

Extrahepatic Manifestations Of Chronic Viral Hepatitis C (Literature Review)

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Abstract: This article summarizes the material of recent studies of extrahepatic manifestations of chronic viral hepatitis C.

Keywords: chronic viral hepatitis C, extrahepatic manifestations

The highest incidence of chronic viral hepatitis C (CVHC) worldwide, including in developed countries, is noted among people of working age [16]. Insufficient effectiveness of therapeutic measures, high-cost drug provision, progression of pathological changes with an outcome in cirrhosis and liver cancer, as well as the development of extrahepatic lesions of various organs and systems determine the urgency of this problem [13, 45].

Currently, there are more than 70 million patients with CVHC in the world, or 23.7 cases per 100,000 people [52], the expert council of Russia pointed out the presence of 4.5 million patients [13, 27].

In the majority of infected individuals, the hepatitis C virus (HCV) persists for a long time in the body, ensuring the chronicity of the disease [44,50], while the clinical manifestations of this pathology

are not observed for a long time or have poor symptoms. According to C.W.Spearman (2019), only 20% of patients with hepatitis C who applied for treatment knew about their diagnosis [52].

Numerous studies indicate that more than 70% of cases of hepatitis C virus contributes to the development of extrahepatic pathology [21]. It is also noted that extrahepatic manifestations of CVHC are associated with the structural features of the virus [35, 51]. The damage to organs and tissues in chronic hepatitis C is possibly caused by immunological reactions due to the direct effect of the virus on immunocompetent cells [16]. The HCV virus triggers the mechanisms of damage to organs and systems, as a result, the clinical picture of chronic viral hepatitis is often accompanied by pathological manifestations. The study of S.I. Semenov (2017) showed that extrahepatic manifestations of chronic hepatitis C were found in 35% of cases, and the most common were articular syndrome, polyarteritis nodosa and kidney damage [21]. The works of E.N. Usolkina (2018) showed that 45% of patients with CVHC have chronic cholecystopancreatitis, 31% of them have diabetes mellitus, 12% have obesity, 56% have arterial hypertension, 34% have pyelonephritis [25]. The study of Kryukova E.V. et al. (2017) analyzed the extrahepatic manifestations of CVHC over the past 10 years, which occurred in 75% of patients: hematological, autoimmune, dermatological, rheumatological, nephrological and peripheral neuropathies [12].

The presence of concomitant diseases in chronic hepatitis C contributes to the further progression of the disease, especially in metabolic syndrome — clinical deterioration was observed in 59% of patients [30].

M. Ramos-Casals et al. (2017) proposed to divide extrahepatic manifestations into autoimmune, inflammatory, metabolic and neoplastic ones [51].

The studies of M.Yu. Marzhokhova (2019), as well as A.M. Ashura (2019), described cases of the development of psoriasis and dermatosis in CVHC [2,15].

The presence of a chronic viral infection of hepatitis C disrupts the functional activity of the pancreas and digestive glands of the stomach [8].

The study by K.V. Zhdanov (2019) proved that chronic hepatitis C causes a violation of the permeability of the intestinal barrier [7].

Authors working in the field of hepatology indicate that the most common manifestations of extrahepatic lesion in chronic hepatitis C are cryoglobulinemia — 37%, cryoglobulinemic vasculitis — 10%, as well as β -cell non-Hodgkin's lymphoma, Melzer's triad (arthralgia, progressive weakness and cutaneous purpura), autoimmune thyroiditis [6, 32]. It has been proven that CVHC increases the risk of developing chronic kidney disease, including cryoglobulinemic glomerulonephritis [10, 22, 48, 52]. In turn, the presence of glomerulonephritis causes a limitation in the use of drugs in the treatment of CVHC [37]. Cryoglobulinemia aggravates the extrahepatic manifestation of CVHC, such as varicose veins of the esophagus with the development of esophageal bleeding [30].

M.A. Nikonorova (2018) found that HCV can be an independent risk factor for thyroid diseases and a trigger in the development of autoimmune thyroiditis [17].

The studies of T.A. Perepletina (2018) noted that CVHC contributes to the development of hyperplastic processes in the endometrium in women of reproductive age and is often accompanied by sexual dysfunction [19].

The development of hepatic encephalopathy with signs of psychological maladjustment against the background of CVHC has been established [55]. The works of E.V. Radaeva (2018) found that with chronic hepatitis C, more than half of the patients had anxiety-depressive disorders [23]. Also, with chronic hepatitis C, cognitive impairments are observed, caused not only by metabolic changes in the liver, but also by the direct effect of hepatitis viruses on the nervous tissue. In patients with CVHC, increased neurotization and depression are observed, more pronounced in people over 40 years old, especially during treatment with antiviral drugs [20]. Other authors also point to an increased level of depression in patients with CVHC [35, 40, 41].

When assessing the quality of life of patients with chronic hepatitis C according to Russian [1] and foreign [38,39] studies, pronounced negative changes affecting the state of mental health were observed. The study of V.V. Ogarev (2017) showed that with chronic hepatitis C, stigmatization, stress, high levels of anxiety and depression, decreased motivation and compliance are noted [18].

In patients with chronic hepatitis C, pronounced asthenization according to the "Asthenic syndrome scale", a decrease in the level of Well-being and Activity according to the "SAN" test was proved; according to MMPI, in the structure of personality disorders, astheno-vegetative syndrome prevailed in 56% of individuals, asthenic syndrome —in 34.5% and astheno-depressive syndrome— in 9.5% [3].

The study of the structural and functional state of the heart in patients with CVHC showed that 45% of them had cardiac arrhythmias. It is noted that the progression of liver fibrosis aggravates endothelial dysfunction, microcirculation disorders and vascular-platelet hemostasis [23]. Multidirectional changes in hematological parameters were established during the progression of chronic hepatitis C, the work of GaleevaN.V. and Kravchenko I.E. (2018) showed disorders of platelet and coagulation hemostasis. [4]. The close relationship of the effect of the CVHC virus on the development of vascular atherosclerosis was shown in the study by S. Petta et al. (2018), where, against the background of antiviral therapy, a decrease in carotid atherosclerosis with the elimination of the virus was noted [49].

In patients with CVHC, a high degree of comorbidity is often observed. Thus, in 60% of cases the pathology of the bronchopulmonary system is revealed, in 42% —the pathology of the digestive system, in 31% —the pathology of the cardiovascular system [11].

Also, with chronic hepatitis C, pathological changes on the part of the visual analyzer are observed — lacrimal dysfunction syndrome (corneal-conjunctival xerosis or dry eye syndrome) [28].

The studies of M.K. Mamedov (2019) showed that in patients with chronic hepatitis C, an increased risk of developing oncopathology of various organs and systems was revealed [14]. Cases of the development of inflammatory myopathy in chronic hepatitis C have been described, which did not stop during the course of antiviral therapy with pegylated interferon alpha-2 and ribavirin [6].

A review of the scientific literature on the issues of extrahepatic manifestations of chronic viral hepatitis C indicates the urgency of the problem of early detection of this pathology and the need for its further study in order to develop new medical technologies and improve pathogenetic therapy.

References

1. Anisimova T.A., Akimova V.P. Chronic Viral Liver Disease and the Quality of Life of Patients.Fundamental'nyye Aspekty Psikhicheskogo Zdorov'ya — Fundamental Aspects of Mental Health, 2018, no. 2,pp.26-29.

2. Ashur Ahmad Mahmoud Hussein. The Level of Malondialdehyde in the Blood of Patients with Psoriasis, Depending on the Presence of Concomitant Viral Liver Damage.ZhurnalInfektologii — JournalofInfectology, no. 1 (11), 2019, pp. 23-24.

3. Bokhan N.A., Prilensky B.Yu., Bukhna A.G., et al. Laboratory-Functional Indicators and Mental Disorders in the Clinical Picture of Patients with Non-Alcoholic Fatty Liver Disease and Chronic Viral Hepatitis C.Meditsinskaya Nauka i Obrazovaniye Urala — Medical Science and Education of the Urals,no. 2 (90), 2017,pp.12-18.

4. Galeeva N.I., Kravchenko I.E. Indicators of Hemostasis in Patients with Chronic Hepatitis C.Epidemiologiya i Infektsionnyye Bolezni —Epidemiology and infectious diseases, no. 6 (23), 2018, pp.279-285.

 Dunaeva N.V. Therapy with Drugs of Direct Antiviral Action of Chronic Hepatitis C Complicated by the Development of Mixed Cryoglobulinemia.Infektologiya — Infectology, no. 4 (10), 2018, pp. 53-63.
DunaevaN.V., GezeiM.A. InflammatoryMyopathywithAutoantibodiestoSignal-RecognizingParticlesinaPatientwithChronicHepatitisC. InfektsionnyyeBolezni — Infectiousdiseases, 2018, no. 16 (2), pp. 109-115.

7. Zhdanov K.V., Semenov A.V., Karjakin S.S., et al. S MadCAM-1 as an Immunological Marker in the "Intestine-Liver"System in Patients with Chronic Hepatitis C and Overweight.Zhurnal Infektologii — Journal of Infectology,vol. 11, no. 2, 2019, pp. 63-70.

8. Zhuraeva M.A., Aleinik V.A. Features of Incretion of Digestive Hydrolases of the Stomach and Pancreas in Chronic Viral Hepatitis C.Molodoy Uchenyy — Young Scientist, no. 25 (211), 2018, pp.175-178.

9. Zaitseva A.A., Chebykina N.S. Chronic Viral Hepatitis B and C as a Cause of Thyroid Damage.Studencheskiy Zhurnal — Student Journal,no. 12-1 (56),pp.31-35.

10. Zubkin M.L., Semenenko T.A., Selkova E.P., et al. Chronic HCV Infection and Kidney Pathology. InfektsionnyyeBolezni — Infectiousdiseases, 2017, no. 15 (4), pp. 68-76.

11. Konyshko N.A., Andreeva O.V. Comorbid Status of Patients with Chronic Viral Hepatitis C. Vestnik Sovremennykh Issledovaniy — Bulletin of Modern Research, no. 5.3 (20), 2018, pp. 58-59.

12. Kryukov E.V., Pop V.P., Rukavitsyn O.A., et al. Influence of Hepatitis Viruses on Lymphoid Tissue and Modern Treatment Options for Virus-Associated Lymphomas.Infektsionnyye Bolezni: Novosti, Mneniya, Obucheniye — Infectious Diseases: News, Opinions, Education, 2017, no. 6, pp. 53-61.

13. Mamedov M.K. On the Spread of Viral Hepatitis in Azerbaijan.Infektsionnyye Bolezni: Novosti, Mneniya, Obucheniye — Infectious Diseases: News, Opinions, Education,2019,no. 1 (8),pp.23-27.

14. Mamedov M.K., Mikhailov M.I. Assessment of Oncological Aspects in the Study of Viral Hepatitis.Infektsionnyye Bolezni: Novosti, Mneniya, Obucheniye — Infectious Diseases: News, Opinions, Education, no. 2 (8), 2019, pp.59-63.

15. Marzhokhova M.Yu. State of Cytokine Balance in Patients with Recurrent Psoriasis Against the Background of Chronic Viral Hepatitis C. The Combination of CHC and Psoriasis Causes an Increase in Pro-Inflammatory and Anti-Inflammatory Blood Cytokines. InfektsionnyyeBolezni — Infectious diseases, no. 2, 2019, pp. 25-31.

16. Mikhailov M.I. Draft Program for the Control and Elimination of Viral Hepatitis as a Public Health Problem in the Russian Federation.Infektsionnyye Bolezni: Novosti, Mneniya, Obucheniye — Infectious Diseases: News, Opinions, Education,2018, vol. 7, no. 2,pp. 52-58.

17. Nikonorova M.A. Autoimmune Thyroiditis in Patients with Chronic Hepatitis C. Byulleten' Meditsinskoy Nauki — Bulletin of Medical Science, no. 3 (11), 2018, pp.72-76.

18. Ogarev V.V. Factors of Motivation for the Treatment of Patients with Chronic Viral Hepatitis C.Sibirskiy Vestnik Psikhiatrii i Narkologii —Siberian Bulletin of Psychiatry and Narcology, 2017, no. 2 (95),pp. 121-126.

19. Perepletina T.A. Clinical and Pathogenetic Significance of Chronic Hepatitis C in the Development of Endometrial Hyperplastic Processes:Thesis Abstractof Candidate of Medical Sciences, 2018, 24p.

20. Plokhotyuk E.N., Sysoev V.N. Dynamics of Indicators of the Functional State of the Body of Patients with Chronic Hepatitis C Receiving Antiviral Therapy Depending on the Age of the Patients.Vestnik Rossiyskoy Voyenno-Meditsinskoy Akademii — Bulletin of the Russian Military Medical Academy, no. 4 (60), 2017, pp.63-66.

21. Semenov S.I., Maksimova S.S. Diversity and Frequency of Extrahepatic Manifestations in Viral Hepatitis B, C.Zhurnal Infektologii — Journal of Infectology,no. 3 (9), 2017,pp.49-50.

22. Sokolova M.V, Starostina E.E., Krasnova T.N., et al. Influence of Allelic Variants of Genes of Endothelial Dysfunction and the Blood Coagulation System on the Clinical Manifestations of Cryoglobulinemia Associated with the Hepatitis C Virus. Rossiyskiy Zhurnal Gastroenterologii,

Gepatologii, Koloproktologii — Russian Journal of Gastroenterology, Hepatology, coloproctology, 2018, no. 28 (1), pp. 33-40.

23. Radaeva E.V. Clinical and Pathogenetic Patterns of Damage to the Cardiovascular System in Chronic Viral Hepatitis:Thesis Abstractof Doctor of Medical Sciences, Chita, 2018, 46p.

24. Ulyukin I.M., Orlova E.S. Medicinal Correction of Cognitive Impairments in Patients with Chronic Viral Hepatitis. Materials of the All-Russian Congress Botkin Readings, ed. Mazurova V.I., Trofimova E.A., 2018, pp. 395-396.

25. Usolkina E.N., Krasnova E.I., Krasilnikova I.V., et al. Clinical and Epidemiological Characteristics of the Course of Liver Cirrhosis in the Outcome of Chronic Hepatitis B and C in the Novosibirsk Region.ZhurnalInfektologii—JournalofInfectology,no. 2 (10), 2018, p. 106.

26. Khasanova G.M., Khasanova A.N. Anemia in Patients with Chronic Viral Hepatitis. Materials of the XI Annual All-Russian Congress on Infectious Diseases, 2019, p.216.

27. Khokhlova Z.A., Nikolaeva N.A., Gileva R.A. et al. Epidemiological Characteristics of Hepatitis A, B and C in a Large Industrial City of Western Siberia.Epidemiologiya i Infektsionnyye Bolezni. Aktual'nyye Voprosy — Epidemiology and Infectious Diseases. Topical Issues, 2018, no. 2. pp. 4-10.

28. Chernakova G.M., Klescheva E.A., Khatsukova B.N., et al. Chronic Hepatitis C and Eye Pathology: The State of the Problem.Epidemiologiya i Infektsionnyye Bolezni. Aktual'nyye Voprosy — Epidemiology and Infectious Diseases. TopicalIssues,2017, no. 2,pp. 39-43.

29. YurkevichI.V., AniskoL.A., KarpovI.A., etal. The Role of Hematological Parameters as Potential Predictors of Liver Fibrosis and Hepatocellular Carcinoma in Patients with HCV Infection.Collection of Materials of the Conference "Innovations in Medicine and Pharmacy-2018", Minsk, 2018, pp.519-524.

30. AbbasO.M., KhalifaK.A.E., MakhloufM.M., etal. Influence of Esophageal Variceal Bleeding on Iron Status in Chronic Hepatitis C patients.Eur J Gastroenterol Hepatol, 2019 Sep 16. doi: 10.1097/MEG.000000000001547.

31. Al-Mahmood A., Al-Jubori A. The Prevalence of Hepatitis C Virus Among Blood Donors Attending Samarra's General Hospital.Infect Disord Drug Targets, 2019 Sep 15.

32. Cacoub P., Vautier M., Desbois A.C.et al. Effectiveness and Cost of Hepatitis C Virus Cryoglobulinaemia Vasculitis Treatment: From Interferon-Based to Direct-Acting Antivirals Era.Liver Int, 2017 Dec;37(12):1805-1813. doi: 10.1111/liv.13465. Epub 2017 May 29.

33. Caldwell H. Preventing, Identifying and Treating Hepatitis C.Nurs Stand, 2019 Jan 8.

34. Comarmond C., Garrido M.Direct-Acting Antiviral Therapy Restores Immune Tolerance to Patients With Hepatitis C Virus-Induced Cryoglobulinemia Vasculitis.Gastroenterology, 2017 Jun;152(8):2052-2062.e2.

Durcan E., Hatemi I., Sonsuz A., et al. The Effect of Direct Antiviral Treatment on the Depression,
Anxiety, Fatigue and Quality of Life in Chronic Hepatitis C Patients. EurJGastroenterol Hepatol, 2019 Aug
20.

/401

36. Elshimi E., Sakr N., Morad W., et al. Direct-Acting Antiviral Drugs Improve the Female Sexual Burden Associated with Chronic HCV Infection.Expert Rev Anti Infect Ther, 2019 Oct 22:1-8. doi: 10.1080/14787210.2019.1682551.

37. Fabrizi F., Cerutti R., Porata G., et al.Direct-Acting Antiviral Agents for HCV-Associated Glomerular Disease and the Current Evidence.Pathogens, 2019 Oct 4, 8(4). pii: E176. doi: 10.3390/pathogens8040176.

38. Guerreiro-Costa L.N.F., Araújo-Filho J.E.O., Marback R.F., et al. Mental Disorders and Quality of Life in Patients Awaiting Liver Transplantation.Arq Gastroenterol, 2019 Oct 14. pii: S0004-28032019005003101. doi: 10.1590/S0004-2803.201900000-63

39. Honrubia López R., Madejón Seiz A., Romero Portales M., et al. Quality of Life Study in Asymptomatic Patients with Hepatitis C.Rev Esp Enferm Dig, 2019 Oct 16. doi: 10.17235/reed.2019.6339/2019.

40. Juanbeltz R., Martínez-Baz I., San Miguel R., et al. Impact of Successful Treatment with Direct-Acting Antiviral Agents on Health-Related Quality of Life in Chronic Hepatitis C Patients.PLoS One, 2018 Oct 9, 13(10):e0205277. doi: 10.1371/journal.pone.0205277. eCollection 2018.

41. KesenO., KaniH.T., Yanartaş Ö., et al. Evaluation of Depression, Anxiety and Quality of Life in Hepatitis C Patients Who Treated with Direct Acting Antiviral Agents.Turk J Gastroenterol, 2019 Sep, 30(9):801-806. doi: 10.5152/tjg.2019.18679.

42. Ly K.N., Miniño A.M., Liu S.J.Deaths Associated with Hepatitis C Virus Infection among Residents in 50 States and the District of Columbia, 2016-2017.Clin Infect Dis, 2019 Oct 5. pii: ciz.976

43. Mallet Vincent, Kamal Hamed, Michaël Schwarzinger, et al.Prognosis of Patients with Chronic Hepatitis B in France (2008-2013): A Nationwide, Observational and Hospital-Based Study. Journal of Hepatology, 2017,vol. 66,issue 3, March,pp. 514-520.

44. Manns M. P., Buti M., Gane E., et al. Hepatitis C Virus Infection. Nature Reviews. Disease Primers. 2017, 3(1). doi: 10.1038/nrdp.2017.6

45. Mindie H. Nguyen, A. Burak Ozbay, Iris Liou, et al. Healthcare Resource Utilization and Costs by Disease Severity in an Insured National Sample of US Patients with Chronic Hepatitis B.Journal of Hepatology, January 2019, vol.70, issue1, pp.24-32.

46. Moorman A.C., Xing J., Rupp L.B., et al. CHeCS Investigators. Late DiagnosisofHepatitis CVirus Infection,2014-2016: Continuing Missed Intervention Opportunities.Am J Manag Care, 2019 Aug, 25(8):369-374.

47. Morales-Arraez D.Risk of Liver Fibrosis Progression in Patients with Suboptimal Diagnosis of Hepatitis C Virus Infection.Eur J Gastroenterol Hepatol, 2019 Sep 3.

48. Mutnuri S., Kassem H., Badalamenti J., et al. Lymphoma-Associated Monoclonal Cryoglobulinemic Glomerulonephritis and Relationship with Hepatitis C Virus Infection: A Case Report.Case Rep Nephrol, 2019 Aug 18, 2019:7940291. doi: 10.1155/2019/7940291.

49. Petta S., Adinolfi L.E., Fracanzani A.L. Hepatitis C Virus Eradication by Direct-Acting Antiviral Agents Improves Carotid Atherosclerosis in Patients with Severe Liver Fibrosis.Journal of Hepatology,2018,vol. 69, issue 1,pp. 18-24.

50. Pouri A.A., Ghojazadeh M., Pourasghari B., et al. Seroepidemiology and Risk Factors of Hepatitis C Virus Infection in East Azerbaijan, Iran: APopulation-Based Azar Cohort study.Caspian J Intern Med, 2019 Summer, 10(3):326-331. doi: 10.22088/cjim.10.3.326.

51. Ramos-Casals M., Zignego A.L., Ferri C. Evidence-Based Recommendations on the Management of Extrahepatic Manifestations of Chronic Hepatitis C Virus Infection. Journal of Hepatology,2017 June,vol. 66,issue 6,pp. 1282-1299.

52. Söderholm J., Millbourn C. Higher Risk of Renal Disease in Chronic Hepatitis C Patients: Antiviral Therapy Survival Benefit in Patients on Hemodialysis. Journal of Hepatology, 2018,vol. 68,issue 5, pp. 904-911.

53. SpearmanC.W., DusheikoG.M., HellardM., et al. HepatitisC.Lancet, 2019 Oct 19, 394(10207):1451-1466.

54. Tada T., Toyoda H., Yasuda S. et al.Natural History of Liver-Related Disease in Patients with Chronic Hepatitis C Virus Infection: An Analysis Using a Markov Chain Model.J Med Virol, 2019 Oct, 91(10):1837-1844.

55. Tapper E.B., Parikh N.D., Green P.K., et al.Reduced Incidence of Hepatic Encephalopathy and Higher Odds of Resolution Associated With Eradication of HCV Infection.ClinGastroenterolHepatol, 2019 Oct 4. pii: S1542-3565(19)31082-1. doi: 10.1016/j.cgh.2019.09.033.

56. Zoe Mariño. Time AssociationBetween Hepatitis C Therapy and Hepatocellular Carcinoma Emergence in Cirrhosis Relevance of Non-Characterized Nodules.Journal of Hepatology, May 2019, vol.70,issue 5, pp. 874-884.