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Diagnostic Criterials of Liver Fibrosis Formation in Patients with Chronic viral Hepatititis C with Extrahepative Manifestations

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Abstract: A comprehensive analysis was performed to assess the prevalence and significance of extrahepatic manifestations among patients diagnosed with chronic hepatitis C virus infection, particularly in the first group with cryoglobulinemia. The results revealed a markedly higher incidence of extrahepatic complications in these patients compared with those without circulating cryoglobulins. In addition, individuals in this group had more advanced stages of liver fibrosis, confirming the correlation between cryoglobulinemia and disease severity. The increased incidence of both liver fibrosis progression and extrahepatic manifestations suggests that the presence of cryoglobulins in the circulatory system serves as a critical aggravating factor that affects not only the clinical course of chronic hepatitis C but also its long-term outcome. These results highlight the need for increased clinical awareness and possibly individualized therapeutic strategies for patients with concomitant hepatitis C and cryoglobulinemia to mitigate disease complications and improve prognosis.

Key words: Chronic hepatitis C, extrahepatic manifestations, cryoglobulinemic vasculitis, hemorrhagic vasculitis.

Introduction.

Chronic hepatitis C (HCV) is widespread all over the world. According to the World Health Organization (WHO), the disease is most common in the Eastern Mediterranean and the European region, where the prevalence in 2015 was 2.3% and 1.5% [1.5]. The activity of the HCV epidemic process is decreasing slowly, it is maintained due to chronic forms of the disease. However, it is less well known that chronic HCV infection leads to a number of systemic disorders and diseases that can often have more serious health consequences than liver disease alone. These disorders are commonly referred to as extrahepatic manifestations of HCV and cover a wide range of conditions, from the clinically insignificant presence of various autoantibodies in the blood serum to vasculitis, skin diseases, kidney damage, lymphoproliferative disorders, diabetes mellitus, and various neurological and neuropsychiatric changes in the patient's body [2,7]. Sometimes extrahepatic concomitant autoimmune diseases, such as cryoglobulinemic vasculitis, can lead to the diagnosis of HCV infection. It has been shown that prolonged HCV eradication with IFN-α or DAA has a beneficial effect on outcomes after these manifestations [4,5]. Specific extrahepatic manifestations of HCV are divided depending on the affected organ or organ system, the pathological mechanism, or the strength of available evidence linking them to chronic hepatitis C infection. The fact that the severity of these disorders does not necessarily correlate with the severity of liver disease is of great clinical importance, because even in cases of moderately active chronic hepatitis, significant impairment of general health and quality of life can occur [10]. The pathophysiological mechanism leading to such outcomes is persistent inflammation, followed by progressive fibrosis and, eventually, vascular and architectural changes in cirrhosis. Timely diagnosis and treatment of advanced fibrosis can prevent complications and death; however, optimal risk stratification is necessary to avoid unnecessary and potentially wasteful resource allocation. [3,9]. Cryoglobulinemia is an immunopathological change characterized by the presence of precipitation of cryoglobulins and precipitation capable of accumulating at temperatures below 37 ° C., as well as deposition of cryoglobulinemic immune complexes into the vessel walls with the development of systemic and immunopathological processes [3]. Clinical manifestations of cryoglobulinemia may include hemorrhagic rash, Raynaud's syndrome, arthralgia, peripheral polyneuropathy, hepatosplenomegaly, glomerulonephritis and renal failure, and other immunopathological processes. The main diagnostic value for the diagnosis of cryoglobulinemia includes blood tests for serum cryoglobulin, RF, anti-HCV and others. [2,6].

Despite the above, all the details of the diagnosis of extrahepatic manifestations of HCV have not yet been definitively revealed, in addition, there is little information on the clinical and diagnostic characteristics of fibrosis in these patients, and materials on the relationship of immune system parameters with the stages of liver fibrosis in this category of patients are rare and scattered. The purpose of the study To study the clinical characteristics of chronic hepatitis C with extrahepatic manifestations and to evaluate the severity of liver fibrosis in patients with chronic viral hepatitis C with extrahepatic manifestations. The object of the study was 120 patients with chronic viral hepatitis C with extrahepatic manifestations with and without cryoglobulinemia. Liver elastography was performed using a Fibroscan ECOSENS 430 machine manufactured in France. Liver elastography (Fibroscan, EchoSens) evaluates the severity of liver fibrosis, based on measuring the elasticity of the liver using ultrasound. The system consists of an ultrasound transducer combined with a vibration probe, which is positioned along the intercostal spaces and sends low-frequency and moderate-amplitude (50 Hz) waves to the right lobe of the liver. Vibration causes a wave that spreads through the liver tissue. Then echo-pulse ultrasound waves measure the speed of the shear wave movement in the liver tissue at a distance of 2.5-6.5 cm below the skin level. This corresponds to a measured distance of 4 cm in the liver tissue. The rate correlates with the stiffness of the liver tissue and, consequently, the degree of fibrosis. The tougher the fabric, the faster the shear wave propagates. The values are written in kilopascals (kPa). The average value is set from ten valid measurements. The technical contraindications of the method are the presence of ascites and obesity. Liver elasticity indices obtained by transient elastography were compared with the results of morphological assessment on the METAVIR scale: in the range of 5.9–7.2 kPa– fibrosis stage F1; in the range of 7.3–9.5 kPa– fibrosis stage F2; in the range of 9.6–12.5 kPa– fibrosis stage F3; indicators greater than 12.5 kPa– fibrosis stage F4. When organizing and conducting research, the principles of evidence-based medicine were observed.

Material and methods

For a more detailed analysis, all 120 patients were divided into 2 representative groups. The first group consisted of patients with CG (total n=52 or 43.33% of the total sample, average age 55 years). The second group consisted of patients in whom KG was not detected in the blood (total n=68 or 56.66%, average age 50 years). The criteria for inclusion in the study were: serological confirmation by enzyme immunoassay (ELISA) of the presence of antibodies against HCV, qualitative and quantitative determination of HCV RNA by polymerase chain reaction (PCR); patient's consent to participate in scientific research. Etiological verification of hepatitis was performed by serological ELISA methods (MINDRAY 96 A, China) with the detection of anti-HCV-core, unprotected proteins NS3, NS4, NS5. Qualitative and quantitative analysis for hepatitis C virus (virus RNA) and virus genotyping were performed by polymerase chain reaction (PCR) using DTlite 4 (Russia). Hematological parameters were studied on an automatic BC-20S hematology analyzer (Mindray, China) with the determination of the number of leukocytes (WBC), lymphocytes (LYM), mononuclears (MONO), and neutrophils (NEU) in blood samples. Blood biochemistry parameters: aspartate aminotransferase (AST), alanine aminotransferase (ALT), glucose (GLU), urea, creatinine, and C-reactive protein (CRP) were determined using an automatic biochemical analyzer Mindray VS – 30 (China). Cryoglobulins form complexes (precipitates) when the temperature drops to 4 °C, and then split again at 37 °C. Blood sampling was performed in the morning from 8 a.m. to 11 p.m. on an empty stomach. The blood sample was at least 5 ml. This was necessary to prevent the sample from cooling down. For this purpose, blood tubes were incubated at 37 °C in a thermostat for 1 hour. After incubation, the tubes were centrifuged for 3-5 minutes at 1,500 thousand rpm. Cryoglobulins have abnormal solubility at temperatures below 37 ° C and can form cryoprecipitates. Liver elastography was performed using a Fibroscan ECOSENS 430 device from 7-10 zones. The results were processed using a Pentium IV personal computer and Microsoft Office Excel-2012 software package. The methods of variational parametric and nonparametric statistics were used to calculate the arithmetic mean (M), the mean square deviation (□), the standard error of the mean (m), and relative values (frequency, %). The statistical significance of the comparative analysis of the averages was assessed by the Student's criterion (t). At the same time, the probability of error (p) was determined when checking the normality of the distribution (the kurtosis criterion) and the equality of the general variances F according to the Fisher criterion. At the first stage, the frequency and spectrum of extrahepatic manifestations of HCV infection were studied. The incidence of cryoglobulinemia in the study population of patients with HCV infection was 43.33 (n=52), of which males accounted for 10.83% (n=13) and females for 32.49% (n=39), (female/male ratio 3/1).

Results and discussion

The results show that some clinical signs do show significant differences between the groups of patients with and without cryoglobulinemia. In total, the results of the detection of 21 clinical signs in patients with HCV were

analyzed, of which 13 parameters significantly differed from each other (P<0.05), the numerical data of 7 indicators were close to each other, there were no significant differences (P>0.05). (Fig. 1.)

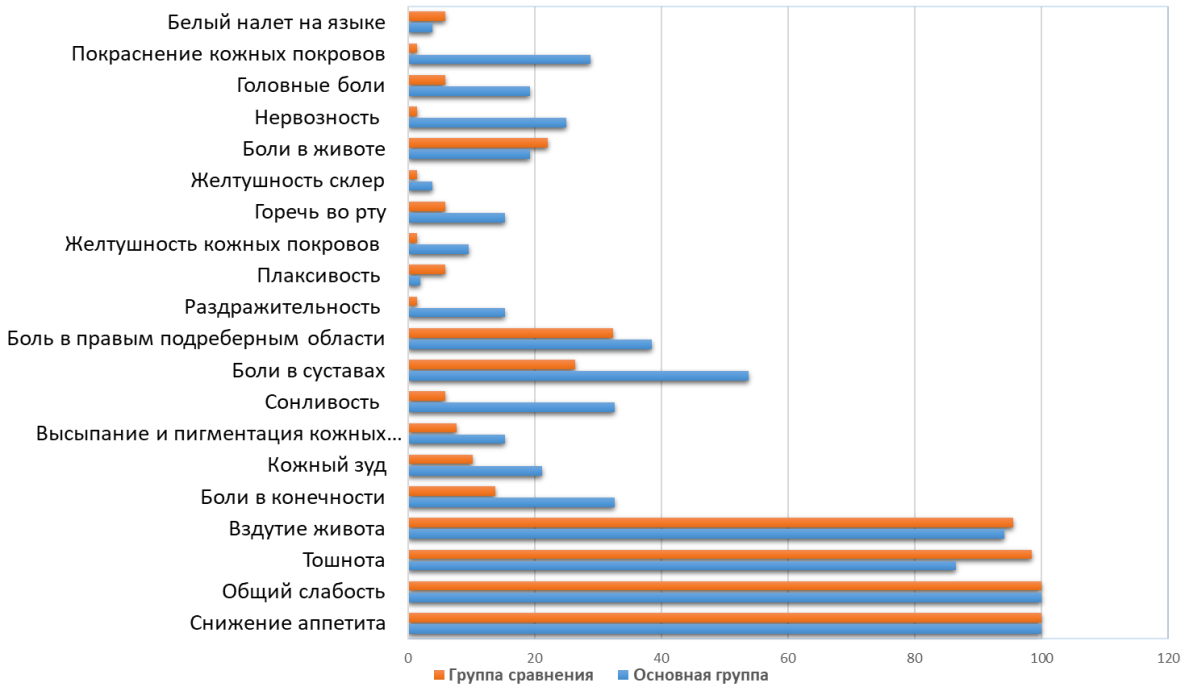

Fig 1. Comparative indicators of clinical manifestation in the examined patients with cryoglobulinemia.

When statistically processing the material for one feature (darkening of urine), the reliability could not be calculated, since one of the compared parameters was zero. It was found that out of 13 statistically significantly different indicators, 12 were elevated in patients with cryoglobulinemia (P<0.05 - P<0.001), only in one case (pain in the right hypochondrium) the parameter was elevated in patients with cryoglobulinemia (P<0.001). The most different among the compared groups in terms of clinical signs in patients were: headaches in the examined HCV patients with cryoglobulinemia were significantly higher by 7.85 times compared with the group of patients without cryoglobulinemia (P<0.001); In other cases, the increased changes were in favor of the group of HCV patients with cryoglobulinemia: scleral jaundice increased 26.16 times, fatigue increased 19.62 times, skin jaundice increased 14.39 times, skin redness 11.78 times, nervousness increased 10.46 times, limb pain increased 7.41 times, drowsiness increased 7.19 times, irritability increased 5.23 skin rashes 4.58 times, joint pain 3.49 times, bitterness in the mouth 2.62 times (P<0.001). This fact indicates that cryoglobulinemia negatively affects the clinical course of HCV patients with extrahepatic manifestations. (Fig. 2.)

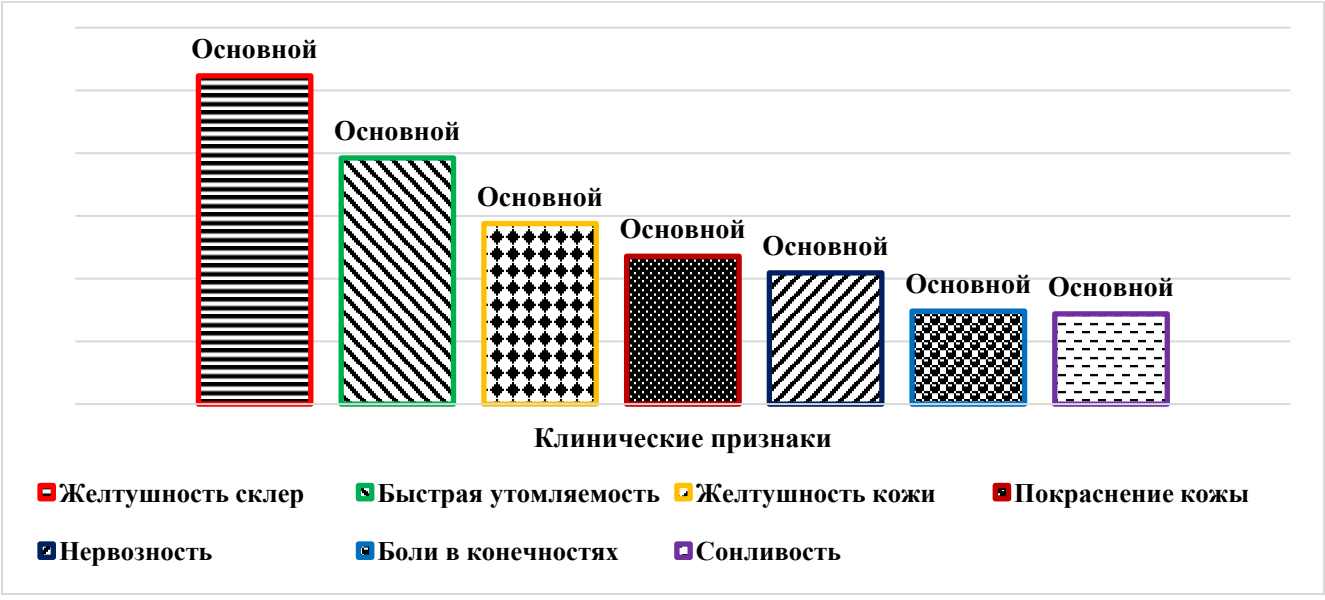

Fig. 2. How many times are there differences in the detection of clinical signs in patients with HCV with and without cryoglobulinemia?

These parameters are clearly visible in Fig. 2, which shows the data of 7 main clinical signs that differed

between the groups by more than 7 times. In this case, the multiplicity of differences in the detectability of clinical signs was in favor of HCV patients with cryoglobulinemia compared with HCV patients without cryoglobulinemia (P<0.001). According to the results of liver elastography of patients, the distribution of fibrotic processes in HCV patients shows that in the first group of patients (main group, n=52) fibrotic processes were: F0 - 9.62±4.09% (n=5), F1 - 30.77±6.40% (n=16), F2 - 32.69±6.50% (n=17), F3 - 19.23±5.47% (n=10), F4 - 7.69±3.69% (n=4) of cases (Table 2). Table-2 Distribution of fibrotic processes in patients with HCV in comparative terms Stages of fibrosis with KG, n=52 without KG, n=68 abs % abs % F0 5 9,62±4,09 13 19,12±4,77* ↑ F1 16 30,77±6,40 23 33,82±5,74 ↔ F2 17 32,69±6,50 23 33,82±5,74 ↔ F3 10 19,23±5,47 8 11,76±3,91 ↔ F4 4 7,69±3,69 1 1,47±1,46* ↓ Note: * is a sign of confidence between the parameters with and without cryoglobulinemia; ↑, ↓ is the direction of the changes; ↔ is not reliable; KG is cryoglobulinemia. In patients of the second group (comparison group, n=68), fibrotic processes were: F0 - 19.12±4.77% (n=13), F1 - 33.82±5.74% (n=23), F2 - 33.82±5.74% (n=23), F3 - 11.76±3.91% (n=8), F4 - 1.47±1.46% (n=1) of cases. Comparison of the given parameters in the table. 2 showed that F0 values were significantly higher in HCV patients without cryoglobulinemia (comparison group) - 9.62±4.09% versus 19.12±4.77% (P<0.05), respectively, and F4 parameters were significantly lower in the comparison group - 7.69±3.69% versus 1.47±1.46%, respectively (P<0.050.05). If in the first case the difference between the compared groups in terms of fibrotic lesions of the F0-F1 stage was 1.31 times in favor of the comparison group (P<0.05), then in the second case, fibrotic lesions of the F2-F3 stage reached a difference of 1.13 times, but in favor of the main group. These facts indicate that the fibroscopic picture in patients of the first group is significantly worse than in patients of the second group. If we assume that there is only one sign between the compared groups (the presence of cryoglobulinemia), then it becomes clear that the presence of cryoglobulins in the blood of patients with HCV complicates the course of this pathology, and also accelerates the process of fibrosis in the liver. The presence of cryoglobulins in the blood has a negative effect not only on the occurrence of liver fibrosis stages in patients, but also negatively affects elastographic parameters. It should be borne in mind that cryoglobulinemia negatively affects both the course of the clinical course itself and the process of fibrosis in the liver, as well as elastometric parameters. In this regard, the definition of cryoglobulinemia in HCV is recommended as an additional clinical and laboratory diagnostic and prognostic criterion for the severity of the disease.Thus, it was found that extrahepatic manifestations associated with cryoglobulinemia are more common among patients of the first group, in addition, higher stages of liver fibrosis are more common in these patients, which suggests that the presence of cryoglobulins in the blood of patients is an aggravating factor in the course and outcome of HCV in patients.

Conclusion

Of the 21 clinical signs identified, 13 parameters significantly differed from each other, of which 12 were elevated in individuals with cryoglobulinemia. This phenomenon negatively affects the hemato-biochemical parameters and the detectability of symptoms, which indicates that cryoglobulinemia negatively affects the clinical course of HCV patients with extrahepatic manifestations. The results of liver elastometry are very important evaluation criteria at all stages of development, which makes it possible to compare their diagnostic value and accuracy with the results of morphological examination of liver tissue. The inability to assess hepatitis activity limits the use of elastometry as an independent method of monitoring the development of liver fibrosis. The fibroscopic picture of the liver in patients with cryoglobulinemia is significantly worse than in patients without cryoglobulinemia. It has been proven that the presence of cryoglobulinemia in the blood of patients with HCV accelerates the process of fibrosis and negatively affects the elastographic parameters of the liver.

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