Extra Length Manifestations Of Viral Hepatitis C: Analysis Of Detected Features Of Associated Arthritis And Their Diagnostic Aspects

Fazilat Narmamatovna Shukurova[1*], Marif Shakirovich Karimov[2], Dinara Ayupovna Parpiboeva[3]

[1]*Assistant of the Department of Propaedeutics of Internal Diseases No.2, Tashkent Medical Academy, Tashkent, Uzbekistan*
[2]*Doctor of Medical Sciences, Professor, Head of the Department of Propaedeutics of Internal Medicine No. 2, Tashkent Medical Academy, Tashkent, Uzbekistan.*
[3]*Phd, Associate Professor, Department of Propaedeutics of Internal Medicine No. 2, Tashkent Medical Academy, Tashkent, Uzbekistan.*
Email: [1]fazilatshukurova@gmail.com

Abstract: Introduction. Chronic viral hepatitis (CVH) is often accompanied by a variety of extrahepatic (systemic) manifestations, often coming to the fore in the clinical picture and, in some cases, determining the prognosis of the disease.
Materials and methods. A cross-sectional study was conducted of 52 patients (mean age 38.54 ± 6.00 years) with a diagnosis of chronic viral hepatitis C (CVHS) who underwent initial consultation with a specialized course of outpatient treatment at the arthrology center (artSCAL) at the Tashkent Medical Academy (TMA) and received inpatient treatment in the departments of the clinic of the Research Institute of Epidemiology, Microbiology and Infectious Diseases of the Republic of Uzbekistan.
Results. Among patients with cryoglobulinemia (CGE), the incidence of articular manifestation was 74.3%. According to liver elastography, the examined patients with CGE had signs of liver fibrosis of the 2nd and 3rd degrees, relative to the indices of the group without CGE, where degrees 1 and 2 of fibrosis were more often observed. According to ultrasound of the joints, synovitis occurred in 46 (88.4%) patients.
Conclusion. In patients with chronic hepatitis C, the most common rheumatologic manifestation is arthralgia (92.3%). The relationship between the duration of hepatitis disease, its activity, the severity of liver fibrosis according to elastography and changes in the levels of the main biochemical and immunological parameters is established. Among patients with CGE, the incidence of articular manifestation was 74.3%, and the articular manifestations of HCV were mostly more severe.

KEY WORDS: Chronic viral hepatitis C; extrahepatic manifestations of HCV; associated arthritis; cryoglobulinemia;

1. INTRODUCTION

Chronic liver diseases of viral etiology are one of the most relevant and serious medical, social and economic problems of modern world medicine [29,31,43]. Moreover, most cases of hepatotropic viral infection are recorded in young people aged 20 to 40 years, i.e. affects the main reproductive and labor potential. According to recent data, there are about 170 million people infected with hepatitis C virus (HCV) in the world, which makes up 3% of the world's population [4,5]. According to the frequency of chronic hepatitis C (chronic hepatitis C), it ranks first among all diseases transmitted through the blood [44]. It is estimated that by 2015-2020. the incidence of HCVV at the stage of liver cirrhosis (CP) will increase, and the number of HCV-associated hepatocellular carcinoma (HCC) will increase [20]. The problem is compounded by the fact that for a long time, most infected patients have no symptoms of the disease [28,36,39]. However, 70-80% of people infected with HCV eventually develop HCV [1]. In approximately 80% of patients, the disease becomes chronic. CP develops in approximately 10-20% of patients with chronic hepatitis C and is detected, as a rule, 10-20 years after infection. Even after the development of CP, many patients live 10 years or more [29,43]. However, as soon as decompensation sets in, survival drops sharply [20,45]. The main feature of HCV is its genetic variability, pronounced ability to mutations. At present, it is considered established that the high frequency (from 50 to 85%) of the formation of chronic hepatitis C is due to the "escape" of the virus from immune surveillance [31]. The main reason for this variability is the lack of corrective activity of the virus dependent RNA polymerase, leading to the frequent introduction of nucleotide substitutions into the genome of the virus. Within the same genotype, sequences are homologous in approximately 95%, and between genotypes only in 65% of cases [30].

Great attention to this infection is determined not only by its widespread prevalence, high frequency of chronicity [6] and their severe complications, but also by the presence of various extrahepatic manifestations. Currently, more than a dozen pathologies associated with CGS have been described, among which are lesions of the joints, muscles, circulatory system, salivary glands, eyes, pancreas, nervous system, kidneys, etc. [3]. HCG C (HCV) is much more than a simple liver infection. Extrahepatic manifestations are clinically manifested in approximately 40-70% of patients and can involve many organs [1]. They mainly include joint disorders (arthritis or arthralgia), mixed cryoglobulinemia, vasculitis of small and medium vessels, glomerulonephritis, lichen planus, B-cell lymphomas and cutaneous porphyria.

HCV is able to act on B-lymphocytes through the CD8 1 receptor, which induces polyclonal activation of B-cells, which leads to the production of cryoglobulins (KG), rheumatoid factor (RF) and a number of autoantibodies [9]. Ueno et al. Indicate that HCV RNA was detected in the synovial fluid by polymerase chain reaction in a patient suffering from non-erosive polyarthritis associated with post-transfusion HCV infection [41]. The Italian group obtained the same results in one of 4 patients with rheumatoid arthritis (RA) with concomitant HCV infection [13].

KG products are strictly associated with HCV. The prevalence of antibodies to HCV in individuals with mixed cryoglobulinemia (CGE) (types II, II – III and III of cryoglobulinemia) varies from 40 to 90% in different regions [34]. The greatest amount of HCV RNA is contained in cryoprecipitate [8]. Lymphocytes of patients producing

cryoglobulin have the ability to concentrate higher amounts of HCV particles on their surface [35]. This event may play a role in the pathogenesis of the disease.

In a large prospective study of MULTIVIRC 1612 patients with chronic HCV infection, 74% of the prevalence of extrahepatic manifestations was reported [11]. In conditions of high prevalence and increasing incidence of chronic hepatitis C, low availability of antiviral therapy, an increase in the number of extrahepatic lesions that occur in about half of patients should be expected.

The pathological processes underlying the extrahepatic manifestations are not well understood. The most common extrahepatic manifestation of HCV infection is joint damage. Cacoub et al reported that 23% of 1614 patients with chronic hepatitis C generally suffered from arthralgia [11]. However, asymptomatic joint damage appears to be much more common. Iagnocco et al. it was found that 96.5% of 29 patients with HCV without articular symptoms had minor inflammatory changes in the knee, hip or shoulder joints with ultrasound, a highly sensitive method for examining joints [19]. However, other joints were not examined. Based on this observation and studies reporting arthritis in only 4-5% or fewer patients with HCV [10,26], it can be assumed that these small percentages represent only the tip of the iceberg of the joint inflammation associated with HCV. In any case, it should be emphasized that some clinical reports regarding extrahepatic manifestations of HCV infection were made by non-rheumatologists who might have mistakenly diagnosed milder forms of arthritis with arthralgia. The clinical picture of HCV-associated arthritis (HCV-A) has been outlined based on several studies [10,17,21,26,32,46]. In 1996, Italian authors hypothesized that HCV could induce a form of arthritis very similar to RA [15]. Later it was found that HCV-A can be distinguished in two clinical subgroups [24,33]: symmetric polyarthritis (SP) and intermittent mono-oligoarthritis (IMO).

In addition, the problem of the treatment of extrahepatic manifestations of HCV, more precisely arthritis associated with HCV infection (HCVaA), remains relevant. So far, HCV-A treatment has been largely empirical since only a few studies have analyzed this hypothesis. The coexistence of various diseases is often regarded as a therapeutic problem. In the case of HCV-A, therapy should be rational, without worsening liver disease or other possible HCV-related autoimmune disorders. HCV-A treatment requires frequent monitoring of liver tests and collaboration between hepatologists and rheumatologists [27]. From the point of view of a rheumatologist, HCV infection is a very serious comorbid pathology. First of all, this is due to the fact that many anti-rheumatic drugs - glucocorticoids (GA), cytotoxic drugs and genetic engineering biological drugs (HIBP) can reduce antiviral immunity to a certain extent and contribute to the exacerbation or reactivation of the infectious process [2, 12.37 , 42]. This is fraught not only with faster progression of CVH, but also with a significant increase in contagiousness, which is determined by active replication of the virus and an increase in the concentration of viable viruses in tissues and biological fluids. On the other hand, a number of drugs (in particular, cytotoxic drugs and non-steroidal anti-inflammatory drugs - NSAIDs) can negatively affect liver function and contribute to the development of dangerous complications, such as liver failure and cirrhosis in patients with active CVH.

Recently, the management of patients with HCVaA has become the subject of active study. However, in our country, scientific studies on the prevalence, diagnosis, and treatment of HCV-associated rheumatic fever are few.

Thus, this study was aimed at assessing the frequency of detection of arthritis in patients infected with HCV (HCVaA), as well as analyzing the revealed features of its manifestations using clinical research methods in this category of patients who are treated in the SCAL TMA and in the departments of the clinic.

2. MATERIALS AND METHODS

Subjects of research and their clinical characteristics

This study has a fundamentally oriented and applied character and is based on general scientific research methods, scientific literature data, the results of our own clinical, laboratory and instrumental observations, including general clinical examination. In our study, we observed 52 patients with a diagnosis of chronic viral hepatitis C (HVHS) who contacted the Republican Specialized Arthrological Center for Outpatient Medicine at the Tashkent Medical Academy (TMA) and received inpatient treatment at the departments of the clinic of the Research Institute of Epidemiology, Microbiology and Infectious Diseases of the Republic Uzbekistan All patients had HCV-associated arthritis (HCV-A). The diagnosis was confirmed by the presence of antibodies to HCV (anti - HCV) and HCV RNA by the method of polymerase chain reaction (PCR). Gender distribution of subjects of the research group: 30 men (M) and 22 women (F), average age 38.54 ± 6.00 years. At the same time, we examined a comparative group, which included 36 patients with chronic hepatitis C virus infection without associated arthritis, who were registered with infectious disease clinics at the Research Institute of Epidemiology, Microbiology and Infectious Diseases of the Republic of Uzbekistan.

Patients who have been diagnosed with heart failure, arterial hypertension, diabetes mellitus, cancer, tuberculosis, other types of hepatitis, cirrhosis of the liver, severe renal failure, a history of intolerance to NSAIDs, who received antiviral therapy for 6 months from the initial level for chronic hepatitis C, diagnosed with systemic rheumatic diseases, pregnant women and carriers of the HIV virus were excluded from the study. All patients voluntarily gave written informed consent to participate in the study.

The study was carried out in two stages: screening questionnaire, diagnostic examination and dynamic observation during the study.

At the first stage, a screening was carried out using a questionnaire, which included passport data of patients, an anamnesis of hepatitis and arthrological syndrome, the main complaints of pain (a history of injuries were excluded) and swelling in the joints indicating the location of the lesion according to joint groups. Also, the duration of these symptoms was taken into account, whether rheumatic diseases were diagnosed before and by which specialists. Rheumatic complaints were examined and included in the study when they were registered for more than 3 months (Table 1).

At the second stage, a diagnostic card was compiled for each patient, including passport data, a history of hepatitis and arthrological syndrome, objective examination data (pain assessment according to the visual analogue scale for pain was used in all patients as a one-dimensional tool for assessing pain intensity) , soreness and swelling in various joints, limiting the range of motion in them; skin changes, liver condition, laboratory data: general blood test (OAC), general urine analysis (GUA); blood biochemical parameters: proteinogram, AlAT, AsAT, bilirubin by fractions, cholesterol (cholesterol), lipid spectrum,

blood glucose, thymol test, C-RB, RF, as well as immunological parameters: CIC, Ig spectrum, ADC, PCR on HCV RNA ; instrumental research methods (liver ultrasound, joint ultrasound, joint radiography, liver elastography) (table 2).

In the visual analogue scale, from one end of the line the inscription "no pain" corresponds to the absence of pain, another point on the scale reflects excruciating unbearable pain - "the most severe pain you can imagine." Subsequently, the patient was asked to evaluate and note the pain present at the time of the study. The symptom of arthralgia was considered and included in the study if it was registered for a period of more than 3 months and was evaluated on the visual analogue scale of ≥ 5, which is considered moderate to high pain, leading to functional limitation.

Sample set

At the second stage, venous blood was collected in an amount of 10 ml into test tubes without additives, by venous puncture in the morning on an empty stomach. Peripheral venous blood was allowed to coagulate at room temperature for 30 minutes. The tubes were centrifuged at 2000 rpm for 15 minutes to obtain serum and serum samples were further aliquoted and stored at -8 ° C until evaluation. Prior to testing, frozen probes were brought to room temperature, avoiding freezing and thawing cycles.

Immunological studies

Serological screening of HCV-A patients was performed at the IRODAMED laboratory.

The diagnosis of HVGS was made on the basis of identification in blood serum of total antibodies of class IgM and IgG to the HS virus (anti-HCV), specific antibodies to structural and non-structural proteins (cor, ns) in the ELISA (MR-96A MINDRAY, China), RNA virus by PCR with determination of the number of copies of the virus in 1 ml of blood plasma (MR-96A MINDRAY, China). To determine anticytrulline AT, ELISA of ADC is used using cyclic citrulline containing peptide immobilized on a solid phase as an AG, which has a higher binding activity against a wide spectrum of AT associated with RA compared with the linear version of this peptide. In the blood serum, the concentration of immunoglobulins (Ig) was determined by the methods of radial immunodiffusion (RID) using antibodies produced by the Research Institute of Vaccines and Sera N. Novogorod (G. Mancini a. Oth, 1965). The content of circulating immune complexes (CICs) was studied in a precipitation reaction with a 3.5 5 solution of polyethylene glycol (Haskova a. Oth, 1978).

CGE was determined using the method of Tomas L. (1998), since this method is available for execution in any laboratories and is easy to use. The determination of cryoglobulin titer was made in all patients. To detect the presence of cryoglobulins in hungry patients, 10 ml of blood was taken, after which, for complete coagulation, the blood tube was placed in a water bath for two hours at a temperature above 37 C. After incubation of blood samples in a water bath, centrifugation was performed at 2000 rpm for 15 minutes for receiving serum. The tubes were placed in a refrigerator at a temperature of 4 ° C. Quantification of cryoprecipitate was carried out spectrophotometrically at a wavelength of 500 nm. Normally, the concentration of KG can occur in the amount of 60 - 80 mg / l and cryocrit can be less than 0.4%.

Instrumental examination

All patients underwent x-ray examination of the affected joints.

Ultrasound of the liver and joints was performed using an ultrasound apparatus of the Mindray DC-8 apparatus (China).

All patients with chronic hepatitis C virus infection underwent liver elastography using the FibroScan apparatus (Echosens company, France). Unlike a biopsy, which allows you to examine only a small area of the liver (from which the biopsy was taken), elastography gives a complete picture of the organ and allows you to determine the degree of fibrosis.

Statistical analysis

Statistical research methods using the programs "Statistica 6.0", Biostat and Excel spreadsheets for Windows XP. When analyzing the material, methods of mathematical statistics were used with the calculation of the main characteristics: average value, mean square deviation, standard error. When checking the significance of differences, standard parametric (Student's test) methods were used with a normal distribution of the sample.

3. RESULTS

Among 52 patients who were initially diagnosed with HCVaA, 57.7% of men (sex ratio: 30 men: 22 women), the average age of HCVaA patients was 38.54 ± 6.00 years.

The distribution of HCVaA patients by gender in 58% of cases of arthritis was found in men with HCV. At the same time, 48% of patients were of working age - 30-40 years (Table 3).

The ratio of men and women, respectively, 1.36: 1, the average age of patients diagnosed with HCVaA (M ± a) was 38.54 ± 6.00 years.

In the majority of all surveyed patients (44 patients -84.6%), the duration of HCV was up to 10 years. Moreover, the distribution of patients in groups with associated arthritis and in the comparison group was approximately the same. In 80.76% (in 42 patients), hepatitis proceeded without arthritis. Thus, the incidence of HCV with articular manifestation was 19.24%.

Regarding rheumatic complaints, arthralgia was the most common manifestation for patients with HCV infections (92.3%) and the frequency of rheumatic complaints had a statistically significant difference between the groups according to statistical analysis. The average VAS value was 6.78 ± 1.42 and the patients were distributed as follows:

- visual analogue scale 1-3 (mild pain): 9.4% of patients with HCV
- visual analogue scale 4-6 (moderate pain): 28.6% of patients with HCV
- visual analogue scale 7-10 (severe pain): 62% of patients with HCV

That is, patients of the main group with a diagnosis of HCVaA complained of joint pain - 48 (92.3%), swelling in the affected joints - 29 (55.7%), and movement restriction in the joints - 20 (38, 4%), 17 (32.7%) for stiffness during movements, and 4 (7.7%) for joint deformity.

In addition, we noted that in 29 (55.7%) patients of the main group, articular manifestation occurred in the form of polyarthritis, in 17 (32.7%) - oligoarthritis of the knee joints, in 5 (9.6%) - oligoarthritis of the ankle joints , 1 (1.9%) - polyarthralgia without signs of inflammatory changes according to the ultrasound of the joints.

In the studied group of patients, we observe a correlation between the severity of pain according to visual analogue scale and the duration of rheumatic complaints (r = 0.51; p

<0.05), as well as hepatitis activity (r = 0.46; p <0.05). At the same time, pain was stronger in patients with a longer course of hepatitis. In addition, there was a weak direct correlation between the severity of joint pain according to visual analogue scale in the main groups and the degree of liver fibrosis according to liver elastography (r = 0.34; p <0.05). That is, in individuals with a more pronounced degree of liver fibrosis according to elastography, higher rates of severity of joint pain according to visual analogue scale were observed.

In our study, we observed that an increase in bilirubin levels: in the main group - in 14 (26.9%) patients, in the comparison group - in 8 (22.2%) patients; AlAT: in the main group - in 45 (86.5%) patients, in the comparison group - in 24 (66.66%) patients; AsAT: in the main group - in 35 (67.3%) patients, in the comparison group - in 24 (66.6%) patients; thymol test: in the main group - in 24 (46.15%) patients, in the comparison group - in 20 (55.55%) patients; decrease in albumin levels: in the main group - in 13 (25%) patients, in the comparison group - in 13 (36.11%) patients. No significant differences were found for other biochemical parameters. Here we found that there is a pronounced direct correlation in the main group of patients with chronic hepatitis C between the degree of hepatitis activity and indicators of AlAT, AsAT and thymol breakdown; average direct correlation between the duration of hepatitis disease and indicators of AlAT, AsAT, between the degree of hepatitis activity and levels of total bilirubin and thymol breakdown, as well as between the severity of joint pain according to visual analogue scale and the severity of the degree of liver fibrosis with levels of AlAT and AsAT; a weak correlation was between the severity of joint pain according to visual analogue scale and the degree of liver fibrosis with levels of total bilirubin, and indicators of thymol breakdown.

An average inverse correlation was observed between the duration of hepatitis disease and albumin levels; a weak inverse correlation was between albumin levels, the degree of hepatitis activity and the severity of joint pain according to visual analogue scale (table 4).

We noticed that a relationship was established between the duration of hepatitis disease, its activity, the severity of liver fibrosis according to elastography, and changes in the levels of the main biochemical parameters. That is, the longer the hepatitis lasts, its degree of fibrosis was expressed, and the more active it was, the higher the levels of bilirubin, AlAT, AsAT, thymol test, more severe joint pain according to visual analogue scale and albuminemia. The latter, in turn, correlates with thymol test values.

In all patients with HCV in both groups, CIC, IgA, IgM, IgG were determined. Data on the average quantitative content of these immunological parameters in the blood serum of patients with chronic hepatitis C are presented in table 5.

The analysis showed that the average serum IgA, M, G in both groups does not differ significantly. At the same time, in the main group, the content of the CIC significantly exceeds this indicator in the control group (p <0.05), which may indicate the development of extrahepatic complications against the background of autoimmune processes occurring in chronic hepatitis C.

In the group of patients diagnosed with HCVaA, degree 3 of immune deficiency of the CIC prevailed (p <0.001), compared with the group without articular manifestation, in which more often the immune deficiency of the CIC was not observed (p <0.001). This is in favor of a more frequent development of autoimmune processes associated with an increase in the content of CIC, as one of the mechanisms for the development of articular manifestations in this category of patients.

In the study group of patients, we observe a weak direct correlation between the levels of the CIC and the duration of hepatitis, its activity, the duration of the articular syndrome, the severity of joint pain according to visual analogue scale treatment, and the presence of swelling in the affected joints. In the comparison group, a weak direct correlation between the serum CIC content and the duration of hepatitis was found, as well as an average direct correlation between the CIC levels and hepatitis activity (table 6).

According to the results of the study, among patients with CGE, the incidence of articular manifestation was 74.3%. At the same time, patients in the group diagnosed with HCV with articular manifestation showed a frequency of occurrence of CGE in 29 patients, in the group of HCV without articular manifestation in 10 patients, the total number of patients with CGE was 39. The duration of articular manifestation of HCV in the group of patients with CGE was more often up to 5 years, and the duration of rheumatological complaints over 10 years was less ($p < 0.05$). In 100% of the cases examined, both groups were worried about joint pain. In 79.3% (23) of patients with CGE, arthropathy proceeded as polyarthritis ($p < 0.001$), and in patients without it, in 65.2% (15) of cases, oligoarthritis of the knee or ankle joints ($p < 0.01$) was detected and polyarthritis was detected only in 34.7% (8) people. In (24), 82.7% of patients with CGE had swelling in the area of several groups of joints, including small joints of the hands and feet ($p < 0.001$), while in patients without CGE only in the knee or ankle joints, and swelling in several groups of joints revealed only in (3) 13.04% of these patients ($p < 0.001$). The presence of stiffness during movements was observed only in small joints of the hands in patients with CGE in 41.37% (12), and without it only in (2) 8.69% of cases ($p < 0.01$). The restriction of movements in several groups of joints was in 55.1% (16) of people with CGE and only in (3) 13.04% of people without it ($p < 0.001$). Joint deformities were not observed in the examined group ($p < 0.001$).

In our study, we observed that in the group with CGE, hepatitis duration up to 10 years ($p < 0.001$) was more common, and in the group without CGE, up to 5 years ($p < 0.05$). In patients with CGE, hepatomegaly according to liver ultrasound data was found in 86.2% (25), which is significantly higher compared with the group of patients without CGE in 17.4% (4) people ($p < 0.001$). According to liver elastography, the examined patients with CGE showed signs of grade 2 and 3 liver fibrosis - in 44.8% (13) and 38% (11) of patients, respectively ($p < 0.05$), relative to the indices of the group without CGE, where more often degrees 1 and 2 of fibrosis were observed - 39.1% (9) and 34.7% (8) of patients, respectively ($p < 0.05$). The highest frequency of extrahepatic manifestations was also observed in the group of patients with CGE - in 17 (58.6%) patients, and in the group without CGE only in 3 (13.04%) patients. In individuals with cryoglobulinemic syndrome in the blood, the average amount of CG was determined, the longest duration of hepatitis was observed, all of these patients had hepatomegaly according to liver ultrasound and mainly grade 3 liver fibrosis according to liver elastography ($p < 0.001$) (table 7).

Thus, in individuals with CGE, the articular manifestations of HCV proceeded mainly more severely in the form of polyarthritis with the largest number of painful and swollen joints per person, more pronounced joint pain according to visual analogue scale compared to the group without CGE.

According to ultrasound of the joints, synovitis occurred in 46 (88.4%) people ($p < 0.001$). Signs of synovitis of a minor nature were observed in 24 (52.1%) patients ($p < 0.001$); moderate in 16 (34.7%) and pronounced in 6 (13.04%).

According to the location of synovitis, the subjects were distributed as follows: 20 (43.47%) - only knee joints, 5 (10.8%) people - only ankle joints, 2 (4.3%) people - only wrist joints and 19 (41, 3%) of a person - several groups of joints, including small joints of the hands and feet.

The presence of signs of bursitis was detected in 11 (21.1%) of the examined. The main localizations of bursitis were: in 7 (63.63%) people - knee joints, in 4 (36.36%) people - ankle joints.

Joint surface erosion was found in 4 (7.7%) patients only in small joints of the hands. It is worth noting that erosion during ultrasound of the joints did not look like true erosion, but "pseudo-erosion". On radiography of joints, erosion was not detected. This is important to consider in the differential diagnosis between HCVaA and RA.

4. DISCUSSION

Hepatitis C virus (HCV) is both hepatotropic and lymphotropic, responsible for a large number of pathological conditions of the liver and extrahepatic immune system, which include the so-called HCV syndrome. The results of a large-scale study with the participation of medical workers suffering from hepatitis C showed that 74% of patients experienced some form of extrahepatic manifestations. The most commonly observed arthralgia (joint pain) - 74%; paresthesia (numbness or tingling) - 17%; myalgia (muscle pain) - 15%; prurit (intolerable itching) - 15%; Sikka's syndrome (dry mouth and eyes) - 11%. HCV-associated rheumatic diseases are characterized by frequent clinical serological overlap; therefore, proper classification of individual patients is necessary before therapeutic decisions are made. This is especially difficult to do, however, due to the coexistence of viral infection and complex autoimmune changes [18]. General clinical manifestations indicate a close association of infection and autoimmune processes. Viral arthropathy must be considered in the differential diagnosis of arthritis, therefore, patients with unspecified articular syndrome should be examined for the presence of hepatitis viruses [1]. The question of the mechanisms of arthritis in patients with chronic hepatitis C is also open. The combination of articular syndrome with chronic hepatitis C can cause additional difficulties in the diagnosis and treatment of such patients. To date, there are no clear and reasonable recommendations for the management of patients in whom arthritis is combined with HCV. Caution regarding hepatitis and knowledge of the features of their extrahepatic manifestations can improve diagnosis [7].

Given the above, the aim of this study was to study the incidence of articular syndrome in patients with HCV and to identify the features of its manifestations using clinical and paraclinical research methods.

To achieve this goal, clinical, laboratory and instrumental methods for examining patients with articular syndrome, adopted in rheumatology and hepatology, were used.

Numerous studies regarding HCV describe clinical manifestations such as arthralgia in 6.5% to 57%, myalgia in 1.3% to 61%, and arthritis in up to 5% of patients [14,16,22,23, 38.40]. In 2 - 20% of patients with chronic hepatitis C, arthritis is detected that is not associated with the presence of any disease [7]. Thus, the question of the frequency of occurrence of articular syndrome requires further study. Previous studies have shown that musculoskeletal symptoms are one of the most common extrahepatic manifestations in

patients with HCV [18,25,38], while the incidence of associated arthritis in patients with HCV was 19.2%, in the group with CGE 74.3%.

According to the literature, the clinical spectrum of arthritis associated with CVHC varies from non-erosive oligoarthritis of large and medium joints to polyarthritis resembling RA [1,7]. Based on the clinical data we obtained, it was found that patients with chronic hepatitis C, having articular syndrome, complained of joint pain in 92.3% of cases, less often swelling in the affected joints - 55.7% of people, and limited movement in the joints - 38.4% of people, 32.7% of people for stiffness during movements, 7.7% of people for joint deformation. Joint pains were more often intermittent in nature, were symmetrical and intensified with an increase in the activity of the underlying disease. In both groups, stiffness was observed symmetrically, mainly in the small joints of the hands. At the same time, the duration of stiffness was in the range of 10 to 20 minutes. In most cases, the swelling in the area of the affected joints was symmetrical. In individuals with this symptom in the area of several groups of joints, it was mainly observed in the small joints of the hands and feet. In 55.7% of patients with chronic hepatitis C, articular syndrome occurred in the form of polyarthritis, 32.7% of patients had oligoarthritis of the knee joints, and 9.6% of people had oligoarthritis of the ankle joints according to joint ultrasound.

It was noted that in the subjects of the study groups there was a correlation between the severity of pain according to visual analogue scale, the duration of the articular syndrome and the activity of hepatitis, while the pain was stronger in patients with a longer course of hepatitis.

For the purpose of differential diagnosis between RA and articular syndrome on the background of chronic hepatitis C, having a rheumatoid-like course, the data of instrumental examination methods (radiography and ultrasound of the joints) were also used. As a rule, in patients with rheumatoid-like course of the articular syndrome, no inflammatory changes were observed in the KLA, RF and C-RB were not always positive, the analysis for the presence of ACCP was negative, erosive processes in the joints, if any, were of the nature of “pseudo-erosion” by ultrasound of the joints.

Based on the results of biochemical studies, a relationship was established between the duration of hepatitis disease, its activity, the severity of liver fibrosis according to elastography and changes in the levels of the main biochemical parameters. At the same time, the longer the hepatitis proceeds and the more actively, and also the liver fibrosis was more pronounced, the higher the levels of bilirubin, AlAT, AsAT, thymol test, joint pain in visual analogue scale joints is more significant. The latter, in turn, correlates with thymol test values.

An analysis of the immunological data of our study allows us to conclude that the more pronounced the activity of hepatitis, the more often a swelling is detected in the area of affected joints, as indicated by a weak direct correlation between the degree of hepatitis activity in the main group and the presence of swelling in the joints.

It has been noted that the development of arthritis can presumably be mediated by immune complexes [7]. The higher the levels of CIC, the stronger the severity of joint pain according to visual analogue scale and more often the presence of swelling in the affected joints was observed, this follows from the presence of a weak correlation between these indicators.

At present, the relationship of HCV with the development of mixed cryoglobulinemia is not in doubt and is confirmed by the high detection rate of cryoglobulins in patients with CHC [3], which varies widely - from 19 to 71% [17–26], averaging, according to Z. Kayali et al. [27] A meta-analysis of 19 studies, 44%. The results obtained in this study are confirmed by data from other studies. The incidence of CGE in the group with articular syndrome was 55.7%, in the comparison group - 27.7%. The duration of hepatitis up to 5 years was more common in the group without CGE, and more than 6 years in the group with CGE. In patients with CGE, hepatomegaly according to liver ultrasound data was found in 86.2% of people, which is significantly more than 17.4% in comparison with the group of patients without CGE. According to liver elastography, the examined patients with CGE had signs of liver fibrosis of the 2nd and 3rd degrees, relative to the indices of the group without CGE, where degrees 1 and 2 of fibrosis were more often observed. The highest frequency of extrahepatic manifestations was also observed in the group of patients with CGE according to liver ultrasound and mainly grade 3 liver fibrosis according to liver elastography. Thus, the obtained data testify in favor of a more severe course of CVHC in patients with the presence of CGE.

The duration of articular syndrome in the group of patients without CGE was more often than in the group with CGE, up to 5 years, and the duration of articular syndrome over 10 years did not occur at all. In 100% of cases, the subjects with CGE and without it were worried about pain in the joints. In 79.3% of patients with CGE, the joint syndrome proceeded in the form of polyarthritis, while in patients without it, in 65.2% of cases, oligoarthritis of the knee or ankle joints was detected, and polyarthritis was detected only in 34.7% of people. The presence of stiffness during movements was observed only in small joints of the hands in patients with CGE in 41.37% of cases.

Thus, in individuals with CGE, the joint syndrome was generally more severe, in the form of polyarthritis with the largest number of painful and swollen joints per person, more pronounced joint pain according to visual analogue scale compared to the group without CGE. This is confirmed by published data, which indicate the presence of symmetric polyarthritis involving the ankle, wrist joints, and small joints of the hands and feet in patients with CGE [6].

In patients with a CGE of the main study group, signs of cholestasis and cytolysis were more pronounced, as indicated by higher levels of relevant biochemical parameters. Thus, it can be noted that against the background of more pronounced changes in hepatic functions that occur with hepatitis, the appearance of CG is noted, although some authors argue that CGE itself may aggravate the course of HCV. There is still no clear data on this issue in the literature.

In the scientific literature there is practically no information about changes in the joints in patients with chronic hepatitis C established by ultrasound. However, it has been noted that arthritis associated with HCV is often accompanied by signs of synovitis [7].

According to the ultrasound of the joints, synovitis occurred in 88.4% of people. Signs of synovitis of an insignificant nature were in 52.1% of people; moderate in nature - 34.7% and pronounced in 13.4% of people. Signs of periarthritis were observed in 21.1% of people. Periarthritis proceeded in the form of tendonitis, ligamentitis and bursitis. Erosion of the articular surfaces was found in 7.7% of people only in small joints of the hands. It is worth noting that erosion during ultrasound of the joints did not look like true erosion, but

"pseudo-erosion". On radiography of the joints, usations were not identified. This is important to take into account in the differential diagnosis between articular syndrome on the background of CVHC and RA.

5. CONCLUSION

In conclusion, it should be noted that the incidence of articular manifestations in patients with chronic viral hepatitis C is 19.2%. In patients with cryoglobulinemia, articular manifestations of HCV are 74.3%. HCVaA is intermittent in nature, proceeds in the form of oligoarthritis mainly of the knee joints or symmetrical polyarthritis involving small joints of the hands and feet. In the presence of cryoglobulinemia, the joint syndrome proceeds mainly in the form of polyarthritis with more pronounced changes in the joints and periarticular tissues according to the ultrasound examination of the joints. In addition, there is a reliable direct relationship between the severity of the articular syndrome in patients with chronic viral hepatitis C, its duration, the duration of hepatitis, the degree of its activity, the high level of circulating immune complexes, the degree of synovitis and the presence of periarthritis according to the ultrasound examination of the joints.

Based on the foregoing, we can say that our study will be useful in the management of patients with HCVaA, monitoring the course of the disease and their diagnosis.

Table 1

Clinical characteristics of patients with a diagnosis of HCVaA

№	Indicators	Number of patients	
		n	%
1	Total number of patients	52	100
2	Duration of hepatitis from the moment of diagnosis:		
	up to 5 years	14	26,9
	6-10 years	30	57,7
	more than 10 years	8	15,4
3	The degree of hepatitis activity:		
	Minimal	38	73,1
	Mild	10	19,2
	Moderate	4	7,7
4	Duration of arthralgia:		
	up to 5 years	10	19,2
	6-10 years	35	67,3
	more than 10 years	7	13,5

5	Joint pain	48	92,3
6	The presence of swelling in the affected joints	29	55,7
7	Stiff joints	17	32,7
8	The presence of restriction of movement in the joints	20	38,4
9	Assessment of the severity of pain on a Visual Analogue Scale (M ± a) before treatment (cm)	6,78±1,42	-

Table 2

Data collected in a standardized questionnaire form

52 patients with HCVrA		
Standardized questionnaire		
Sociological and demographic data	**Clinical data**	Laboratory and imaging data
Identification	Rheumatic complains, which kind of them, how long conspicuous (not less than 3 months) and what joints?	**Serological profile:** HCV RNA by PCR, anti HCV +; spectrum of immunoglobulins
Gender	Arthralgia VAS?	**General:** general blood analysis, general urine analysis, biochemical blood analysis, rheumatoid factors, CRP
Age	Joint swelling?	Screening for some specific diseases: Anti CCP, X-ray, joints and liver ultrasonography, liver elastography et sit.
Educational level	Arthritis?	
	Or others…	

Table 3

Clinical characteristics of patients

Group of examined	**Number of patients**		**Sex**			
			M		F	
	n	%	n	%	N	%
Main group – HCVaA	50	100	30	57,7	22	42,3

Comparison Group - HCV Without Arthritis	36	100	22	61,1	14	38,9

Table 4

The main correlation between the biochemical parameters of the main group of patients with chronic hepatitis C and the duration of hepatitis, hepatitis activity, severity of joint pain according to the Visual Analogue Scale, degree of liver fibrosis ($p < 0.05$)

Indicator	Total bilirubin	AlAT	AsAT	Albumin	Thymol test
Hepatitis Disease	0,378*	0,678**	0,663**	-0,445*	0,451*
The degree of hepatitis activity	0,612**	0,971***	0,891***	-0,617**	0,782***
Severity of pain according to the Vizual Analogue Scale before treatment	0,488*	0,583**	0,627**	-0,364*	0,508*
The severity of liver fibrosis	0,491*	0,571**	0,598**	-0,523**	0,341*

* -weak correlation dependence

** - average correlation dependence

*** - strong correlation

Table 5

The average content (M ± a) of CIC and IgA, IgM, IgG in the blood serum of patients of the main group and the comparison group

Groups	CIC	IgA (g / l)	IgM (g / l)	IgG (г/л)
HCVaA (N = 52)	228,72±148,24	2,56±1,26	2,52±0,74	17,01±5,48
HCV without articular manifestation (N = 36)	148,80±99,59	2,24±1,64	2,38±0,88	15,12±5,92
P	<0,05	Нд	Нд	нд
Normal	До 80	1,5-2,5	1,1-1,9	10-20

Table 6

Indicators of the correlation between the content of CIC in serum and some indicators for the main group and the control group

Main characteristics	Main group (N = 52)	Comparison Group (N = 36)
Hepatitis Duration	0,372*	0,382*
Hepatitis activity	0,441*	0,610**
Hepatitis activity	0,338*	
The severity of joint pain according to visual analogue scale pre-treatment	0,321*	
The presence of swelling in the affected joints	0,368*	

p <0.05 * -weak correlation dependence
** - average correlation dependence

Table 7

Joint manifestations in patients with chronic hepatitis C of the main group, depending on the presence or absence of CGE

	Signs of articular manifestation of HCV	P	HCV with CGE (N = 29)		HCV without CGE (N = 23)	
			n	%	n	%
1	Main complaints					
	Arthralgia	-	29	100	10	43,4
	Swelling	<0,001	24	82,7	3	13,4
	Stiffness	<0,01	12	41,37	2	8,69
	Motion restriction	<0,001	16	55,1	3	13,4
2	Nature of the course of arthropathy					
	Polyarthritis	<0,001	23	79,3	8	34,7
	Oligoarthritis	<0,01			15	65,2

3	Assessment of the severity of joint pain on a visual analogue scale before treatment (cm) (M ± o) overall rate	<0,001 <0,001 <0,01	6,06± 1,04/ 5,86± 0,91/ 6,44± 1,23		5,10± 1,07/ 5,06± 1,06/ 5,50± 0,89	
4	Joint deformities	<0,001	2	6,9	0	0

6. REFERENCES

[1] Ananyeva L.P. Chronic erosive seropositive arthritis in a patient with chronic viral hepatitis C / L.P. Ananyeva, T.M. Ignatova, A.B. Smirnov // Scientific and Practical Rheumatology.-2008. -№1.-S.78-84.

[2] Belov BS, Lopatkina TN, Nasonov EL. Rheumatoid arthritis and chronic viral hepatitis: problems and prospects. Russian medical journal. 2012; 30: 1493-8.

[3] Dunaeva N.V. Cryoglobulinemia and hepatitis C virus / N.V. Dunaeva E.V. - Esaulenko // Journal of Infectology.-2011.-T. 3.- No. 2.-S. 15-20.

[4] Ivashkin V.T. Pathogenetic and clinical rationale for the use of ademetionine in the treatment of patients with intrahepatic cholestasis / V.T. Ivashkin, A.O. Buyev // Health of Ukraine.-2010.- No. 2.-C.

[5] Ivashkin V.T., Yushchuk N.D., Mayevskaya M.V. Recommendations for the diagnosis and treatment of adult patients with hepatitis C. Russian Journal of Gastroenterology, Hepatology and Coloproctology 2013; 2: 41–70.

[6] Malyshko E.Yu. Cryoglobulinemia associated with HCV infection / E.Yu. Baby, H.A. Konstantinova, E.H. Semenova // Clinical Medicine.-2001.-No. 1.-S.9-12.

[7] Olyunin Yu.A. Chronic arthritis in patients infected with hepatitis B and C viruses / Yu.A. Olyunin // Scientific and Practical Rheumatology. -2008.-№5.-C.39-44.

[8] Agnello V., Chung R.T., and Kaplan L.M .: A role of hepatitis C virus infection in type II cryoglobulinemia. N Engl J Med 1992; 327: pp. 1490-1495

[9] Antonelli A., Ferri C., Galeazzi M., Giannitti C., Manno D., Mieli-Vergani G., et al: HCV infection: pathogenesis, clinical manifestations and therapy. Clin Exp Rheumatol 2008; 26: pp. S39-S47

[10] Buskila D., Shnaider A., Neumann L., Lorber M., Ziberman D., Hilzenrat N., et al: Musculoskeletal manifestations and autoantibody profile in 90 hepatitis C virus infected Israeli patients. Semin Arthritis Rheum 1998; 28: pp. 107-113

[11] Cacoub P., Poynard T., Ghillani P., Charlotte F., Olivi M., Piette J.C., et al: Extrahepatic manifestations of chronic hepatitis C. Arthritis Rheum 1999; 42: pp. 2204-2212

[12] Cansu D.U., Kalifoglu T., Korkmaz C. Short-term course of chronic hepatitis B and C under treatment with etanercept associated with different disease-modifying antirheumatic drugs without antiviral prophylaxis. J Rheumatol. 2008; 35: 421-4.

[13] Cimmino M.A., Picciotto A., Sinelli N., Brizzolara R., and Accardo S .: Has hepatitis C virus a specific tropism for the synovial membrane? Br J Rheumatol 1997; 36: pp. 505-506

[14] Cheng Z, Zhou B, Shi X, Zhang Y, Zhang L, Chen L, etc. Extrahepatic manifestations of chronic hepatitis C virus infection: 297 cases from the tertiary medical center in Beijing, China. Chin Med J (English). 2014; 127 (7): 1206-10. [Links]

[15] D'Amico E., Palazzi C., Fratelli V., Di Matteo L., Di Girolamo G., and Consoli G.: High prevalence of HCV infection in patients with rheumatoid arthritis. J Clin Rheumatol 1996; 2: pp. 234-235

[16] El GARF A., El Zorkani B., Gate R., Sheba V. H., Moneim G. A., El Garfet K. Prevalence and clinical manifestations of hepatitis C virus among patients admitted to the rheumatology Department. Rheumatol Int. 2012; 32 (9): 2691-5. [Links]

[17] Fadda P., La Civita L., Zignego A. L., and Ferri C .: Epatite C e artrite. Studio clinico-sierologico dell'artrite in pazienti con e senza sindrome crioglobulinemica. Reumatismo 2002; 54: pp. 316-323

[18] Ferri C.A., Ramos-Casals M., Zinego A.L., Arkaini L., Roccatello D., Antonelli A., etc. International diagnostic guidelines for patients with extrahepatic manifestations associated with HCV. Interdisciplinary expert opinion. Autoimmun Rev. 2016; 15 (12): 1145-60. [Links]

[19] Iagnocco A., Coari G., Mammarella A., Basili S., Donnarumma L., Valesini G., et al: Joint sonography in asymptomatic patients with HCV correlated hepatitis. Clin Exp Rheumatol 2004; 22: pp. 43-48

[20] Loguercio C., Andreone P., Brisc C. et al. Silybin combined with phosphatidylcholine and vitamin E in patients with nonalcoholic fatty liver disease: a randomized controlled trial // Free Radical Biology & Medicine. 2012. Vol. 52, no. P. 1658-1665.

[21] Lovy M.R., Starkebaum G., and Uberoi S .: Hepatitis C infection presenting with rheumatic manifestations: a mimic of rheumatoid arthritis. J Rheumatol 1996; 23: pp. 979-983View article

[22] Mazzaro C, Dal Maso L, Urraro T, Mauro E, Castelnovo L, Casarin P, et al. Cryoglobulinemic vasculitis associated with hepatitis b virus: a multicenter open - label study conducted by Gruppo Italiano di Studio delle Crioglobulininie-GISC. Dig the liver dis. 2016; 48 (7): 780-4. [Links]

[23] Mohammed R. H., El Mahzangi H. I., Gamal A., Mekki F., El Qassas M., Mohammed N. et al. The prevalence of rheumatological manifestations of chronic hepatitis C virus infection among Egyptians. Wedge Rheumatol. 2010; 29 (12): 1373-80. [Links]

[24] Olivieri I., Palazzi C., and Padula A .: Hepatitis C virus infection and arthritis. Rheum Dis Clin North Am 2003; 29: pp. 111-122

[25] Palazzi C, D'Amico E, D'Angelo S, Gilio M, Olivieri I. Rheumatic manifestations of chronic hepatitis C virus infection: indications for correct diagnosis. World J Of Gastroenterology. 2016; 22 (4): 1405-10. [Links]

[26] Palazzi C., Olivieri I., D'Amico E., Cacciatore P., and Pennese E .: Difficulties in the differential diagnosis between primitive rheumatic diseases and hepatitis C virus-related disorders. Clin Exp Rheumatol 2005; 23: pp. 2-6View article

[27] Palazzi Carlo, Salvatore D'Angelo and Ignazio Olivieri .: Hepatitis C virus-related arthritis. Autoimmunity Reviews, 2008-10-01, Volume 8, Issue 1, Pages 48-51, Copyright © 2008 Elsevier B.V.

[28] Parola M, Pinzani M. Liver fibrosis: Pathophysiology, pathogenetic targets and clinical issues. Mol. Aspects Med. 2019; 65: 37-55. doi: 10.1016 / j.mam.2018.09.09.002.

[29] Poynard, T. Noninvasive Markers of Hepatic Fibrosis in Chronic Hepatitis B / T. Poynard, Y. Ngo, M. Munteanu, D. Thabut, V. Ratziu // Curr. Hepat. Rep. - 2011.– V. 10. - No. 2. - P. 87-97.

[30] Ramos-Casillas M., Fonda J., Ingelmo M. Prevalence and clinical significance of hepatitis C virus infection in systemic autoimmune diseases. Med Clin (Bark) 2001 may 19; 116 (18): 701-709.

[31] Rino Y, Yukawa N, Yamamoto N. Does herbal medicine reduce the risk of hepatocellular carcinoma? // World J Gastroenterol. 2015. Vol. 21, No. 37. P. 10598-10603.

[32] Rivera J., García-Monforte A., Pineda A., and Millan Nuñez-Cortes J .: Arthritis in patients with chronic hepatitis C virus infection. J Rheumatol 1999; 26: pp. 420-424

[33] Rosner I., Rozenbaum M., Toubi E., Kessel A., Naschitz J.E., and Zuckerman E .: The case for hepatitis C arthritis. Semin Arthritis Rheum 2004; 33: pp. 375-387

[34] Sansonno D., Carbone A., De Re V., and Dammacco F .: Hepatitis C virus infection, cryoglobulinaemia, and beyond. Rheumatology (Oxford) 2007; 46: pp. 572-578

[35] Sansonno D., Lauletta G., Montrone M., Tucci F.A., Nisi L., and Dammacco F .: Virological analysis and phenotypic characterization of peripheral blood lymphocytes of hepatitis C virus-infected patients with and without mixed cryoglobulinemia. Clin Exp Immunol 2006; 143: pp. 288-296

[36] Sarvazyan, A. P. Quantitative elastography of liver fibrosis and spleen stiffness in chronic hepatitis B carriers: comparison of shear-wave elastography and transient elastography with liver biopsy correlation / A.P. Sarvazyan, O.V. Rudenko, S.D. Swanson, J.B. Fowlkes, S.Y. Emelianov // Radiology. - 2013. - V.– No. 3. - P. 910-918.

[37] Shouval D, Shibolet O. Immunosuppression and HBV reactivation. Semin Liver Dis. 2013 May; 33 (2): 167-77. doi: 10.1055 / s-0033-1345722. Epub 2013 Jun 8.

[38] Tengan F. M., Levi-Neto M., Miziara I. D., Dantas B. P., Maranyo L. Extrahepatic manifestations of chronic hepatitis C infection: a sequential study in Brazilian patients. Braz J Infect. 2017; 21 (2): 209-10. [Links]

[39] Tianhui, L. Molecular Serum Markers of Liver Fibrosis / L. Tianhui, Xiaoming Wang, M.A. Karsdal, D.J. Leeming // Presse Med. 2012. - No. 7. - P. 105-117.

[40] Tinsley M., Meriem G., Aykac A., Sur K. Hepatitis C virus infection among patients admitted to the rheumatology Department in Northern Cyprus. The Egyptian rheumatologist. 2017; 39 (4): 245-7. [Links]

[41] Ueno Y., Kinoshita R., Kishimoto I., and Okamoto S .: Polyarthritis associated with hepatitis C virus infection. Br J Rheumatol 1994; 33: pp. 289-291

[42] Vassilopoulos D, Calabrese LH. Management of rheumatic disease with comorbid HBV or HCV infection. Nat Rev Rheumatol. 2012; 8: 348-57. doi: 10.1038 / nrrheum.2012.63

[43] Weber S.N. Liver fibrosis: from animal models to mapping of human risk variants / S.N. Weber, H.E. Wasmuth // Best Pract Res Clin Gastroenterol.- 2010.- Vol. 24, No. 5.- P.635-646.

[44] Yang, J. D. Hepatocellular carcinoma: a global view / J. D. Yang, L. R. Roberts // Nat. Rev. Gastroenterol. Hepatol. - 2010. - V. 7. - P. 448.

[45] Zheng, Z. Exposure to fine airborne particulate matters induces hepatic fibrosis in murine models / Z. Zheng, X. Zhang, J. Wang, A. Dandekar, H. Kim, Y. Qiu, X. Xu, Y. Cui , A. Wang, LC Chen, S. Rajagpalan, Q. Sun, K. Zhang // Journal of Hepatology. - 2015. - V. 63. - No. 6. - P. 1397-1404

[46] Zuckerman E., Keren D., Rozembaum M., Toubi E., Slobodin G., Tamir A., et al: Hepatitis C virus related arthritis: characteristics and response to therapy with interferon alpha. Clin Exp Rheumatol 2000; 18: pp. 579-584