and

III genotypes.

Thus, in our republic I, II, III and IV genotypes HCV are circulating. Among the patients HCV in the Republic of Uzbekistan the most widespread were I genotype (66,7%), III genotype (26,7%), and also their combination to 10,0% occur. II genotype 15% was also revealed in combination with genotype I 5%, and, IN' genotype in combination with I genotype was 6,1%. We stated the fact, that in patients suffering HCV I genotype was revealed in 66,7% and 37,5% in persons with asymptomatic course. Further, by the frequency of revealing is II type from 26,7% in patients suffering HCV to 22,5% in the donors. II genotype was determined in the group of donors in 15% cases, and it wasn't revealed in group of patients, suffering HCV.

III genotype was determined in 6,7% cases in group of patients, suffering HCV and was determined in the group of donors. In 5 cases (16,7%) in group suffering from HCV and in 12 cases (30,0%) in the group of donors' seroprobes PCR were negative. Combined revealing I+II genotypes HCV in 5,0% cases were revealed in the groups of donors, but they were not revealed in the group of patients, suffering from HCV. I+III and I+IV genotypes were revealed in the group of patients suffering from HCV in 10, 0% and 6,7% cases accordingly.

IV genotype was determined in 6,7% cases in group of patients, suffering HCV and was determined in the group of donors. In 5 cases (16,7%) in group suffering from HCV and in 12 cases (30,0%) in the group of donors' seroprobes PCR were negative. Combined revealing I+II genotypes HCV in 5,0% cases were revealed in the groups of donors, but they were not revealed in the group of patients, suffering from HCV. I+III and I+IV genotypes were revealed in the group of patients suffering from HCV in 10, 0% and 6,7% cases accordingly. Genotypes HCV were caused different frequency occurrence of the raw clinical symptoms, and, at the same time, not making true influence on their continuation accordingly, and, the course of acute HCV-infection at presenting I genotype will be more severe. In comparison of groups at general flow of patients with definite genotype we don't notice true difference of clinical symptomatic, and, by that, proving the necessity of genotypes determination with the aim of preventive process chronisation for taking interferonotherapy. It was revealed, that I, III, I+III and IV genotypes, circulating in the Republic were the causes mainly manifesting forms of disease, and, at the same time, II genotype was the typical asymptomatic form of disease.

Conclusions

Considerable reduce of HBV morbidity for children's population is observed in the Republic.

Seasonality is typical for hepatitis B. raise of morbidity is observed in autumn- winter period, and it is mainly connected with attraction of people under 14 years old in epidemic process.

The specific gravity of hemocontact virus hepatitis among all patients with virus hepatitis was 54,7+1,5%.

In our republic in 13,3% patients A- genotype, in 10,8% C-genotype, in 73% D- genotype, and, in 2,7% G-genotype of HBV infection are circulated.

Genotypic landscape of HCV in the Republic of Uzbekistan was presented by I, II, II and IV genotypes. The most widespread are I and II genotypes to 66,1% and