Medicinska istaživanja 2024; 57(3):19-25 | DOI: 10.5937/medi57-48168

OPEN ACCESS

Medical Research | Published by Faculty of Medicine University of Belgrade

ORIGINAL ARTICLE

Neurological complications of hepatitis C in Serbian population

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Recived: 10 December 2023
Revised: 05 April 2024
Accepted: 05 April 2024

Check for updates

Funding information:
The authors received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Competing interests:
The authors have declared that no competing interests exist

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Summary

Introduction: Approximately 58 million people live with chronic hepatitis C virus (HCV) infection across the globe. Over half of the patients develop at least one extrahepatic complication throughout the disease. Neuropsychiatric disorders have been described in up to 50% of HCV patients. Peripheral neuropathies seem to be the most common complication.

Aim: To explore a wide range of neurological complications of chronic HCV infection in Serbian patients.

Materials and Methods: From the medical electronic system of the Neurology Clinic, a sample of 79 HCV patients was obtained (57% were male, average age was 59.0 ± 13.7 years, and average hepatitis duration was 12.4 ± 7.8 years).

Results: Of the 79 registered HCV patients, 14 (17.7%) were newly diagnosed at the Neurology Clinic. There were 29 different primary neurological diagnoses on record. The most frequent complication was polyneuropathy (PNP) found in 28 (35.4%) patients. The most common type was distal symmetric PNP. The average age of patients with PNP was significantly higher compared to those without it. Prevalence of diabetes mellitus and heart disease was more common in patients with PNP. Furthermore, glomerulonephritis was registered only in HCV patients with PNP.

Conclusion: Elderly HCV patients with comorbidities such as diabetes mellitus and/or heart disease seem to be at an increased risk of polyneuropathies and should be screened accordingly.

Key words: hepatitis C virus (HCV), chronic infection, neurological complications, peripheral neuropathy, polyneuropathy

Cite this article as: Perić S, Nikolić L, Zlatar J, Mitrović N, Dajević M, Božović I, Ralić B, Basta I, Kačar A. Neurological complications of hepatitis C in serbian population; Medicinska istaživanja 2024; 57(3):19-25 DOI: 10.5937/medi57-48168

INTRODUCTION

Hepatitis C virus (HCV) is a single-stranded positive sense RNA virus that belongs to the Flaviviridae family. As an RNA virus, it has a high mutation rate, and an incubation period ranging from 2 weeks to 6 months with roughly 80% of cases being asymptomatic. Only 15-45% of those with acute infection have the infection cleared within 6 months, with the remainder remaining chronically infected (1). HCV is not only hepatotropic, but lymphotropic and neurotropic as well, with an estimated 40-74% of patients developing at least one extrahepatic complication (EHC) during the disease (2). Many EHCs are postulated to be immunologic in origin, with one cause thought to be due to infected B lymphocytes producing monoclonal or polyclonal autoantibodies with cryoglobulin (CG) or rheumatoid factor (RF) properties (3). This may also be due to the activation of autoreactive T cells with cross-reactivity against neuronal and other tissues (4). The most prevalent and well documented EHCs are nephropathy, diabetes mellitus type 2, cardiovascular diseases, non-Hodgkin lymphomas and neuropsychiatric disorders (2).

Among the neurological EHCs of HCV, distal symmetric sensorimotor axonal peripheral neuropathy is the most common and best-established entity, present in around 10% of patients (5). This is particularly true among CG positive individuals, with peripheral neuropathies present in up to 86% of CG positive patients (6), and in approximately 65% of those who develop vasculitis (7). Other neuropathies associated with HCV infection include polyradiculopathies, as well as small fiber neuropathies with paresthesia and autonomic dysfunction (8).

Less commonly, the central nervous system (CNS) can be involved. The pathophysiology is incompletely understood but may involve IL-1β altering the blood-brain barrier, active viral replication within the CNS, as well as direct and indirect HCV neurotoxicity. CNS complications include encephalopathies, myelopathies, hemorrhagic stroke in younger patients, and psychiatric symptoms (9).

Use of immunosuppressive agents, such as steroids and cytotoxic drugs are not recommended in those with HCV because of the threat of increases in viral load (10). Pegylated interferon (PEG IFN) and ribavirin (RBV) combination, an immunomodulatory therapy, has been used for decades but with a low rate of success in achieving a stable virological response (SVR) of about 50%. From 2014, direct-acting antiviral (DAA) medications began to be used in therapy, which significantly improved the treatment success, over 90% nowadays. The problem is the price of these drugs, which is why they are unavailable in a significant number of countries around the world (11). Patients treated with an interferon-based regimen have different neuropsychiatric manifestations such as the development of irritability in 30-40%, severe insomnia and depression requiring antidepressant therapy in 25%, so they need to be screened for neuropsychiatric diseases prior to starting this therapy (4). These are thought to occur due to interferon induced cytokine production and inhibition of serotonin synthesis. Sensory and motor neuropathies and autoimmunity have been described in relation to interferon therapy, but these side effects are rare (12). With the use of new DAA medications for treatment of chronic HCV infection as IFN free regimes, these manifestations have become less significant.

The aim of this paper was to further investigate the broad spectrum of neurological complications of chronic HCV infection from the perspective of a neurologist, while shedding more light toward peripheral neuropathies as the most common manifestations.

MATERIALS AND METHODS

Data were collected from a sample of patients with the diagnosis of chronic hepatitis C and a history of hospitalization at the Neurology Clinic, University Clinical Center of Serbia, between January 1, 2010 and December 31, 2019. Retrospective and completely anonymous data were used, thus signed informed consent was not requested.

Inclusion into the sample was based on a diagnosis matching one of the following codes according to the international classification of diseases, 10th revision, (ICD-10): B18 (Chronic viral hepatitis), B18.2 (Chronic viral hepatitis C), B18.8 (Other chronic viral hepatitis), B18.9 (Chronic viral hepatitis, unspecified), B19 (Unspecified viral hepatitis), K73 (Chronic hepatitis, not elsewhere classified), K73.0 (Chronic persistent hepatitis, not elsewhere classified), K73.8 (Other chronic hepatitis, not elsewhere classified), and K73.9 (Other chronic hepatitis, not elsewhere classified). We checked if the diagnosis of HCV infection was confirmed by serological test and/or positive quantitative HCV polymerase chain reaction (PCR) test in patients' electronic medical records. Furthermore, patients' electronic medical records were studied in detail to confirm the presence of at least one neurological diagnosis, justifying their inclusion into the sample. This resulted in a sample of 165 individuals. In 38 patients diagnoses of hepatotropic viruses other than hepatitis C were found, and in 48 patients no specific infectious causes of hepatitis were found, and these patients were hence excluded from the sample.

Electronic medical records were investigated for variables of interest. These included sociodemographic parameters such as age, gender, and presumed way of transmission. The clinical parameters related to chronic hepatitis C included duration of illness, whether it was newly diagnosed, current activity of disease expressed through the degree of hepatocellular necrosis, previous antiviral treatment, and the presence of hepatic complications. We assessed neurological diagnoses, duration of

neurological disease, and temporal association between HCV infection and neurological disease. Peripheral neuropathies were of particular interest. The type and degree of PNP was further described based on the patients' clinical picture and electrophysiological testing trough nerve conduction studies (NCS). PNP was defined as sensory, motor, or sensorimotor; symmetrical or asymmetrical; axonal, demyelinating, or axonal-demyelinating; and its severity was graded in relation to the patients' ability to walk. Data were also collected regarding other chronic illnesses, such as glomerulonephritis, thyroid dysfunction, diabetes, heart disease, lung disease, connective tissue diseases, hematological diseases, cancer, and others.

The data was analyzed using the arithmetic mean, standard deviation, and proportions, as descriptive methods. Fisher test, Chi-squared test and Students t test were used to compare subgroups of patients, with the level of statistical significance set at $p<0.05$. Statistical analyses were carried out with Statistical Package for the Social Sciences (SPSS) version 23 (IBM Corp, Armonk, NY, USA).

RESULTS

After excluding duplicates and those with non-HCV hepatitis, the sample yielded 79 patients that fit the inclusion criteria. Of these, 45 (57%) were male, and the average age was 59.0 ± 13.7 years, ranging between 31 and 91 years **(Table 1)**. The most frequent known route of transmission was intravenous drug abuse in 17 (21.5%) patients, with a single (1.3%) patient with known routes of transmission, namely via transfusion, occupationally, or from a partner. Of all patients, there were 14 (17.7%) newly diagnosed, i.e. diagnosis of chronic HCV infection was made as a part of their work-up during their stay at the Neurology Clinic. In patients with previous diagnosis of HVC, average duration of hepatitis was 12.4 ± 7.8 years. The disease was found to be active in the observed period in 39 (49.4%) patients, and inactive in 21 (26.6%) patients. The majority of patients (59.5%) had no treatment for hepatitis C on record. Among those treated, the most commonly used drug both alone and in combination was PEG IFN, in 6 (7.6%) alone and in 9 (11.4%) in combination with a DAA. RBV was used in 5 (6.3%) patients, all in combination with PEG IFN at least. Finally, DAA alone or combined were used in 14 (17.7%) patients - sofosbuvir (5, or 6.3%), velpatasvir (4, or 5.1%), grazeprovir (4, or 5.1%), ledipasvir (3, or 3.8%), elbasvir (3, or 3.8%), with boceprevir, telaprevir, pibrentasvir, and glekaprevir only being used in single patients (1.3%). DAA were also often used in combination with PEG IFN (5, or 6.3%).

Neurological complications most often occurred after the diagnosis of HCV infection, as was found in 55 (69.6%) patients. The remainder of those with a known specific chronology evenly divided into 9 (11.4%) with concomitant hepatitis and neurological complications, and 9 (11.4%) with a neurological diagnosis before the diagnosis of hepatitis. On average, each patient had 1.8 ± 1.0 neurological diagnoses in their history, ranging between 1 and 5, and 2.8 ±2.0 other chronic illnesses, ranging between 0 and 9. There were 29 different primary neurological diagnoses within the sample **(Table 2)**.

The most frequent neurological complication present in the sample was PNP, occurring in 28 (35.4%) patients, for 24 (30.4%) of whom it was the primary neurological diagnosis. Headache was the second most frequent complication, documented in 20 patients (25.3%) of whom 8 patients (10%) had it as their primary neurological diagnosis. Mononeuropathy occurred in 3 (3.8%) patients, as a compressive ulnar lesion, optic neuritis, and trigeminal neuritis, respectively. Brachial plexitis was found as a primary neurological diagnosis in 1 (1.3%) patient, while another had a secondary diagnosis of lumbosacral plexitis. The next most frequent neurological diagnosis was epilepsy, present in 17 (21.5%) patients, for 11 (13.9%) of whom it was the primary diagnosis. In those for whom epilepsy was a secondary diagnosis, the history of seizures was either a direct consequence of the primary neurological diagnosis, e.g. hemorrhagic stroke in 2, or superseded by a more progressive clinical entity, e.g. amyotrophic lateral sclerosis and progressive multifocal encephalopathy in another 2, or with inadequate medical history on the seizures as it was in the final 2. While cognitive deficit was the primary neurological diagnosis in only 1 patient, 12 patients

Table 1. Sociodemographic, clinical and laboratory features of HCV patients with neurological diseases, page 7.

Feature	Mean ± SD or number (%) of patients
Male gender	45 (57.0%)
Age	59.0 ± 13.7 years
Route of transmission	
Intravenous drug use	17 (21.5%)
Transfusion	1 (1.3%)
Occupational	1 (1.3%)
Sexual route	1 (1.3%)
Duration of HCV infection	12.4 ± 7.8 years
Newly diagnosed	14 (17.7%)
Disease activity	
Active	39 (49.4%)
Inactive	21 (26.6%)
Treatment	
No treatment	47 (59.5%)
Interferon alone	6 (7.6%)
DAA*	9 (11.4%)
Combination	10 (12.7%)
Unspecified treatment	7 (8.9%)
Positive HCV serology and/or PCR	57 (70.9%)

* direct-acting antiviral therapy

Table 2. Frequency of primary neurological diagnoses in patients with chronic HCV, page 8.

Primary Neurological Diagnosis	**Number (%) of patients**
Polyneuropathy	24 (30.4%)
Brachial plexitis	1 (1.3%)
Mononeuropathy	3 (3.8%)
Chronic back pain	1 (5.1%)
Encephalopathy	4 (1.3%)
Idiopathic cognitive deficit	1 (1.3%)
Vascular dementia	1 (1.3%)
Epilepsy	11 (13.9%)
Hemorrhagic stroke	1 (1.3%)
Ischemic stroke	2 (2.5%)
Ischemic optic neuropathy	1 (1.3%)
Recurrent hemiplegia	1 (1.3%)
Hemihypesthesia	1 (1.3%)
Spastic paraplegia	2 (2.5%)
Spastic quadriplegia	1 (1.3%)
Headache	8 (10.1%)
Hydrocephalus	1 (1.3%)
Intracranial tumor	1 (1.3%)
Myopathy	2 (2.5%)
Myesthenia gravis	1 (1.3%)
Parkinsonism	2 (2.5%)
ALS	1 (1.3%)
Cerebellar ataxia	1 (1.3%)
Vertigo	1 (1.3%)
Multiple sclerosis	3 (3.8%)
Clinically isolated syndrome	1 (1.3%)
Progressive multifocal encephalopathy	1 (1.3%)
Acute disseminated encephalomyelitis	1 (1.3%)

had it as a secondary finding, for a total prevalence of 13 (16.5%). A total of 8 (10.1%) patients had encephalopathy, half (5.1%) of whom had it as a primary neurological diagnosis. Altogether, there were 8 (10.1%) patients with a history of stroke, of whom 5 (6.3%) were hemorrhagic and 3 (3.8%) were ischemic. Only 2 (2.5%) ischemic strokes and 1 hemorrhagic stroke were primary neurological diagnoses. Multiple sclerosis occurred in 3 (3.8%) patients exclusively as a primary neurological diagnosis. Finally, parkinsonism was documented in 2 (2.5%) patients. Other conditions classified as primary neurological diagnosis that occurred in single patients (1.3%) included the following: progressive multifocal encephalopathy, acute disseminated encephalomyelitis, clinically isolated syndrome, vascular dementia, ischemic optic neuropathy, spastic paraplegia, spastic quadriplegia, recurrent hemiplegia, hemihypoesthesia, amyotrophic lateral sclerosis, cerebellar ataxia, vertigo, hydrocephalus, intracranial tumor, myopathy, mitochondrial myopathy, myasthenia gravis, and chronic back pain. Non-neurological diagnoses in hepatitis C patients are presented in **Table 3**.

Table 3. Frequency of non-neurological diagnoses in patient with chronic HCV infection, page 9.

Primary Neurological Diagnosis	**Number of patients**
Cirrhosis	21
Hepatocellular Carcinoma	6
Gammopathy	5
Anemia	4
Pancytopenia	1
Hemophilia A	1
Immune Thrombocytopenia	1
Non-Hodgkin Lymphoma	1
Vasculitis	8
Glomerulonephritis	6
Concomitant Infection	4
Hyperthyroidism	1
Hypothyroidism	3
Sjogren Syndrome	2
Sjogren Syndrome with Rheumatoid Arthritis	1
Arthropathy	3
Purpura	3
Angioedema	1

In patients with PNP, normal gait was observed in 10 (35.7%) of 28 patients, difficulty walking was found in 11 (39.3%), one-sided support was necessary for one (3.6%), bilateral support was needed for four (14.3%) patients, and one (3.6%) subject was unable to walk. Sensorimotor impairment was the most prevalent, seen in 19 patients (67.9%), while isolated sensory and isolated motor were present in 3 (10.7%) each. Pathophysiological typing was not specified in 14 (50%) patients, the remaining half being demyelinating (21.5%), and axonal-demyelinating or pure axonal (14.3% patients each). Furthermore, symmetric changes were far more prevalent (71.4%) compared to asymmetric (10.7%). Serological testing in these patients showed positive CG in 4 (14.3%) of the 7 (25.0%) patients tested, 1 (3.6%) positive for ANA of the 5 (17.9%) patients tested, and neither of the 2 (7.1%) patients tested for ANCA were positive. As would be expected from the findings above, the most common subtype observed was distal symmetric PNP, found in nine patients (32.1%). The other two types included small fiber PNP in one and Guillain-Bare Syndrome in another patient (3.6% each).

There was a statistically significant difference between the average age of patients with PNP when compared to those without PNP (64.4 ± 9.0 vs. 56.1 ± 15.0 years, $p<0.01$) (Table 4). Additionally, 35.7% of patients with PNP were found to have diabetes as opposed to only 7.8% of those without PNP ($p<0.05$). Similarly, there was a statistically significant difference in the frequency of the heart disease in patients with PNP vs. those without PNP (42.9% vs. 19.6%, $p<0.05$). Additionally, there were no glomerulonephritis cases among the patients without PNP, whereas 21.4% of those with PNP had glomerulone-

phritis ($p<0.05$). Lastly, it is interesting to note that while 17.9% of those with PNP were found to have vasculitis compared to only 5.7% of those without PNP ($p=0.09$).

DISCUSSION

The finding of PNP as the most frequent neurological disorder in the setting of chronic HCV infection (35%) with neurological comorbidity is very much in line with literature where it was reported in 40% to 75% of all HCV patients (4). The effects of CG on the peripheral nerves are thought to be the most common cause of PNP in this setting. Types 2 and 3 CG, also known as mixed CGs, are most often found in the setting of chronic HCV infection (13). Our own findings, where just over half of tested PNP patients were positive for CG, are much greater than the expected 25% to 30%, and almost certainly accounted for by the very low sample size of those tested in our cohort. Though various peripheral neuropathies have been described in association with CG, those most found are PNP of the distal, symmetric, sensory or sensorimotor type (5). This type was also most frequently present in our cohort.

The reality at play is more complex, as PNP is also a frequent finding in those without circulating mixed CGs (8). In these patients, PNP is similarly thought to be due to the lymphotropic nature of HCV, but due to its effect on infected T cells (14). One of the mechanisms that connect HCV infections and PNP, which does not include CG, could be in immune response dysfunction during chronic hepatitis C. Thus, HCV causes disorders of the innate and adaptive arms of the immune response, which includes dendritic cells (DC), macrophages (Kupffer cells), natural killer (NK) cells, CD4+ and CD8+ T cells, such as B cells and peripheral blood mononuclear cells (PBMC) which are also reservoirs for HCV (15, 16). Impaired synthesis of various cytokines such as interleukin 1, 2, 6, 12, 15, 18, as well as interferon (type I and III) can be of importance in the pathogenesis of PNP (17).

The association that was found between glomerulonephritis and PNP in our cohort of patients may also be supported by the link between CG and PNP. The presence of mixed CGs in the setting of either systemic vasculitis or glomerulonephritis has been termed "mixed cryoglobulinemia syndrome" (MCS) (18), and can be thought of as a symptomatic outcome of high circulating CG levels. Again, while not the only etiological agent that results in MCS, the relationship between chronic HCV infection and MCS has been well established (19), as well as the relationship between MCS of all etiologies and PNP (20). Thus, we can conclude that, while a significant association between PNP and vasculitis was not made at this sample size, the association that was found between PNP and glomerulonephritis was significant and potentially hinting at CGs as the underlying cause of both. Alternatively, the strong association between glomerulonephritis and PNP may be due to the reduced renal clearance of toxic metabolites (21). Unfortunately, this study lacked adequate data on the chronological relationship between these two conditions. Namely, if glomerulonephritis were to emerge earlier, the resultant uremia and other toxic metabolites might in fact, be causing a uremic PNP (22), whereas, if they occur concomitantly or there was no temporal pattern, a shared pathophysiological mechanism such as MCS would be more likely. It is of note that the majority of our patients had length dependent neuropathy, while in uremia it is typical for short fibers to be affected. Thus, it is less likely that observed neuropathy in hepatitis C is of toxic origin. This would be an interesting avenue for future study.

Correlation that was found between PNP and diabetes is likely the result of synergy between the pathological mechanisms through which HCV and diabetes bring about PNP. At the level of the pancreatic β cells, HCV has the ability to promote diabetes as an EHC (2). The effects of diabetes could be explained in several ways. Some patients with diabetes may have pre-existing nerve injury due to ischemia, inflammation, and metabolic changes, so further injury from chronic hepatitis C makes things worse (23,24). Reduced rates of nerve regeneration were found early in diabetes even before symptoms and signs of neuropathy appeared, while the presence of diabetic neuropathy was associated with a further decrease in the capacity to regenerate (25). In accordance with this, regenerative deficit with reduced axonal sprouting and Schwann cell migration was shown to be common in diabetes and supposed to underlie the development of neuropathy (23). Diabetes may also increase inflammation in chronic hepatitis C since both diseases are associated with systemic inflammation including an increased level of different cytokines (24,26).

We also noticed correlation between PNP and older age of patients, independent of the duration of hepatitis C. This could be a result of synergism between the biological age of the patient and other comorbidities such as diabetes (11). An additional downside of age may be due to the side effect profile of the only therapeutic options available in the past - PEG IFN with RBV. While usually better known for their neuropsychiatric and physiological side effects, several case reports associate their use with worsening or induction of peripheral neuropathies, among a number of other clinical entities (27–30).

Other than PNP, the broad scope of neurological complications encountered in the study is also in line with the literature. Cognitive deficit is known to occur in up to 50% of those with chronic HCV infection (31). It can also mask the initial stages of encephalopathy, which may be both hepatic and directly due to active viral replication in the CNS. Stroke, both ischemic and hemorrhagic, is also reported to occur more frequently in this population, at younger ages as well (32). While the number of stroke

Table 4. Comparison of chronically HCV infected patients with and without polyneuropathy, page 10.

Feature	non-PNP Mean ± SD or number (%) of patients	PNP Mean ± SD or number (%) of patients	p
Number	51	28	
Age	56.1 ± 15.0	64.4 ± 9.0	p<0.01
Glomerulonephritis	0 (0%)	6 (21.4%)	p<0.05
Diabetes	4 (7.8%)	10 (35.7%)	p<0.05
Heart disease	10 (19.6%)	12 (42.9%)	p<0.05
Vasculitis	3 (5.4%)	5 (17.9%)	p=0.09

Sociodemographic, laboratory and clinical features without statistical difference were not presented in the Table.

patients within our sample was admittedly too small for any significant associations to be made, it is interesting to note that the average age of patients with a history of hemorrhagic stroke was almost nearly 8 years lower than both the sample average, and the average of those with ischemic strokes. This correlation is thought to potentially result from MCS or an increased rate of atherosclerosis associated with HCV (33).

CONCLUSION

In summary, peripheral neuropathies are common manifestations of chronic hepatitis C present in approximately one third of patients and should not be overlooked since they can affect patients' abilities. Physicians, including neurologists, should also think of other extrahepatic complications of this infection, thus requesting multidisciplinary approach in this chronic disorder.

Acknowledgments

None.

Conflicts of interest

None to declare.

Ethical approval

In this paper only retrospective data were used from medical records, thus Ethical approval was not obtained. Corresponding author and his collaborators undertake that the processed data in this research are presented in a way that does not allow the identification of an individual subject. All data are related only and exclusively to the topic of the research and without the possibility of connecting the data with the identity of the persons.

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NEUROLOŠKE KOMPLIKACIJE HEPATITISA C U SRPSKOJ POPULACIJI

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Sažetak

Uvod: Oko 58 miliona ljudi širom sveta boluje od hroničnog hepatitisa C. Preko polovine pacijenata razvije barem jednu ekstrahepatičnu komplikaciju u toku bolesti. Neurološki i psihijatrijski poremećaji centralnog i perifernog nervnog sistema opisani su u sklopu HCV infekcije kod čak oko polovine pacijenata. Od neuroloških komplikacija, najčešće su periferne neuropatije.

Cilj: Ispitivanje širokog opsega neuroloških komplikacija hronične hepatitis C infekcije u srpskoj populaciji.

Materijali i metode: Uzorak od 79 pacijenata prikupljen je iz elektronskog sistema Klinike za neurologiju Univerzitetskog kliničkog centra Srbije. Četrdeset pet (57%) pacijenata bilo je muškog pola, a prosečna životna dob iznosila je 59.0 ± 13.7 godina. Hepatitis C infekcija je u proseku trajala 12.4 ± 7.8 godina.

Rezultati: Od ukupno 79 pacijenata, kod 14 (17.7%) je novodijagnostikovan hepatitis C za vreme boravka na Klinici. Opisano je 29 različitih primarnih neuroloških dijagnoza. Polineuropatija je bila najčešća neurološka komplikacija opisana kod 28 (35.4%) pacijenata. Distalna simetrična polineuropatija je bila najčešća forma. Pacijenti sa polineuropatijom su bili stariji. Učestalost dijabetesa i učestalost srčanih oboljenja bili su znatno češći kod pacijenata sa polineuropatijom u odnosu na ostatak uzorka. Glomerulonefritisi su uočeni isključivo kod pacijenata sa polineuropatijom.

Zaključak: U neurološkoj praksi često se susreću pacijenti sa HCV. Stariji pacijenti, koji pored hroničnog HCV boluju i od drugih oboljenja poput dijabetesa i/ili srčanih oboljenja u povećanom su riziku da razviju polineuropatiju.

Ključne reči: hepatitis C, hronična infekcija, neurološke komplikacije, periferne neuropatije, polineuropatije.

Primljen: 10.12.2023. I **Revizija:** 05.04.2024. I **Prihvaćen:** 05.04.2024.

Medicinska istaživanja 2024; 57(3):19-25