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CLINICAL AND DIAGNOSTIC CRITERIALS OF LIVER FIBROSIS FORMATION IN PATIENTS WITH CHRONIC VIRAL HEPATITIS C WITH EXTRAHEPATIVE MANIFESTATIONS

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Abstract: Background: Chronic viral hepatitis C (CVHC) is often associated with various extrahepatic manifestations, which may complicate the disease's progression. **Specific Background:** Cryoglobulinemia, characterized by the presence of cryoglobulins in the blood, has been implicated in the exacerbation of liver conditions, yet its role in CVHC remains inadequately explored. **Knowledge Gap:** Despite existing knowledge of the relationship between cryoglobulinemia and liver disease, the specific impact of cryoglobulinemia on the severity of liver fibrosis and associated extrahepatic manifestations in CVHC patients requires further elucidation. **Aims:** This study aims to investigate the prevalence of extrahepatic manifestations and the extent of liver fibrosis in patients with CVHC who also present with cryoglobulinemia, thereby determining the clinical implications of cryoglobulin presence. **Results:** Our findings indicate that patients with cryoglobulinemia demonstrate a significantly higher prevalence of extrahepatic manifestations and advanced stages of liver fibrosis compared to those without cryoglobulinemia. **Novelty:** This research contributes novel insights into the aggravating role of cryoglobulins in the clinical course of CVHC, highlighting their potential as biomarkers for disease severity. **Implications:** These results underscore the need for enhanced clinical monitoring and tailored therapeutic approaches for CVHC patients with cryoglobulinemia, as their condition may predict a more severe disease trajectory and necessitate more aggressive management strategies.

Keywords: Chronic Hepatitis C, Extrahepatic Manifestations, Cryoglobulinemic Vasculitis, Hemorrhagic Vasculitis

Introduction

Chronic hepatitis C (CHC) is widespread throughout the world. According to the World Health Organization (WHO), the disease is most often found in the Eastern Mediterranean and European regions, where prevalence in 2015 was 2.3% and 1.5% [*1-5*]. The activity of the HCV epidemic process decreases slowly, it is maintained by chronic forms of the disease.

However, it is less well known that chronic HCV infection results in 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 spectrum of conditions, from clinically insignificant presence of various autoantibodies in the blood serum to vasculitis, skin diseases, kidney damage, lymphoproliferative disorders, diabetes mellitus, various neurological and psychoneurological changes in the patient's body [2-7].

Occasionally, extrahepatic coexisting autoimmune diseases such as cryoglobulinemic vasculitis may lead to the diagnosis of HCV infection. Long-term HCV eradication with IFN-α or DAA has been shown to have a beneficial effect on outcomes after these manifestations [4,5].

Specific extrahepatic manifestations of CHC are classified according to the organ or organ system affected, the pathological mechanism, or the strength of the available evidence linking them

to chronic hepatitis C infection. The fact that the severity of these abnormalities 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 may occur [10].

The pathophysiological mechanism leading to these outcomes is persistent inflammation followed by progressive fibrosis and ultimately vascular and architectural changes of 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 the ability to accumulate as sediment at temperatures below 37 °C , as well as the deposition of cryoglobulinemic immune complexes in the walls of blood vessels with the development of systemic and immunopathological processes [3].

Clinical manifestations of cryoglobulinemia may include the following changes such as 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 chronic hepatitis C have not yet been fully identified; in addition, there is little information on the clinical and diagnostic characteristics of fibrosis in these patients; materials on the relationship between immune system indicators and the stages of liver fibrosis in this category of patients are rare and scattered.

Purpose of the study

To study the clinical characteristics of chronic hepatitis C with extrahepatic manifestations and to assess the severity of liver fibrosis in patients with chronic viral hepatitis C with extrahepatic manifestations.

The object of the study were 120 patients with chronic viral hepatitis C with extrahepatic manifestations with and without cryoglobulinemia.

Liver elastography was performed using the Fibroscan ECOSENS 430 apparatus manufactured in France . Liver elastography (Fibroscan, EchoSens) evaluates the severity of liver fibrosis and is 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, moderate-amplitude (50 Hz) waves to the right lobe of the liver. The vibration causes a wave that propagates through the liver tissue. Then, echo-pulse ultrasound waves measure the speed of movement of the shear wave 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 speed correlates with the rigidity of the liver tissue and, therefore, the degree of fibrosis. The stiffer the tissue, the faster the shear wave propagates. The values are recorded in kilopascals (kPa). The average value is established from ten valid measurements. Technical contraindications to the method are the presence of ascites and obesity.

The liver elasticity indices obtained by transient elastography were compared with the results of morphological assessment using 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; indices greater than 12.5 kPa – fibrosis stage F4.

The principles of evidence-based medicine were followed when organizing and conducting

the research.

Methods

For a more detailed analysis, all 1 20 patients were divided into 2 representative groups. The first group consisted of patients with CG (total n = 52 or 43, 33 %). of the entire sample , average age 55 years). The second group consisted of patients in whom CG was not detected in the blood (total n= 68 or 56.66%, average age 50 years).

The inclusion criteria for the study were: serological confirmation using enzyme-linked immunosorbent assay (ELISA) of the presence of antibodies against HCV, qualitative and quantitative determination of HCV RNA using polymerase chain reaction (PCR) ; patient consent to participate in scientific research.

Etiological verification of hepatitis was performed by serological methods of ELISA (MINDRAY 96 A, China) with detection of anti-HCV-core, unprotected proteins NS3, NS4, NS5. **Qualitative and quantitative analysis for hepatitis C virus** (RNA of the virus) and **genotyping of the virus were performed by** the polymerase chain reaction (PCR) method using DTlite 4 (Russia).

Hematological parameters were studied using an automatic hematological analyzer BC-20S (Mindray, China) with determination of the number of leukocytes (WBC), lymphocytes (LYM), mononuclear cells (MONO), 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 BC - 30 (China).

Cryoglobulins form complexes (precipitates) when the temperature drops to 4°C, and then break down again at 37°C. Blood was collected in the morning from 8 to 11 a.m. on an empty stomach. At least 5 ml of blood was collected. This was necessary to prevent the sample from cooling. For this purpose, the tubes with blood 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 revolutions. Cryoglobulins have abnormal solubility at temperatures below 37°C and can form cryoprecipitates.

Liver elastography was performed using the Fibroscan ECOSENS 430 device from 7-10 zones.

The obtained results were processed using a Pentium IV personal computer and the Microsoft Office Excel-2012 software package. The methods of variational parametric and nonparametric statistics were used with the calculation of the arithmetic mean parameter (M), the standard deviation (σ), the standard error of the mean (m), and relative values (frequency, %). The statistical significance value in the comparative analysis of average indicators was estimated using the Student criterion (t). In this case, the probability of error (p) was determined when checking the normality of distribution (the excess criterion) and the equality of general variances F using the Fisher criterion.

At the first stage, the frequency and spectrum of extrahepatic manifestations of HCV infection were studied. The frequency of occurrence of cryoglobulinemia in the studied population of patients with HCV infection was 43.33 (n= 52), of which males were 10.83% (n=13) and females were 32.49%. (n= 39), (female/male ratio 3/1).

Results and Discussion

The obtained results show that some clinical signs do show reliable differences between the groups of patients with and without cryoglobulinemia . In total, the results of detection of 21 clinical signs in patients with CHC were analyzed, of which 13 parameters were significantly different from

each other (P<0.05), the digital data of 7 indicators were close to each other, and there were no reliable differences (P>0.05). (Fig. 1.)

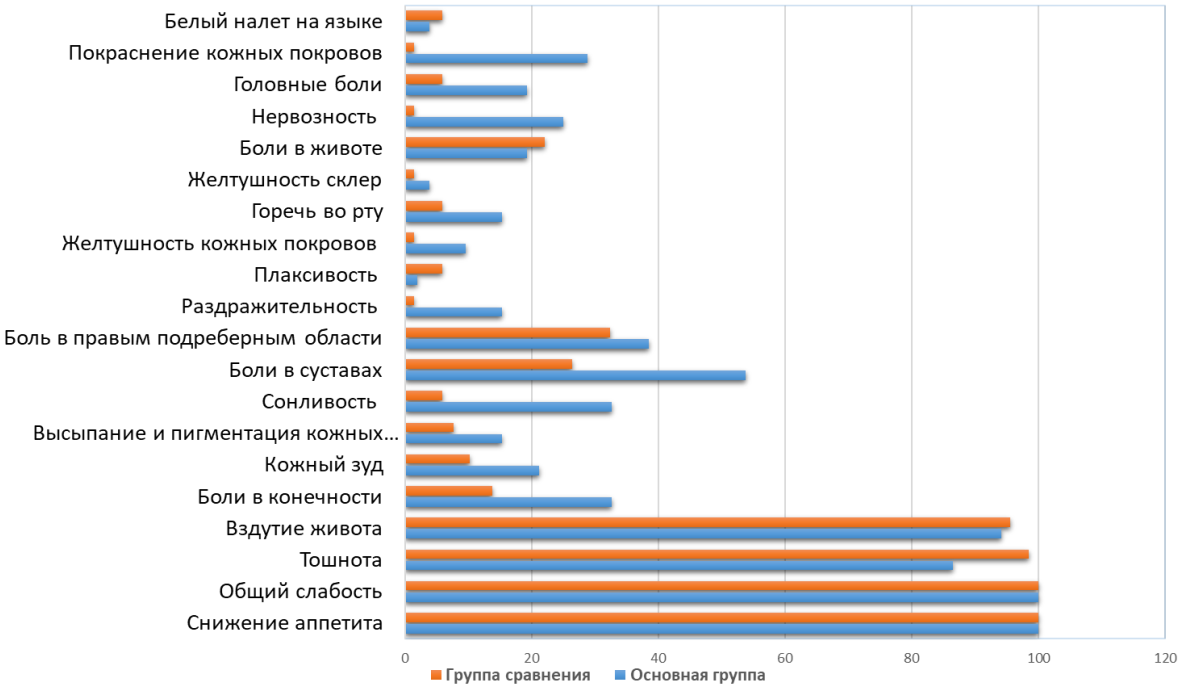

Fig. 1. Comparative indicators of clinical manifestations in examined patients with cryoglobulinemia.

During statistical processing of the material for one sign (darkening of urine), it was not possible to calculate the reliability, since one of the compared parameters was equal to zero. It was established that out of 13 statistically significantly different indicators, 12 were elevated in individuals with cryoglobulinemia (P<0.05 - P<0.001), only in one case (pain in the right hypochondrium) was the parameter elevated in patients with cryoglobulinemia (P<0.001).

The most different clinical signs among the compared groups in patients were: headaches in the examined patients with CHC with cryoglobulinemia were significantly higher by 7.85 times compared to the group of patients without cryoglobulinemia (P<0.001); in other cases, the increased changes were in favor of the group of patients with CHC with cryoglobulinemia: scleral jaundice increased by 26.16 times, rapid fatigue by 19.62 times, skin jaundice by 14.39 times, skin redness by 11.78 times, nervousness by 10.46 times, pain in the limbs by 7.41 times, drowsiness by 7.19 times, irritability by 5.23 times, skin rashes by 4.58 times, joint pain by 3.49 times, bitterness in the mouth by 2.62 times (P <0.001).

According to the results of liver elastography of patients, the distribution of fibrotic processes in patients with CHC 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 chronic hepatitis C in comparative terms

Fibrosis stages	with CG, n=52,	without CG, n=68
	abs%	abs%
F0	59.62±4.09	1319.12±4.77* ↑
F1	1630.77±6.40	2333.82±5.74 ↔
F2	1732.69±6.50	2333.82±5.74 ↔

F3 1019.23±5.47811.76±3.91 ↔

F4 47.69±3.6911.47±1.46* ↓

Note: * - reliability indicator between parameters with and without cryoglobulinemia; ↑, ↓ - direction of changes; ↔ - no reliability; KG - 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 parameters presented in Table 2 showed that the F0 values were significantly higher in patients with CHC without cryoglobulinemia (comparison group) - 9.62±4.09% versus 19.12±4.77% ($P<0.05$), respectively; in addition, the F4 parameters were significantly lower in the comparison group - 7.69±3.69% versus 1.47±1.46% ($P<0.05$), respectively.

If in the first case the difference between the compared groups in fibrous lesions of stage F0-F1 was 1.31 times in favor of the comparison group ($P<0.05$), then in the second case the difference in fibrous lesions of stage F2-F3 reached 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 consider 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 CHC complicates the course of this pathology, and also accelerates the process of fibrosis formation in the liver.

The presence of cryoglobulins in the blood has a negative effect not only on the incidence of liver fibrosis stages in patients, but also on elastographic indices. It should be taken into account that cryoglobulinemia has a negative effect on both the clinical course itself and the process of fibrosis formation in the liver, as well as on elastometric indices. In this regard, the determination of cryoglobulinemia in CHC is recommended as an additional clinical and laboratory diagnostic and prognostic criterion for the severity of the disease. Thus, it has been established that among patients of the first group, extrahepatic manifestations associated with cryoglobulinemia are more common, in addition, these patients more often have higher stages of liver fibrosis, which gives reason to believe that the presence of cryoglobulins in the blood of patients is an aggravating factor in the course and outcome of chronic hepatitis C in patients.

Conclusion

Of the 21 clinical signs identified, 13 parameters were significantly different from each other, of which 12 were elevated in individuals with cryoglobulinemia. This phenomenon negatively affects hemato-biochemical parameters and the detection of symptoms, indicating that cryoglobulinemia negatively affects the clinical course of patients with CHC with extrahepatic manifestations.

The results of liver elastometry are very important criteria for evaluation at all stages of development, which allows us to compare their diagnostic value and accuracy with the results of morphological examination of liver tissue. The impossibility of assessing the activity of hepatitis limits the use of elastometry as an independent method for 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 CHC accelerates the process of fibrosis formation and negatively affects the elastographic indices of the liver.

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