Revista da Sociedade Brasileira de Medicina Tropical
Journal of the Brazilian Society of Tropical Medicine
Vol.:52:e20180407: 2019
doi: 10.1590/0037-8682-0407-2018

Major Article

Rheumatological Manifestations Associated with Viral Hepatitis B or C

***Ídila Mont'Alverne Xavier de Oliveira*[1],[2] *and Rita do Socorro Uchôa da Silva*[1],[2]**

[1]. Universidade Federal do Acre, Programa de Pós-Graduação Stricto Sensu em Ciências da Saúde na Amazônia Ocidental, Rio Branco, Acre, Brasil.
[2]. Secretaria de Saúde do Estado do Acre, Rio Branco, Brasil.

Abstract

Introduction: Rheumatological findings and rheumatic diseases may be associated with hepatitis virus infection. This study assessed the frequency of these manifestations in a reference unit in Acre, Brazil. **Methods**: This was a cross-sectional study with a convenience sample of patients having their first consultation at the rheumatology outpatient clinics of a referral unit in Rio Branco, Acre, from March to November 2017. Sociodemographic, clinical, laboratory, and imaging data registereds using a standardized questionnaire form. **Results**: Among the 600 patients with rheumatic complaints, 3.0% were newly diagnosed with hepatitis B virus (HBV) or hepatitis C virus (HCV), and 8.7% were previously diagnosed with hepatitis. Among the 70 patients with hepatitis, 54.3% were carriers of HBV and 45.7% of HCV. For patients infected with HBV and HCV, arthralgia was the most prevalent rheumatic manifestation in 97.4% and 90.6%, followed by myalgia in 81.6% and 65.6%, and arthritis in 26.3% and 40.6% of patients, respectively, according to the descriptive analysis performed using the Statistical Package for the Social Sciences software. In comparative analyses using the chi-squared test, despite the fact that fibromyalgia was the most prevalent rheumatic disease only the Rheumatoid Arthritis there were differences in distribution between the carriers of HCV (18.8%) and HBV (2.6%). According to the Fisher's exact test, hypothyroidism was the most frequent comorbidity in patients with HCV (21.9%). **Conclusions**: An increased frequency of musculoskeletal manifestations, better than those reported in the medical literature, in patients infected with HBV and HCV was observed.

Keywords: Viral hepatitis. Arthralgia. Rheumatic diseases. Rheumatoid arthritis. Western Amazon.

INTRODUCTION

Viral hepatitis B and C are considered a significant public health problem. The World Health Organization estimates that 240 million people are chronically infected with hepatitis B virus (HBV) and approximately 150 million with hepatitis C virus (HCV)[1,2].

In Brazil, from 1999 to 2016, more than 212,000 hepatitis B and 319,000 hepatitis C cases were confirmed, and in 2016, the detection rates in Brazil were 6.9 and 13.3 per 100,000 inhabitants, respectively, for HBV and HCV[3]. Regarding the State of Acre, these rates were higher for HBV (40.3/100,000 inhabitants) and similar for HCV (12.9/100,000 inhabitants)[3].

Corresponding author: Rita do Socorro Uchôa da Silva.
e-mail: rita.uchoa.acre@gmail.com
Orcid: 0000-0003-0481-0732
Received 5 December 2018
Accepted 13 November 2019

The HBV and HCV infections primarily affect the liver; nevertheless, several studies significantly describe extrahepatic clinical findings, including rheumatic, hematological, renal, dermatological, neurological, and other systemic autoimmune disorders[4-15]. The origin of these rheumatological manifestations involves a disruption in the immune system caused by the tropism of these viruses for lymphoid cells[4,16], and their association with rheumatic diseases such as mixed cryoglobulinemia or other vasculitis, rheumatoid arthritis (RA), systemic lupus erythematosus, fibromyalgia (FM), Sjögren syndrome, and other rheumatic conditions has also been described[17-28].

It is challenging to determine whether rheumatic symptoms such as arthralgia and arthritis occur due to HCV or HBV primary chronic infection or due to a secondary process of rheumatic disease development, but it is important to make this distinction considering that specific treatment against the virus may lessen/bring an end to rheumatic complaints, similar to other treatment modalities, as they may also worsen the

symptoms of rheumatic diseases, making the clinical scenario confusing[10,14].

Considering the high prevalence of rheumatic complaints in the general population and that patients diagnosed with hepatitis may present different rheumatic disorders within their clinical spectrum, it is believed that these could be the first manifestations of a clinically silent hepatic disease, leading to a late hepatitis diagnosis when they are not investigated, which increases the likelihood of complications[4,5,9,10]. Therefore, this study aimed to assess the frequencies of rheumatological findings and rheumatic diseases in patients infected with HBV or HCV treated at an outpatient reference health unit in the Brazilian Amazon, in addition to describing their clinical and epidemiological profiles.

METHODS

This was a cross-sectional study comprising a convenience sample, conducted at the Rheumatology Outpatient Care Department and the Specialized Care Service ("Serviço de Atenção Especializada"-SAE), which is considered to be the reference center in hepatology and infectious diseases in the State of Acre. Both are located in "Hospital das Clínicas de Rio Branco," Acre, Brazil. All patients aged greater than 18 years who were newly diagnosed with viral hepatitis B or C and who were referred to their first consultation at rheumatology outpatient clinics for the evaluation of rheumatic complaints and patients who were already cared for with a previous diagnosis of HBV or HCV having rheumatic complaints from March 2017 to November 2017 were included in the study. Patients who did not undergo all the requested examinations for the assessment of rheumatic disease, Indian patients, pregnant women, and HIV virus carriers were excluded from the study. All patients were interviewed after obtaining an informed consent form, and their data were registered in a standardized questionnaire form containing the results of the requested medical examinations, which were conducted at the clinical pathology laboratory of the aforementioned hospital (**Figure 1**).

The rheumatic complaints were considered and included in the study when they were reported for a period of more than 3 months. The Visual Analogue Scale (VAS) for pain was used in all patients as a one-dimensional instrument to assess pain intensity. In this scale, one end of the line was marked with "no pain" and at the other, with "worst pain imaginable"[29]. The patient was subsequently asked to evaluate and mark the pain present at that time.

The arthralgia symptom was considered and included in the study when it was reported for a period of more than 3 months and when it had a VAS score of ≥ 5, which is considered as a moderate to high pain, relatively leading to a functional limitation.

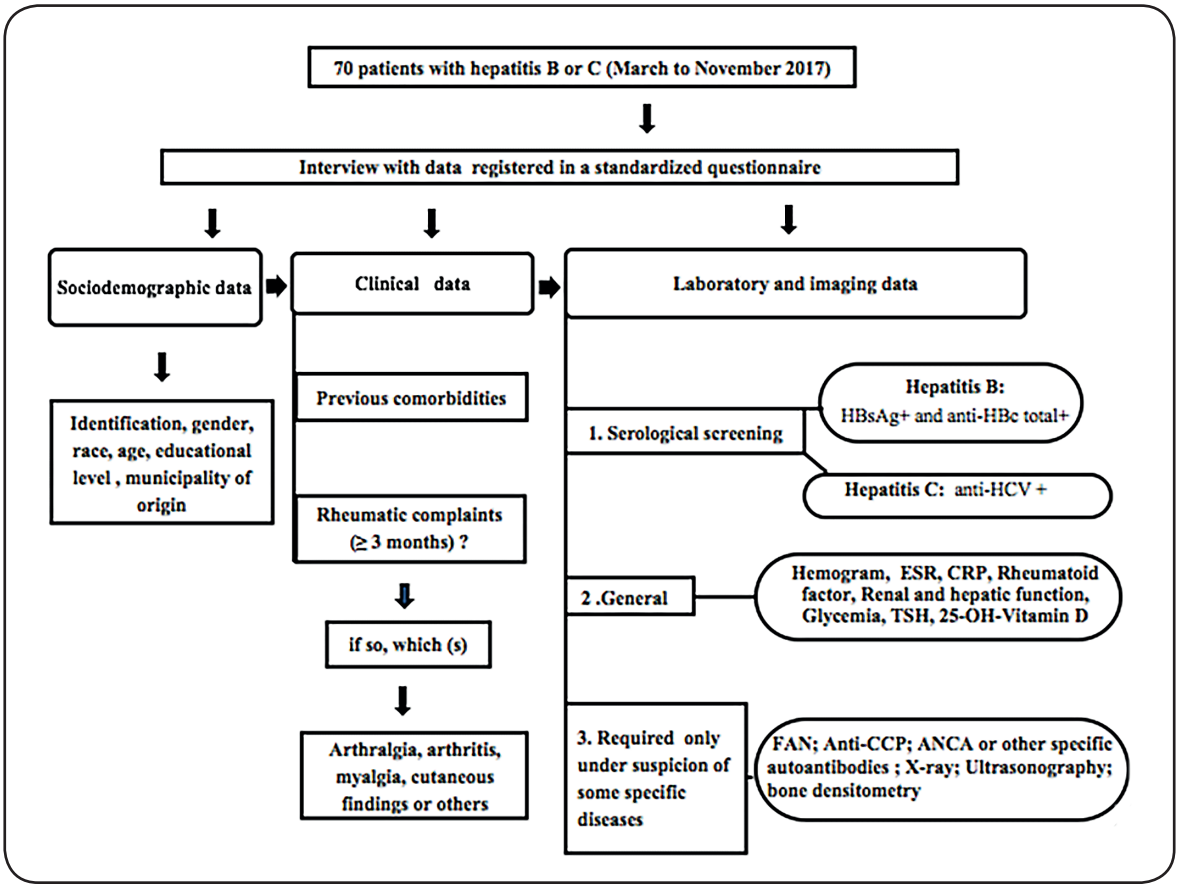

FIGURE 1: Collected data in a standardized questionnaire form.

To evaluate the results of the requested examinations, a return visit was scheduled for each patient after 60 days, at the most. Those with serology reactive to hepatitis B or C who did not have a previous viral hepatitis diagnosis were referred for a consultation within a week with an infectious disease specialist or gastroenterologist at the SAE for the confirmation of the HCV infection (quantitative HCV-ribonucleic acid [HCV-RNA]) and follow-up for HBV infection (quantitative HBV-deoxyribonucleic acid).

The final diagnoses were as follows: (a) *HBV infection* (reactive hepatitis B surface antigen), (b) *HCV infection* (reactive anti-HCV and HCV-RNA with viral load detection), (c) *rheumatological manifestation considered as extrahepatic manifestation of hepatitis* (this assessment was established after the exclusion of other autoimmune conditions [RA, systemic lupus erythematosus, Sjögren syndrome, other forms of vasculitis] and FM, according to the well-established criteria by the American College of Rheumatology [ACR] for the definition or exclusion of rheumatic diseases[30], or yet the presence of other disorders that justified the rheumatic complaints), and (d) *overlapping of rheumatic disease and hepatitis B or C virus infection* (for cases in which the patient met the serological hepatitis criteria and ACR criteria for rheumatic disease alike).

Data were evaluated using the Statistical Package for the Social Sciences version 23.0 software through descriptive analysis consisting of average, standard deviation, and frequencies calculation. Pearson's chi-squared test was used to compare proportions between subgroups (HBV versus HCV). For the 2 x 2 tables, in which the expected values were below 5, Fisher's exact test was performed, and when the expected values were higher than 5, the usual chi-squared test was used. $p<0.05$ was considered statistically significant.

This study was approved by the Research Ethics Committee of "União Educacional do Norte," UNINORTE (registration number: 1.938.922) on February 22, 2017.

RESULTS

From March to November 2017, 600 patients referred for rheumatic complaints were evaluated, resulting in a new diagnosis of viral hepatitis B or C in 18 patients (3.0%) and having 52 patients (8.7%) already under treatment. for these viral hepatitis. Hence, a total of 70 patients were included in the study. Among these patients, 74.3% were previously diagnosed with hepatitis, and 25.7% had a new diagnosis of hepatitis B or C. Thirty-eight patients (54.3%) were diagnosed with hepatitis B and 32 (45.7%) with hepatitis C.

The average age of the patients was 55.7 years, ranging from 29 to 73 years among patients with HBV and from 49 to 84 for HCV carriers, with women: men ratios of 32:6 and 27:5, respectively. Moreover, 64.3% (56/70) of patients stated that they had completed the secondary level as their maximum educational grade level, and majority of the patients lived in the City of Rio Branco, the state's capital, for both the hepatitis B (76.3%) and hepatitis C groups (78.1%) (**Table 1**).

Regarding rheumatic complaints, arthralgia was the most prevalent manifestation for patients with both HBV (97.4%) and HCV (90.6%) infections, and the frequency of rheumatic complaints had no statistically significant difference between the groups according to statistical analysis.

No significant difference in VAS scores for pain was observed between the groups. The mean VAS was 7.388, and the patients were distributed as follows:

- VAS 1-3 (mild pain): 2.6% of HBV patients and 9.4% of those with HCV
- VAS 4-6 (moderate pain): 28.9% of HBV patients and 15.6% of those with HCV
- VAS 7-10 (intense pain): 68.5% of HBV patients and 75% of those with HCV

Hypothyroidism was the only comorbid condition that presented a significant difference regarding its frequency between the HCV (21.9%) and HBV (2.6%) groups (p=0.020) (**Table 2**).

Fibromyalgia was the most frequent rheumatic condition, occurring in 42.9% of patients. Despite the difference in percentage regarding the existence of rheumatic diseases between HBV and HCV carriers, only their RA frequency had a statistically significant result, being more commonly found among carriers of HCV (p=0.042) than that of HBV. From the whole sample, 40% of patients presented with nonspecific symptoms, which were considered to be extrahepatic disorders associated with viral hepatitis, considering that they did not meet the diagnostic criteria for any of the rheumatic diseases (**Table 3**).

Among the HBV carriers, 3 patients (7.9%) had coinfection with hepatitis D virus. Of these, the first patient was diagnosed with HBV-associated RA, with initial symptoms of arthralgia and arthritis. Since his viral load was low, treatment for hepatitis was not required, and his symptoms improved with specific medication treatment for rheumatic disease. The second patient had severe muscle pain as an extrahepatic symptom associated with HBV, which showed significant improvement after antiviral treatment with entecavir. The third patient reported complaints of generalized myalgia and arthralgia, meeting the criteria for the diagnosis of FM associated with HBV, but antiviral treatment was not necessary because the patient had a low viral load, with improvement of symptoms after specific treatment for FM.

Most of the patients presented with an HBV viral load below 2,000 UI/ml (55.3%), 42% underwent treatment with antiviral drugs, 57.9% were inactive carriers (chronic hepatitis B phase 3), and 39.5% were in phase 4 or viral reactivation. Only one patient experienced chronic hepatitis phase 2 (immune-clearance), and none of the patients experienced the first phase of the disease (immune-tolerance).

There was no association between HBV viral load values and the frequency of arthralgia (p=0.174), arthritis (p=0.140), cutaneous findings (p=0.174), and myalgia (p=0.073).

Among the HCV carriers, 60% presented with detectable viral load, 34.4% of which had viral load ranging between

TABLE 1: Comparative sociodemographic profile among patients infected with hepatitis B or C viruses, assisted in a reference health unit in Rio Branco, Acre, Brazil, from March to November 2017.

Characteristics	Viral hepatitis						P value (HBV vs. HCV)
	HBV		HCV		Total		
Gender	**N**	**%**	**N**	**%**	**N**	**%**	
Female	32	84.2	27	84.4	59	84.3	0.985*
Male	06	15.8	05	15.6	11	15.7	
Age range (years)							
≤30	01	2.6	00	0.0	01	1.4	0.092*.**
31-40	06	15.8	00	0.0	06	8.6	
41-50	05	13.2	07	21.9	12	17.1	
51-60	15	39.5	12	37.5	27	38.6	
61-70	09	23.7	07	21.9	16	22.9	
>70	02	5.3	06	18.8	08	11.4	
Skin color							
Brown	26	68.4	23	71.9	49	70.0	
White	07	18.4	05	15.6	12	17.1	0.944*.**
Black	05	13.2	04	12.5	09	12.9	
Educational level							
Illiterate	01	2.6	03	9.4	04	5.7	
Literate	04	10.5	04	12.5	08	11.4	
Elementary school	19	50.0	14	43.8	33	47.1	0.430*.**
High school	08	21.1	03	9.4	11	15.7	
College education	06	15.8	08	25.0	14	20.0	
Occupation							
Housewife	17	44.7	10	31.3	27	38.6	
Other occupations	09	23.7	13	40.5	22	31.4	
Retired	04	10.5	05	15.6	09	12.8	
Farmer	03	7.9	02	6.3	05	7.1	0.234*.**
Cook	00	0.0	02	6.3	02	2.9	
Janitor	02	5.3	00	0.0	02	2.9	
Administrative assistant	02	5.3	00	0.0	02	2.9	
Self-employed	01	2.6	00	0.0	01	1.4	

*Pearson's chi-squared test. **Fisher's exact test.

100,000 and 1,000,000 UI/ml, and 25% had viral load over one million copies. Regarding genotypes of hepatitis C, genotype 1a was the most prevalent (47%), followed by 3a (28%) and 1b (25%), and statistical association with the presented rheumatic manifestations was not observed.

Additionally, there was no statistical association between the categories of HCV viral load values and the frequency of arthralgia (p=0.174), arthritis (p=0.477), cutaneous findings (p=0.583), and myalgia (p=0.403).

DISCUSSION

Previous studies have demonstrated that musculoskeletal symptoms are among the most common extrahepatic manifestations of patients with HCV and HBV[4-7] . Little is known about the frequency of these extrahepatic manifestations in Brazil, although 57% of patients had myalgia and 50% presented with myalgia in a recently published study from São Paulo with HCV carriers[6]. Other studies regarding HCV described arthralgia in 6.5% to 57%, myalgia in 1.3% to 61%, and arthritis in up to 5% of patients[6,13-14,20-22]. In HBV carriers, a frequency of arthralgia ranging from 3% to 53%, myalgia in 3% to 58%, and arthritis in less than 2% has been reported[12,18,24].

Therefore, this study presents a high frequency of musculoskeletal manifestations, superior to those reported in the medical literature, for HBV- and HCV-infected patients, resulting in frequencies of 97.4% and 90.6% for arthralgia, followed by myalgia in 81.6% and 65.6%, and arthritis in 26.3% and 40.6%, respectively, for HBV and HCV infection. These findings may be the result of sampling bias and are possibly overestimated in this Rio Branco study, considering that the selected patients presented with rheumatic symptoms and only then were they referred to a consultation with a rheumatologist. Another possible reason for these results was the active investigation of these symptoms, even if there were no statistical differences between the groups, hypothetically due to sample homogeneity. There is also a possible underestimation of these complaints in other studies given that these manifestations are not systematically investigated in all healthcare services, probably attributable to its subtle and frequently subclinical course[4,6,11-12].

It is worth noting that 40% of this patient sample had nonspecific rheumatic complaints, which were not consistent with any specific rheumatic disease, probably as a consequence of viral replication. El Garf et al.[20] in Cairo, Egypt, also

TABLE 2: Clinical profile of the 70 patients infected with hepatitis B or C virus, assisted in a reference health unit in Rio Branco, Acre, Brazil, from March to November 2017.

Clinical profile	Viral hepatitis						P value (HBV vs. HCV)
	Hepatitis B		Hepatitis C		Total		
	N	%	N	%	N	%	
Clinical manifestations							
Arthralgia	37	97.4	29	90.6	66	94.3	0.226*
Myalgia	31	81.6	21	65.6	52	74.3	0.128*
Arthritis	10	26.3	13	40.6	23	32.9	0.204*
Cutaneous findings	01	2.6	04	12.5	05	7.1	0.110**
Duration of rheumatic complaints							
< 3 months	02	5.3	03	9.4	05	7.1	0.252**
3-6 months	06	15.8	09	28.1	15	21.4	
7-12 months	02	5.3	01	3.1	03	4.3	
>12 months	28	73.6	19	59.4	47	67.2	
Comorbidities							
Systemic arterial hypertension	13	34.2	15	46.9	28	40.0	0.281*
Dyslipidemia	14	36.8	07	21.9	21	30.0	0.173*
Hepatic steatosis	08	21.1	04	12.5	12	17.1	0.344**
Hypothyroidism	01	2.6	07	21.9	08	11.4	**0.020****,***
Diabetes mellitus	02	5.3	03	9.4	05	7.1	0.506**
HDV coinfection	03	7,9	00	0.0	03	4,3	0.060**
Physical examination							
Trigger points	26	68.4	21	67.7	47	68.1	0.952*
Impingement syndrome****	03	7.9	06	19.4	09	13.0	0.160**
Alopecia	02	5.3	00	0.0	02	2.9	0.195**
BMI							
Underweight	00	0.0	01	3.1	01	1.4	0.936*,**
Normal weight	05	13.2	04	12.5	09	12.9	
Overweight	19	50.0	16	50.0	35	50.0	
Obesity first degree	10	26.3	08	25.0	18	25.7	
Obesity second degree	03	7.9	02	6.3	05	7.1	
Obesity third degree	01	2.6	01	3.1	02	2.9	

*Pearson's chi-squared test. **Fisher's exact test. ***Statistically significant. ****Positive maneuvers for impingement syndrome: clinical examination suggestive of tendinopathy.

TABLE 3: Distribution according to rheumatic disease diagnosis of the 70 patients infected with hepatitis B virus or hepatitis C virus, assisted in a reference health unit in Rio Branco, Acre, Brazil, from March to November 2017.

Manifestations/rheumatic diseases	Viral hepatitis						P value
	HBV		HCV		Total		
	N	%	N	%	N	%	
Fibromyalgia	14	36.8	16	50.0	30	42.9	0.268*
Nonspecific disorders/extrahepatic	19	50.0	09	28.1	28	40.0	0.064*
osteoporosis	04	10.5	07	21.9	11	15.7	0.323**
Osteoporosis	05	13.2	06	18.8	11	15.7	0.522*
Tendinopathy	03	7.9	06	19.4	09	13.0	0.160**
Rheumatoid arthritis	01	2.6	06	18.8	07	10.0	**0.042****,***
Epicondylitis	02	5.3	01	3.1	03	4.3	0.764**
Systemic erythematosus lupus	02	5.3	01	3.1	03	4.3	0.565**
Carpal tunnel syndrome	00	0.0	02	6.3	02	2.9	0205**
Scleroderma	01	2.6	00	0.0	01	1.4	0.355**

*Pearson's chi-squared test. **Fisher's exact test. ***Statistically significant.

distinguished these complaints in 157 HCV carriers and reported a 62% frequency of concurring rheumatic disease and 38% of extrahepatic manifestations. Distinguishing these rheumatic complaints between extrahepatic manifestation and rheumatic disease is important for therapeutic decision, considering that a variety of drugs for the treatment of rheumatic diseases are hepatotoxic and a successful antiviral treatment may lessen/bring an end to rheumatic symptoms[4,6,27,28] or even triggering symptoms. For instance, 36% of patients with HCV infection included in the Rio Branco study had been previously treated with interferon (IFN), which is associated with some musculoskeletal symptoms and recognized as a triggering or exacerbating factor for rheumatic diseases, thus contributing to an increased frequency of complaints[4,7,11].

Regarding rheumatic diseases, there was a higher prevalence of FM among the patients in this study (42.9%), a finding that is consistent with the results of other studies, as reported by Ozsahin et al.[24] and Yazmalar et al.[25] with 22.0% and 32.2%, respectively, for HBV patients and by Mohammad et al.[23] with 57% for HCV carriers. This increased frequency may be justified by the stress and anxiety caused by the establishment of a chronic infectious disease diagnosis such as hepatitis, leading to neuropsychiatric disorders, which may trigger FM[23-25].

Regardless of the high FM prevalence obtained, RA was even more frequent than the former in HCV patients compared to HBV carriers, having reached statistical significance (p=0.042). When comparing the results of hepatitis frequency in patients with rheumatic disease to other published data, according to El Garf et al.[20], despite having found a higher positive HCV prevalence (18.5%), mainly associated with RA and systemic lupus erythematosus, the overall number of patients with rheumatic complaints (n=157) was inferior compared to the overall number of patients in this study (n=600). Feuchtenberger et al.[8], despite analyzing data from a more numerous cohort (n=1,338) than the one from the Rio Branco study, detected HBV infection in only 0.2% of patients, which also presented with Rheumatoid Arthritis- AR. Tinazli et al.[21], also in a study with a reduced number of patients (n=154), did not detect a single patient who tested positive for HCV, probably because the general prevalence of HCV positivity reported for Turkey (0.1%-1%) is lower than that in Brazil[2-3]. These differences in frequencies compared with other studies may reflect local features in each healthcare institution and country, considering the wide geographical distribution of rheumatic diseases. Hsu et al.[26] detected 9.3% of Chinese RA patients having HBV, and Abdel Mohsen D et al.[28] reported a 15% frequency of HCV in a large Egyptian cohort having RA, supporting the hypothesis that HBV and HCV had a pathogenic role in RA by means of a synovial deposition of viral antigens[17-19,26-28], although further studies are necessary to clarify these molecular mechanisms.

The increased hepatitis endemicity in the State of Acre[3] may have affected the frequency of viral hepatitis obtained in this study, considering that over a 9-month period, 600 patients were assisted in the Rheumatology Outpatient Department for rheumatic complaints and 11.7% of the patients obtained the diagnosis of hepatitis B or C.

Among patients included in the study, a higher prevalence of HBV or HCV infection was observed in women (84.3%) than in men, a fact that may be related to men seeking less healthcare, be it for the prevention or treatment of their medical conditions, or yet be explained by the employment of a convenience sample comprising a population of patients referred to specialized rheumatological assessment, given that in most rheumatic diseases, women are more frequently affected than men[30-31], for example, FM was the most prevalent rheumatic condition in this study with an overall estimated prevalence of 3.4%-4.9% in females and 0.5%-1.6% in males[23-25].

Autoimmune rheumatic diseases are known as independent risk factors for major cardiovascular events, with HBV and/or HCV patients having an even greater risk, regardless of their hepatic disease severity[4,11-12,32]. In this study, among the diagnosed comorbidities, only hypothyroidism was more prevalent in the HCV group (21.9%) compared to the HBV group (2.6%). Thyroid disorders are common in patients with rheumatic diseases and in viral hepatitis patients[4], and several studies suggest a close association between HCV infection and autoimmune thyroiditis, such as reported by Qadeem K et al.[33], having obtained HCV in 4% and HBV in 1% of patients with thyroiditis ($p<0.05$), and Antoneli et al.[34] who obtained an increased frequency of hypothyroidism in patients with HCV (13%) in relation to HBV (4%), consistent with the present study. Therefore, these results imply that both HCV and HBV may be possible environmental triggers for autoimmunity mechanisms against the thyroid by means of an IFN-alpha-induced systemic inflammatory reaction that may lead to a plethora of other rheumatic diseases.

It is worth noting that the majority of patients with HBV or HCV included in this study presented with a low viral load count (justified by the fact that the majority of HBV patients were under antiviral treatment at the time of the study and the majority of the HCV carriers had already concluded their antiviral treatment, causing viral replication suppression), and they all had rheumatic complaints, confirming that minimal viral replication could explain the extrahepatic manifestations in these patients, in addition to those with active infection, and highlighting the importance of evaluating these complaints at a viral hepatitis outpatient setting routine.

In conclusion, the high prevalence of rheumatological manifestations and rheumatic diseases diagnosed in patients with hepatitis B and C infections during this study emphasizes the importance of considering viral hepatitis as the differential diagnosis for patients with rheumatic symptoms and also of hepatitis serological testing as a routine investigation protocol for rheumatic diseases, particularly in countries with high prevalence of hepatitis such as Brazil. Moreover, approaching all chronic hepatitis patients in a multidisciplinary setting for the investigation of extrahepatic manifestations is significantly recommended.

ACKNOWLEDGMENTS

We offer our deepest thanks to the institutions Hospital das Clínicas do Acre, Brazil, and to the Federal University of Acre for providing technical support for the development and implementation of this study.

Conflicts of interest

The authors declare that there are no conflicts of interest.

REFERENCES

1. Ott JJ, Stevens GA, Groeger J, Wiersma ST. Global epidemiology of hepatitis B virus infection: New estimates of age-specific HBsAg seroprevalence and endemicity. Vaccine. 2012;30(12):2212-9.
2. Petruzziello A, Marigliano S, Loquercio G, Cozzolino A, Cacciapuoti C. Global epidemiology of hepatitis C virus infection: An up-date of the distribution and circulation of hepatitis C virus genotypes. World J Gastroenterol. 2016;22(34):7824-40.
3. Brasil, Ministério da saúde (MS), Secretaria de Vigilância em Saúde (SVS). Hepatites Virais 2017. Boletim Epidemiológico - Hepatites Virais. Brasília: Ministério da Saúde, 2017;48(24).
4. Ferri CA, Ramos-Casals M, Zignego AL, Arcaini L, Roccatello D, Antonelli A, et al. International diagnostic guidelines for patients with HCV-related extrahepatic manifestations. A multidisciplinary expert statement. Autoimmun Rev. 2016;15(12):1145-60.
5. Cacoub P, Comarmond C. New insights into HCV-related rheumatologic disorders: A review. J Adv Res. 2017;8(2):89-97.
6. Tengan FM, Levy-Neto M, Miziara ID, Dantas BP, Maragno L. Extrahepatic manifestations of chronic hepatitis C infection: A consecutive study in Brazilian patients. Braz J Infect. 2017;21(2):209-10.
7. Palazzi C, D'Amico E, D'Angelo S, Gilio M, Olivieri I. Rheumatic manifestations of hepatitis C virus chronic infection: Indications for a correct diagnosis. World J Gastroenterol. 2016;22(4):1405-10.
8. Feuchtenberger M, Schäfer A, Philipp Nigg A, Rupert Kraus M. Hepatitis B serology in patients with rheumatic diseases. Open Rheumatol J. 2016;10:39-68.
9. Aydeniz A, Namiduru M, Karaoglan I, Altindag O, Yagiz E, Gursoy S. Rheumatic manifestations of hepatitis B and C and their association with viral load and fibrosis of the liver. Rheumatol Int. 2010;30(4):515-7.
10. Satsangi S, Gupta, N. Rheumatologic manifestations of viral hepatitis B and C. J Hep. 2015;1(1:3):1-5.
11. Cacoub P, Comarmond C, Desbois AC, Saadoun D. Rheumatologic manifestations of hepatitis C virus infection. Clin Liver Dis. 2017;21(3):455-64.
12. Cacoub P, Terrier B. Hepatitis B-related autoimmune manifestations. Rheum Dis Clin North Am. 2009;35(1):125-37.
13. Mohammed RH, El Makhzangy HI, Gamal A, Mekky F, El Kassas M, Mohammed N, et al. Prevalence of rheumatologic manifestations of chronic hepatitis C virus infection among Egyptians. Clin Rheumatol. 2010;29(12):1373-80.
14. Cheng Z, Zhou B, Shi X, Zhang Y, Zhang L, Chen L, et al. Extrahepatic manifestations of chronic hepatitis C virus infection: 297 cases from a tertiary medical center in Beijing, China. Chin Med J (Engl). 2014;127(7):1206-10.
15. Vassilopoulos D, Manolakopoulos, S. Rheumatic manifestations of hepatitis. Curr Opin Rheumatol. 2010; 22(10):91-6.
16. Mandell GL, Bennett JE, Dolin R. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. 7th ed. New York: Elsevier; 2010.
17. Su FH, Wu CS, Sung FC, Chang SN, Su CT, Shieh YH, et al. Chronic hepatitis C virus infection is associated with the development of rheumatoid arthritis: A nationwide population-based study in Taiwan. PLoS ONE. 2014;9(11):e113579.
18. Vukatana G, Gamal N, Trevisani M, Cursaro C, Andreone P, Malavolta N. THU0283 Serological prevalence of hepatitis B virus infection among patients with different rheumatic disease: A prospective study. Ann Rheum Dis. 2014;73:281.
19. Watanabe R, Ishii T, Kobayashi H, Asahina I, Takemori H, Izumiyama T, et al. Prevalence of hepatitis B virus infection in patients with rheumatic diseases in Tohoku Area: A retrospective multicenter survey. Tohoku J Exp Med. 2014;233(2):129-33.
20. El Garf A, El Zorkany B, Gheith R, Sheba VH, Moneim GA, El Garfet K. Prevalence and clinical presentations of hepatitis C virus among patients admitted to the rheumatology ward. Rheumatol Int. 2012;32(9):2691-5.
21. Tınazlı M, Meryem G, Aykaç A, Süer K. Hepatitis C virus infection among patients admitted to a rheumatology ward in northern Cyprus. The Egyptian Rheumatologist. 2017;39(4):245-7.
22. Mazzaro C, Dal Maso L, Urraro T, Mauro E, Castelnovo L, Casarin P, et al. Hepatitis B virus related cryoglobulinemic vasculitis: A multicentre open label study from the Gruppo Italiano di Studio delle Crioglobulinemie - GISC. Dig Liver Dis. 2016;48(7):780-4.
23. Mohammad A, Carey JJ, Storan E, Scarry M, Coughlan RJ, Lee JM. Prevalence of fibromyalgia among patients with chronic hepatitis C infection: Relationship to viral characteristics and quality of life. J Clin Gastroenterol. 2012;46(5):407-12.
24. Ozsahin M, Gonen I, Ermis F, Oktay M, Besir FH, Kutlucan A, et al. The prevalence of fibromyalgia among patients with hepatitis B virus infection. Int J Clin Exp Med. 2013;6(9):804-8.
25. Yazmalar L, Deveci Ö, Batmaz I, İpek D, Çelepkolu T, Alpaycı M, et al. Fibromyalgia incidence among patients with hepatitis B infection. Int J Rheum Dis. 2016;19(7):637-43.
26. Hsu CS, Lang HC, Huang KY, Lin HH, Chen CL. Association of rheumatoid arthritis and hepatitis B infection: A nationwide nested case-control study from 1999 to 2009 in Taiwan. Borg. Med (Baltimore). 2016;95(18):e3551.
27. Chen MH, Chen MH, Liu CY, Tsai CY, Huang DF, Lin HY, et al. Hepatitis B virus reactivation in rheumatoid arthritis patients undergoing biologics treatment. J Infect Dis. 2017;215(4):566-73.
28. Abdel Mohsen D, Hamza SH, Morshedy NA, Miller FD, Elzalabany MS. Prevalence of hepatitis C virus infection in Egyptian patients with rheumatoid arthritis. Arthritis Rheumatol. 2017; 69 (suppl 10).
29. Pimenta CAM. Escalas de avaliação de dor. In: Teixeira MD, editors. Dor conceitos gerais. São Paulo: Limay. 1994; p. 46-56.
30. American College of Rheumatology - ACR. Diseases and Conditions [Internet]. Disponível em; [cited 2018 Jan 5]. Available from: <http://www.rheumatology.org/I-Am-A/PatientCaregiver/Diseases-Conditions>.
31. Senna ER, De Barros AL, Silva EO, Costa IF, Pereira LV, Ciconelli RM, et al. Prevalence of rheumatic diseases in Brazil: A study using the COPCORD approach. J Rheumatol. 2004;31(3):594-7.
32. Younossi ZM, Stepanova M, Marcellin P, Afdhal N, Kowdley KV, Zeuzem S, et al. Treatment with ledipasvir and sofosbuvir improves patient-reported outcomes: Results from the ION-1, -2, and clinical trials. Hepatology. 2015;61(6):1798-808.
33. Qadeem K, Muhammad Z, Niaz A, Aakifullah K, Khayyam H, Mahboob-ul H. Prevalence of hepatitis B and C infection in autoimmune thyroid patients. J Entomol Zool Stud. 2017;5(2):1335-7.
34. Antonelli A, Ferri C, Pampana A, Fallahi P, Nesti C, Pasquini M, et al. Thyroid disorders in chronic hepatitis C. Am J Med. 2004;117(1):10-3.