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HEPATOCELLULAR CARCINOMA AMONG PATIENTS WITH CHRONIC VIRAL HEPATITIS AND LIVER CIRRHOSIS OF ALCOHOLIC ETIOLOGY

The high incidence of parenteral viral hepatitis B, C and D markers is determined in patients with hepatocellular carcinoma (HCC). The data on higher rates of progression of HCC among patients with hepatitis B, C and D in comparison with patients with liver cancer in the absence of markers of hepatitis viruses are obtained. HCC with the greatest frequency occurred in HCV-infection with genotype Ib, HBV-infection - genotype D and HDV-infection - genotype I.

Keywords: viruses, hepatitis, hepatocellular carcinoma.

Introduction. The study of hepatocellular carcinoma (HCC) is rather complicated in comparison with the study of cancer at other sites, because this form of diagnosis is difficult, and the frequency of distribution is much lower than the stomach, lung and other organs. According to world literature, the frequency of HCC among men takes 5th place after lung cancer, stomach, prostate, and colorectal cancer and accounts for 13.1 per 100 thousand people. The incidence of liver cancer among women is in 8th place after breast cancer, cervical, colorectal, lung, stomach, ovary, uterus, and amounts to 3.5 per 100 thousand people [9]. Every year in the world is recorded more than 600,000 new cases of HCC. Mortality from this form of cancer takes the third place among all human malignancies [8, 13]. Hepatitis B and C are the most important etiological factors for the development of HCC [10, 14].

Thus, the detection rate of HBsAg among patients with HCC in Africa and Asia is 85-95%, in Japan, Italy and Spain - 50-75% in Western Europe and the United States - 10-25% [2].

The frequency of cirrhosis among patients who abuse alcohol is 10-20% and increases depending on the length of alcohol abuse. Therefore, there is particularly high risk of developing HCC in the older age group (over 60). Alcohol plays a cofactor role in carcinogenesis in patients with cirrhosis of the liver in the presence of viral infection and is a major and independent factor that induces the rapid progression of chronic hepatitis to cirrhosis and development of HCC [6,7].

Many studies have found that the similarity of clinical and biochemical symptoms of HCC with chronic progressive liver disease causes significant difficulties in the diagnosis of liver cancer at an early stage of the disease [3, 4].

Objective: based on a study of clinical and laboratory results, to identify features of HCC among patients with chronic viral hepatitis, taking into account the presence of markers of hepatitis viruses.

Materials and methods. To study and compare the clinical and laboratory characteristics of

HCC, depending on the presence or absence of hepatitis virus markers it were examined 178 newly diagnosed patients. Patients were divided into two groups. The first group included 53 patients with cancer of the liver without viral hepatitis. Among the men surveyed was 75.5%, women - 24.5%, between the ages of 54 to 76 years. The second major group consisted of 125 patients with liver cancer associated with viral hepatitis B, C and D at the age of 20 to 82 years, among them males accounted for 60.8%, women - 39.2%. Clinical, laboratory and instrumental, serological, molecular biological, histomorphological and statistical methods were used.

Results. HCC patients with a second group of hepatitis viruses most often diagnosed among people of working age (up to 39 and 40-49 years) at 7.2 and 19.2%. In the first group of 53 patients without hepatitis viruses, liver cancer is often encountered in older age groups from 50 and older. Liver focal lesions was identified among 18.9% of patients of the first group without hepatitis during the ultrasound examination while dispensary. It should be noted that these patients hadn't any complaints and the characteristic features of liver cancer. 66% of patients were sent to the Oncology Center for detecting their tumors in the liver during the medical examination at the worsening of chronic diseases of the gastrointestinal tract. 15.1% of patients in the dispensary on the compensated cirrhosis of the liver (for re-inspection within six months after the last visit) complaint about the reduction in amount of urine, abdominal increase, increase unwarranted weakness, weight loss, while maintaining appetite. However, these patients sought help in the later stages of the disease with an increase in signs of decompensated liver cirrhosis.

75.2% of patients with cancer of the liver associated with hepatitis viruses (second group), the reason for treatment in the health care setting have been signs of decompensated cirrhosis, in contrast to liver cancer patients without markers of hepatitis (first group). Among them 12.8% of patients in emergency indications were taken to hospital with bleeding from the varices of the esophagus and stomach. Liver cancer was diagnosed accidentally among 28,4% of patients, who came to the clinic, because of acute chronic diseases of the gastrointestinal tract.

Considering the fact that the majority of patients pass numerous medical procedures, blood serum of all patients were screened for markers of viral hepatitis by enzyme immunoassay to determine the most significant factor for HCC. In the sera of patients of the first group specific markers of hepatitis viruses did not reveal: HBsAg, anti-HBc IgM, anti-HBc IgG, HBeAg, anti-HDV, anti-HCV. In the first group, 54.7% of patients pointed to alcohol abuse. Probably this group of patients has primary liver cancer, which is developed in the outcome of liver cirrhosis of alcoholic etiology. Patients of the second group have HCC due to the outcome of chronic viral hepatitis, which was confirmed by the presence of hepatitis B virus markers and detection of viruses

B, C and D by enzyme immunoassay. In this case HBsAg found in 56.8% of patients. In 15.5% of patients HBsAg was not detected, the diagnosis of hepatitis B was confirmed on the basis of the presence in serum of other antibodies: anti-HBc IgM - 20,0 and anti-HBc IgG - 14,4%, anti-HBc total - 10,4%, HBeAg - 14,4 and anti-HBeAg - 9,6%. Among patients passed survey 17.6% of cases showed a-HDV IgM, in 11,2% - a-HDV IgG. From the total number of surveyed a-HCV IgM detected in 28.0% of patients, a-HCV IgG - in 4.8% of patients in the absence of other serological markers of viral hepatitis (Fig. 1).

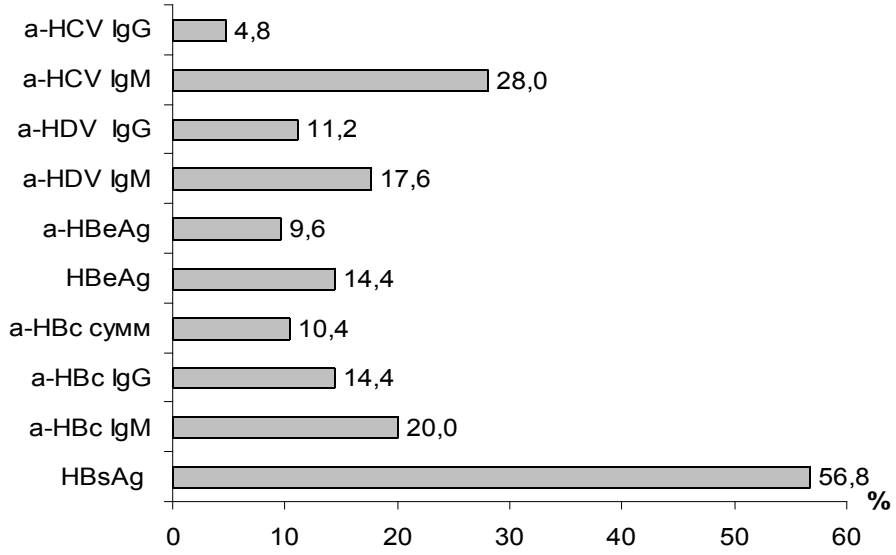

Fig.1. Serological markers of hepatitis B virus liver cancer patients (n = 125).

2.4% of patients aged 20 to 25 years of the second group firstly identified diagnosis of chronic viral hepatitis B during the medical survey. The mothers of these patients were hepatitis B virus carriers. This circumstance was regarded as the vertical infection with hepatitis B virus, which consistent in the literature [11, 12].

Comparing the frequency of manifestations of the main symptoms between the two groups, it was revealed significantly more severe course of HCC in cirrhotic patients in the outcome of chronic viral hepatitis. Most of the patients in Group 2 with markers of hepatitis viruses, asked for help with an increase in pain (83.2%), with signs of hepatic encephalopathy in 33.6% of cases with asthenic syndrome, manifested unwarranted weakness, fatigue in 88.8% cases. The phenomena of cancer intoxication in the form of reduced body weight and temperature subfebrile found in 68.8% of patients, signs of bleeding from the gastrointestinal tract in 28.0%. 5 (4.0%) patients had a strong, arching pain throughout the abdomen with the accession of bleeding from the gastrointestinal tract in the form of vomiting with coffee grounds and meleny.

The main reason for seeking medical attention were depletion of the autonomic nervous

system (60.4%) and pain (35.4%) syndrome among the first group of patients without markers of hepatitis viruses. Cancer toxicity was detected among 26.4% of patients. According to dynamic observation, 18.8% of patients had signs of liver failure.

Icterus as a sign of poor prognosis, and measure the vastness of liver damage was observed among patients of the second group in 44.8% of cases, the high frequency of hepatomegaly - in 60.8% of cases. Thus, among the first group of patients, icterus was detected in 13.2% of patients, increased liver in 32.1% of patients. The frequency of signs of decompensation of cirrhosis was significantly higher among patients of the second group than the first group (splenomegaly - 24.8 and edematous-ascitic syndrome - 35.2% against 16.9 and 9.4% respectively, $p < 0.05$).

Comparative analysis of the main laboratory parameters between the groups showed a statistically significant difference on a number of indicators (Table 1). It was revealed a significant increase in aminotransferase activity, indicators of total bilirubin and alkaline phosphataseand thrombocytopenia and hypoalbuminemia among patients of the second group with markers of hepatitis viruses in comparison with patients from the first group without markers of hepatitis viruses.

The most important diagnostic feature of HCC is increasing of serum concentration of α-fetoprotein - a protein produced in large quantities in the fetal liver of the fetus, followed by a rapid decline. After repeated determination of tumor marker, levels of α-fetoprotein among patients of group 2 with markers of hepatitis viruses was significantly higher in comparison with a group without markers of hepatitis viruses.

Table 1.

The average values of laboratory parameters among patients with hepatocellular carcinoma

Indicators	The first group without markers of hepatitis viruses (n=53)	The second group with markers of hepatitis viruses (n=125)
	M±m	M±m
Erythrocytes 3-5*10^{12}/l	3,6±0,1	3,4±0,1
Hemoglobin 120-140 g/l	103,6±1,3	109,6±2,0
Platelets 180-320*10^{9}/l	150,0±3,5	112,7±4,6*
The erythrocyte sedimentation rate (ESR) 6-9 mm/h	43,3±0,7	44,0±1,1
Albumin 35-50 g/l	29,1±0,2	25,2±0,5*
Alanine Aminotransferase (ALT) 0-40 u/l	122,8±2,3	170,2±5,2*
Aspartate Aminotransferases (AST) 0-40 u/l	98,9±5,3	135,5±9,2*
Total bilirubin 8,5-20,5 мcmol/l	31,4±3,8	112,2±10,5*
Alkaline phosphatase 0-270 ед/л	235,6±10,8	398,8±13,1*
Cholesterol 3,3-5,2 mmol/л	6,7±0,2	6,4±0,8
Glucose 3,5-5,5 mmol/л	4,3±0,1	3,8±0,1*
Prothrombin index (PTI) 80-110%	55,3±0,2	55,8±0,5
α-fetoprotein 10 ME/мл	292,4±31,2	321,6±30,5

* Statistically significant difference in comparison with the first group, p<0,05;

To study the metabolic changes in the liver, observed under the influence of alcohol and hepatitis viruses, we determined the activity of alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (AlDG). The activity of dehydrogenases, and their ratio among patients with liver cancer varied depending on the etiology of the disease. Among 41.5% of patients without markers of hepatitis viruses, the ratio of ADH / AlDG was lower than among 59.6% of patients with viral hepatitis. It is noted that the increase in the ratio of ADH / AlDG leads to prolonged viral replication, and therefore more massive cytolysis virusinfitsirovannyh liver cells [1]. Found that the activity of these enzymes determines high risk of developing alcoholic liver disease in the indigenous population of Yakutia [5].

The presence of III degree of varices of the esophagus and ascites in the second group with markers of viral hepatitis showed great severity of portal hypertension in comparison with the first group with no markers of hepatitis B virus (14.4 vs. 5.7% and 35.2 vs. 9.4%). Complication of portal hypertension was bleeding from the EW, which led to the death 18.4% of patients from the second group. These ultrasound and computed tomography with contrast enhancement of liver tissue found malignant formation and the prevalence of liver cancer. 44.9% of patients with liver

biopsy confirmed the clinical diagnosis. Summary data of laboratory and instrumental studies have shown that 3rd and 4th stages of the disease by the TNM system were detected among patients from the second group, and the third stage of liver cancer among patients from the first group.

Two groups of patients with markers of hepatitis viruses since the detection of malignant tumors in the liver were observed during 3 months. The causes of early death were decompensated liver cirrhosis, variceal bleeding, tumor thrombosis of the portal vein and inferior vena cava and the rupture of the tumor sites. Terms observations of patients from the first group with no markers of hepatitis viruses were more persistent (year and 1.5 years).

According to the results of serological and molecular biological studies it was noted a high incidence of HCC among patients in the outcome of chronic hepatitis B and C (38.4 and 32.8% respectively). Low frequency of detection of liver cancer among patients with chronic hepatitis D (28,8%) showed a quickly progressing disease course, in which patients did not live up to the formation of cancer of the liver (Fig. 2).

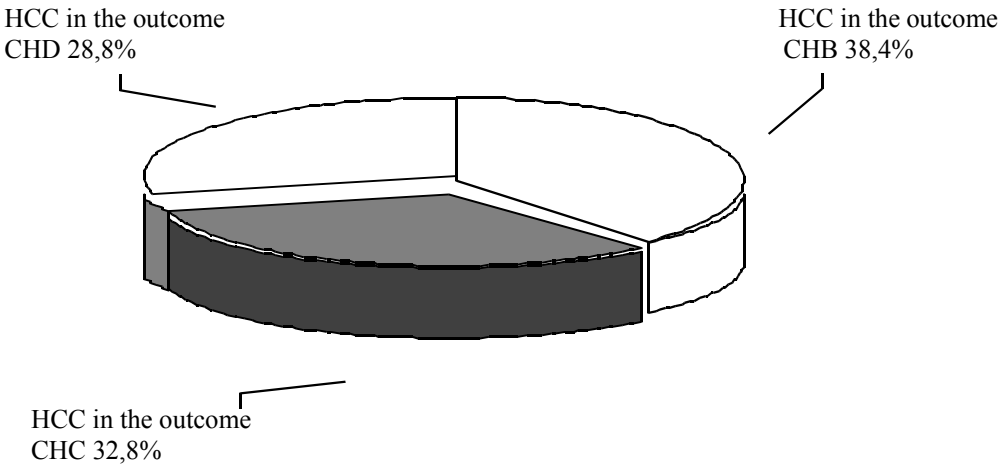

Fig. 2. Distribution of patients with hepatocellular carcinoma, taking into account markers of viral hepatitis (n=125).

Important to note that replication of hepatitis virus was observed in end-stage of cirrhosis, liver cancer. Most patients with HCC in the outcome of chronic hepatitis B and C indicated an active DNA replication of hepatitis B and hepatitis C RNA. RNA monoreplication of hepatitis D among patients with liver cancer in the outcome of hepatitis D showed high activity. In a third of the cases it was found mixedreplication of two viruses: hepatitis D RNA and DNA of hepatitis B. In the study of hepatitis virus genotypes among patients with HCC it was found a high frequency of formation of the cancer pathology with genotype Ib hepatitis C, genotype D viral hepatitis B and genotype I viral hepatitis D.

Conclusion. Thus, late detection of HCC caused by the absence of symptoms in the initial stages of the disease. The native inhabitants of the republic have a risk of developing liver cancer among alcoholic patients in relation to the low activity of the enzymes alcohol dehydrogenase and aldehyde dehydrogenase. The comparative analysis revealed a more severe progressive course of HCC in the presence of viral hepatitis in comparison with cancer patients without viral hepatitis. The vast majority of patients with HCC in the outcome of viral hepatitis were hospitalized in an advanced stage of disease, which determined the severity and course of disease. Obtained data may have prognostic significance in the outcome of viral hepatitis B, C and D with genotypes.

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