

Clinical evaluation and prevalence of fibromyalgia in hepatitis C patients

Avaliação clínica e prevalência de fibromialgia em pacientes portadores de hepatite C

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ABSTRACT

BACKGROUND AND OBJECTIVES: The worldwide distribution and etiology of fibromyalgia are poorly understood. It is believed that different factors are involved, such as hepatitis C virus infection. The aim of this study was to estimate the prevalence of fibromyalgia in hepatitis C virus infected patients, trying to identify the occurrence of liver injury, extrahepatic clinical manifestations, anxiety, depression, and the impact on the quality of life.

METHODS: This is a cross-sectional study of patients (n=118) with hepatitis C virus infection who were compared with a group of clinically stable patients not infected with the hepatitis C virus (n=118). The Anxiety and Depression Questionnaire was applied, and for those diagnosed with fibromyalgia, the Fibromyalgia Impact Questionnaire. Liver biopsies were analyzed according to the METAVIR classification. The Schirmer test was performed to investigate abnormal tear production in the studied patients. Data analysis was performed using the *Statistical Package for Social Sciences* (SPSS) software, v.10.0.

RESULTS: The prevalence of fibromyalgia in infected patients was 7.6%. In patients infected with fibromyalgia, a significant prevalence of anxiety and depression was observed. Fibromyalgia Impact Questionnaire scores were higher in infected patients with fibromyalgia. When comparing the complementary tests in infected patients with and without fibromyalgia, no significant differences were found for the Schirmer test, viral genotype, and degree of fibrosis and liver inflammation.

CONCLUSION: In females, there was a positive relationship between hepatitis C virus infection, fibromyalgia, and extrahepatic symptoms, which translates into a higher prevalence of anxiety and depression and impaired quality of life.

Keywords: Chronic pain, Fibromyalgia, Hepatitis C.

RESUMO

JUSTIFICATIVA E OBJETIVOS: A fibromialgia tem distribuição mundial e etiologia pouco compreendida. Acredita-se no envolvimento de diferentes fatores, como a infecção pelo vírus da hepatite C. O objetivo deste estudo foi estimar a prevalência de fibromialgia em pacientes infectados pelo vírus da hepatite C, procurando identificar a ocorrência de lesão hepática, manifestações clínicas extra-hepáticas, ansiedade, depressão e o impacto na qualidade de vida.

MÉTODOS: Trata-se de um estudo de corte transversal com pacientes (n=118) portadores de infecção pelo vírus da hepatite C que foram comparados a um grupo composto de pacientes clinicamente estáveis e não infectados pelo vírus da hepatite C (n=118). Foi aplicado o Questionário de Ansiedade e Depressão, e para os que obtivessem o diagnóstico de fibromialgia, o Questionário de Impacto da Fibromialgia. As biópsias hepáticas foram analisadas de acordo com a classificação METAVIR. Foi realizado o teste de Schirmer para a pesquisa de lacrimagem anormal nos pacientes estudados. A análise dos dados foi realizada através do programa *Statistical Package for Social Sciences* (SPSS) v.10.0.

RESULTADOS: A prevalência de fibromialgia em pacientes infectados foi de 7,6%. Nos pacientes infectados com fibromialgia observou-se prevalência significativa de ansiedade e depressão. A pontuação do Questionário de Impacto da Fibromialgia foi maior nos pacientes infectados e com fibromialgia. Quando se relacionou os exames complementares em infectados com e sem fibromialgia, não foram constatadas diferenças significativas para o teste de Schirmer, genótipo viral e grau de fibrose e inflamação hepática.

CONCLUSÃO: Nos indivíduos do sexo feminino, observou-se uma relação positiva entre a infecção pelo vírus da hepatite C, fibromialgia e sintomas extra-hepáticos, que se traduz em maior prevalência de ansiedade e depressão e em comprometimento na qualidade de vida.

Descritores: Dor crônica, Fibromialgia, Hepatite C.

INTRODUCTION

Fibromyalgia (FM) is a chronic disease that affects approximately 0.2-6.6% of the world's population, with a prevalence of 0.7 to 11.4% in urban areas and from 0.1 to 5.2% in rural areas¹. In

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Brazil, it is also present in 2.5% of the population². FM is more prevalent in young women and has a variable behavior depending on the evaluation period and the diagnostic criterion.

FM was defined by the American College of Rheumatology (ACR) in 1990³ as a musculoskeletal pain syndrome lasting more than three months in which the patient reports pain at 11 of the 18 possible painful points on both sides of the body, above and below the waist, and pain in the axial skeleton³. This concept, however, has changed over time. In 2010⁴, the diagnostic criterion considered widespread pain index (WPI) ≥ 7 ; symptom severity scores (SS) ≥ 5 or WPI between 3-6 and SS ≥ 9 ; pain for more than three months and no other disease that explained the pain. Fatigue, non-restful sleep, and cognitive disorders were evaluated as absent, mild, moderate, and severe on a scale from zero to 3. Somatic complaints such as paresthesia, headache, depression, anxiety, irritable bowel syndrome, mouth and/or eye symptoms and Raynaud's phenomenon, among others, were classified according to the number of symptoms (0=no symptoms; 1=few symptoms (10-20); 2=moderate number of symptoms (20 to 30); 3=large number of symptoms (30 to 41)). In 2011, after reviewing the 2010 criteria⁵, only the somatic symptoms that persisted for six months were considered as headache, pain, or colic in the lower abdomen and depression with a score between zero and 3. Finally, in 2016⁶, the 2011 criteria were further revised, and it was validated that the WPI should be between 4-6 and the SS scale ≥ 9 . Pain is also required in 4 of 5 regions (4 quadrants and axial skeleton), except for the face and abdomen, and there may be another causal relationship morbidity with FM. Despite all the reflection on the diagnostic concept, the different definitions only contributed to the increase of FM diagnosis in males⁷.

FM may be related to genetic predisposition and inadequate activation of the hypothalamic-pituitary-adrenal axis and autonomic nervous system (ANS) in response to stress⁸. It can also occur after infectious and autoimmune diseases, physical and psychic trauma, systemic diseases, and viral infections, such as hepatitis C virus (HCV) infection⁹.

Hepatitis C is a chronic infection caused by a *Flaviviridae* RNA virus, whose transmission occurs through contact of contaminated biological materials with continuity solutions^{10,11}. It is estimated a prevalence of 1.0% for HCV infection worldwide. HCV causes hepatic inflammation and steatosis, changes that may progress to liver fibrosis, cirrhosis and hepatocellular carcinoma, or may be associated with extrahepatic manifestations such as essential mixed cryoglobulinemia, membranous proliferative glomerulonephritis, systemic vasculitis, Sjögren's syndrome, rheumatoid arthritis, systemic lupus erythematosus, myalgia, arthritis, and FM^{12,13}. The role of HCV infection in the pathophysiology of FM is not yet established¹⁴⁻¹⁷; however, possible autoimmune¹⁸, inflammatory^{10,19}, and/or psychogenic disorders have been suggested as essential elements in this process. Patients with HCV infection develop anxiety and depression generated by the presence of chronic disease. This can also contribute to global illness and FM development¹⁶.

The prevalence of FM in patients with chronic HCV infection is 1.9 to 57%²⁰, a finding that is not confirmed by other authors²¹.

This variation may occur due to the diagnostic criteria chosen for the definition of FM²². Regardless of its prevalence, it is important to note that HCV infection may be associated with the etiology of FM¹².

This study aimed to estimate the prevalence of FM in HCV-infected patients from a university service located in northeastern Brazil. Secondary objectives are to identify the occurrence of liver injury, extrahepatic clinical manifestations, psychiatric disorders, as well as the impact on the quality of life of patients infected or not with FM.

MÉTODOS

This was a study of patients with HCV infection who were compared to a group of clinically stable and non-HCV uninfected patients. The calculated sample was 118 with infection and 118 without infection for a power of 80%; $\alpha=5\%$, considering a prevalence of FM in infected individuals around 14% *versus* an average of 3% found in the population without infection²³.

To start the evaluation, the patients were asked about their interest in participating in the research by signing a Free and Informed Consent Term (FICT).

The HCV group consisted of patients treated at the Liver Nucleus, linked to the University Hospital of the Federal University of Maranhão (HUUFMA), from January 2009 to January 2010, who had the ELISA (Enzyme-Linked Immunosorbent Assay) positive test and subsequent confirmation of viral RNA in peripheral blood.

Patients in the HCV infection group completed questionnaires, underwent a physical exam and laboratory tests, were over 18 years, had no other liver or infectious disease, neurological, psychiatric, neuromuscular, rheumatological, autoimmune diseases and had not used interferon during the last six months.

The group without infection consisted of randomly selected patients from the medical clinic, with the same mean age, gender ratio, and characteristics already mentioned, with serology for hepatitis C negative, according to the ELISA test¹⁵.

Participants had medical records reviewed, and epidemiological data such as age, gender, and monthly income were recorded. For those infected, data were recorded regarding risk factors for infection and viral genotype. During the interview, the following symptoms were investigated in both groups: fatigue, Raynaud's phenomenon, myalgia, arthralgia, subjective complaints of dry eye (*sicca*), paresthesia, diabetes, hypertension, purpura, and pruritus¹⁵.

To diagnose dry eye, all patients underwent the Schirmer test (ST), which was performed using a millimeter tape made with an absorptive paper. The tape was left for five minutes in contact with the patient's lower ocular mucosa at the junction of the middle third with the lateral. The test was read after 10s of its removal from the ocular mucosa. In this study, only values lower than 5mm were considered as a positive criterion for dry eye²⁴.

The diagnosis of FM was based on the 1990 ACR criteria, recommended at the time of the study. Generalized pain was evaluated quantitatively via verbal numeric scale (VNS), and qualitatively through characteristics attributed by the patient himself (*sting-*

ing, stabbing, etc.). We also studied the presence of FM-related symptoms such as headache, paresthesia, non-restorative sleep, fatigue, *sicca*, colds, and subjective edema, among others.

The emotional impact caused by the chronic disease was evaluated through the Hospital Anxiety and Depression Scale Questionnaire (HADS)²⁵ and the Fibromyalgia Impact Questionnaire (FIQ), the latter for those individuals diagnosed with FM²⁶. Both questionnaires have already been validated in the national territory, with their respective socio-cultural adaptations^{27,28}.

The HADS consists of 14 questions, of which seven score for the diagnosis of anxiety and seven for the diagnosis of depression. The answers have weights ranging from zero to 3 points. The cutoff point considered was 9 for anxiety and 9 for depression.

The FIQ consists of 10 items that evaluate (1) functional capacity, (2) well-being, (3) work absences, (4) work difficulties, (5) pain, (6) fatigue, (7) stiffness, (8) sleep, (9) anxiety, (10) depression. The total score ranges from 0 to 100, being stratified by scores above or equal to 70 for a degree of intense FM involvement, and between 50-70 for a moderate degree.

Liver biopsy results were recorded if the patient had a test performed less than or equal to a year ago, and were analyzed according to the METAVIR classification, which shows degrees of fibrosis and hepatic necroinflammatory activity. The degree of fibrosis was stratified from 0 to 4, where F0 = absence of fibrosis, F1 = portal fibrosis without septa, F2 = few septa, F3 = numerous septa without cirrhosis, F4 = cirrhosis. Necroinflammatory activity was also measured in A0 = absence of inflammatory activity, A1 = mild activity, A2 = moderate activity, A3 = intense activity²⁹.

This study was approved by the UFMA Research Ethics Committee, protocol 001911/2008.

Statistical analysis

Data analysis was performed using the *Statistical Package for Social Sciences* (SPSS) v.10.0 program. The Chi-square test was used to compare categorical variables (sociodemographic characteristics, symptoms, genotypes, ST biopsies, Student's *t* for age between the group with and without infection, and those infected with and without FM. A descriptive analysis was performed for the other variables. Variables with $p < 0.05$ were considered a significant difference.

RESULTS

A total of 336 patients (118 with HCV and 118 without HCV) were analyzed, evaluated for their sociodemographic characteristics, which did not differ significantly between the groups (Table 1).

Of the infected patients, 47 (40%) reported not being exposed to risk factors for HCV. Twenty-eight subjects (24%) reported having had blood transfusion, nine (7.5%) had a history of drug use and/or tattoos, 16 (13.5%) had used glass syringes, six (5%) had reported occupational exposure, six (5%) had contacts with infected and six (5%) reported other risk factors. Of the 118 infected patients, 42 underwent liver biopsy less than or equal to one year ago. In addition, 20 patients already had a di-

Table 1. Sociodemographic characteristics in HUPD patients with and without hepatitis C virus. São Luís, MA, 2009

Variables	HCV+		HCV-		p-value
	n=118	or $\bar{X}\%$	n=118	or $\bar{X}\%$	
Age (years old)	52.44		52.34		0.9
Gender					1
Female	42	35.6	42	35.6	
Male	76	64.4	76	64.4	
Income					0.62
No income	23	19.5	24	20.3	
Up to 1MW	33	28	41	34.7	
1-5 MW	52	44	44	37.4	
>5MW	10	8.5	9	7.6	
Marital status					0.99
Married	81	68.7	80	67.8	
Divorced	9	7.6	9	7.6	
Single	17	14.4	20	16.9	
Widower/widow	11	9.3	9	7.6	

n = number of patients; % = percentage; * $p < 0.05$ for statistically significant values; \bar{X} = average.

agnosis of liver cirrhosis. Thus, a total of 62 patients with known hepatic fibrosis were classified according to the METAVIR criteria. It was observed that 21 (33.87%) were in F4; one (1.60%) in F3; 11 (17.7%) in F2; 16 (25.8%) in F1; 13 (20.96%) in F0. When analyzing the necroinflammatory degree, it was found that of the 42 known, 18 (42.8%) patients were in stage A0; 20 (47.6%) in A1; 3 (7.1%) in A2 and 1 (2.38%) in A3.

Of the 118 infected patients, 74 had viral genotypes distributed as follows: 52 (70.27%) had genotype 1; six (8.3%) genotype 2 and 16 (22.22%) genotype 3.

Regarding the symptoms reported by the patients, complaints of arthralgia, fatigue, myalgia, dizziness, subjective edema, pruritus, and headache were statistically significant, with a higher predominance in the HCV positive group (Table 2).

There was no statistical difference between groups when anxiety was evaluated ($p=0.772$). On the other hand, there was a higher prevalence of depression in the infected group ($p=0.051$).

There was a significant difference between the groups when the ST was applied, with 23.7% of the infected presenting dry eye ($p=0.001$). A significant relationship was found between HCV infection and FM. Of those infected, 9 had FM (7.6%), while in the uninfected group, only one patient (0.8%) had FM ($p=0.01$). The only patient in the FM group without infection was female, married, with a monthly income of less than one minimum wage.

The infected group was then divided into patients with and without FM, and the sociodemographic data were compared (Table 3).

Females were statistically significant in the FM group. The analyses were performed, taking into consideration only the female group. There were no differences in mean age between infected women with and without FM, nor regarding other demographic data.

Table 2. Prevalence of symptoms in hepatitis C virus-infected compared to uninfected treated at HUPD in São Luís, MA, 2009

Variables	HCV+ n=118 (%)	HCV- n=118 (%)	p-value
Paresthesia	37(31.4)	27 (22.9)	0.143
Sicca	22(18.6)	16(13.6)	0.288
Arthralgia	54(45.8)	22(18.6)	<0.001*
Myalgia	43(36.4)	29(24.6)	0.048*
Purple	7(5.9)	11(5.9)	0.367
Raynaud's Syndrome	1(0.8)	1(0.8)	1
Pruritus	20(16.9)	7(5.9)	0.008*
Fatigue	46(39)	27(22.9)	0.015*
Subjective edema	29(24.6)	15(12.7)	0.019*
Headache	5(4.2)	0	0.024*
Constipation	26(22)	28(23.7)	0.594
Nonrestorative sleep	22(18.6)	20(16.9)	0.734
Morning stiffness	25	20(16.9)	0.474
Urinary Urgency	21	12(10.2)	0.183
Difficulty concentrating	20(16.9)	15(12.7)	0.360
Bad memory	40(33.9)	39(33.1)	0.890
Dizziness	40(33.9)	26(22)	0.042*
Cold sensitivity	19(16.1)	30(25.4)	0.078

n = number of patients; % = percentage; * p<0.05 for statistically significant values.

In evaluating exposure to risk factors in FM-infected individuals, blood transfusion was the most common route (4/9), followed by the unknown route (2/9) and subsequently by occupational exposure, tattooing, and other forms in equal proportions (1/9). Of the patients infected with FM, two had a liver biopsy, and two already had the diagnosis of cirrhosis. Regarding the degree of liver fibrosis, according to the METAVIR criteria, it was observed that one (25%) patient presented with F1, 1(25%) with F2, and two cirrhotic (50%) with F4. Regarding the inflammatory degree, one patient was A1 and the other A0. When comparing the degrees of fibrosis and necroinflammatory activity between those infected with and without FM, no statistically significant differences were observed.

Regarding the viral genotype of FM-infected patients, of the 118 infected patients, 74 had viral genotype distributed as follows: 52 (70.27%) had genotype 1, 6 (8.3%) genotype 2, and 16 (22.22%) genotype 3. When these patients were compared to those infected without FM, no statistical significance was observed between the groups (p=0.097).

No statistical differences were found for viral genotype (p=0.225) and degree of liver fibrosis (p=0.722) when considering only women infected with and without FM.

Regarding the symptoms reported by the patients, complaints of arthralgia, fatigue, myalgia, non-restorative sleep, dizziness, paresthesia, sicca, constipation, cold sensitivity, subjective edema, purpura, headache, and complaints of Raynaud's phenomenon were statistically significant with higher prevalence in those infected with FM (Table 4)

Table 3. Epidemiological profile of hepatitis C virus patients with and without fibromyalgia treated at the HUPD Liver Nucleus in São Luís, MA, 2009

Symptoms	HCV+			p-value
	FM- n=109	% or X̄%	FM+ n=9 or X̄%	
Age (years old)	59.70		57.06	0.83
Gender				0.007*
Female	36	33	7	77.8
Male	73	67	2	22.2
Income				0.810
No income	21	19.3	2	22.2
Up to 1MW	30	27.5	3	33.3
1-5 MW	48	44	4	44.4
>5MW	10	9.2	0	
Marital status				0.232
Married	76	69.7	5	55.6
Divorced	7	6.4	2	22.2
Single	15	13.8	2	22.2
Widower/Widow	11	10.1	0	
Activity				0.039*
No activity	45	41.3	2	22.2
Remunerated	44	40.4	2	22.2
Retired	8	7.3	3	33.3
Pensioners and others	12	11	2	22.2

n = number of patients; % = percentage; * p<0.05 for statistically significant values; X̄ = average.

When analyzing only women infected with FM, it was observed that the most significant complaints had a similar pattern to the previous group regarding pain complaints, fatigue, paresthesia, dizziness, sleep alteration, and morning stiffness. In the infected group, when comparing those who did not have FM with those who had FM, there were no statistically significant differences regarding ST (p=0.206), although there was a significance regarding the complaint of dry eye by those infected with FM.

In infected patients, there was a significant prevalence of anxiety in 77.7% and depression in 66.7% in the FM group (p<0.001). Similar results were found when considering only women in the FM-infected group compared to the group without, with an association with anxiety and depression in 71.4% (p=0.047) and 57.1% (p=0.005), respectively. For ST, no associations were found (p=0.455).

Regarding pain intensity, the average grade obtained by VNS was 7.5 in FM-infected patients. Regarding the quality of pain in patients with FM, 77.7% of patients complained of stabbing pain; 66.6% stinging pain; 55.5% throbbing pain; 44.4% pain in weight; 22.2% burning pain; 22.2% other types (Figure 1).

Table 4. Reported symptoms of patients with positive hepatitis C virus, with and without fibromyalgia, treated at HUPD, São Luís, MA, 2009

Symptoms	FM-		HCV+		p-value
	n=109	%	FM+ n=9	%	
Arthralgia	45	41.3	9	100	0.001*
Fatigue	38	34.9	8	88.9	0.001*
Myalgia	36	33	7	77.8	0.007*
Nonrestorative sleep	15	13.8	7	77.8	0.000*
Dizziness	33	30.3	7	77.8	0.004*
Paresthesia	30	27.5	7	77.8	0.002*
Sicca	16	14.7	6	66.7	0.000*
Constipation	20	18.3	6	66.7	0.001*
Morning stiffness	19	17.4	6	66.7	0.001*
Cold sensitivity	14	12.8	5	55.6	0.001*
Subjective edema	24	22	5	55.6	0.025*
Bad memory	36	33	4	44.4	0.487
Pruritus	17	15.6	3	33.3	0.173
Purple	4	3.7	3	33.3	0.000*
Urinary urgent	18	16.5	3	33.3	0.205
Concentration difficult	17	15.6	3	33.3	0.173
Headache	3	2.8	2	22.2	0.005*
Raynaud's Syndrome	0	0	1	11.1	0.000*

n = number of patients; % = percentage; *p<0.05 for statistically significant values.

Table 5. Reported symptoms of patients with positive hepatitis C virus with and without fibromyalgia treated at HUPD, São Luís, MA, 2009

Symptoms	FM-		Women HCV+		p-value
	n=35	%	FM+ n=7	%	
Arthralgia	15	42.9	7	100	0.006*
Fatigue	15	45.9	6	85.7	0.038*
Myalgia	15	42.9	6	85.7	0.038*
Nonrestorative sleep	4	11.4	6	85.7	0.000*
Dizziness	14	40	6	85.7	0.012*
Paresthesia	12	34.3	6	85.7	0.012*
Sicca	5	14.3	5	71.4	0.001*
Constipation	12	34.3	4	54.1	0.256
Morning stiffness	7	20	6	85.7	0.001*
Cold sensitivity	6	17.1	3	42.9	0.130
Subjective edema	8	22.9	4	57.1	0.067
Bad memory	19	54.3	3	43.9	0.580
Pruritus	5	14.3	1	14.3	1
Purple	3	8.6	2	28.6	0.136
Urinary urgency	7	20	3	42.9	0.195
Concentration difficulty	6	17.1	2	28.6	0.482
Headache	11	31.4	5	71.4	0.061
Raynaud's Syndrome	0		0		

n = number of patients; % = percentage; * p<0.05 for statistically significant values.

In the patient with FM without infection, the pain characteristic was stabbing, with VNS of 8.

When the FM impact on the quality of life questionnaire was evaluated, an average of 59.77 points was observed in the HCV group and 43.58 points in the group without infection. Of the patients with FM and HCV, seven (77.44%) had a moderate to intense FIQ score (score above 50). Regarding the only patient with FM and without HCV, this one had a score below 50 in the FIQ, a value related to a mild impact. The means for each item in the FIQ are shown in table 5, highlighting a higher average for the difficulty in working due to pain.

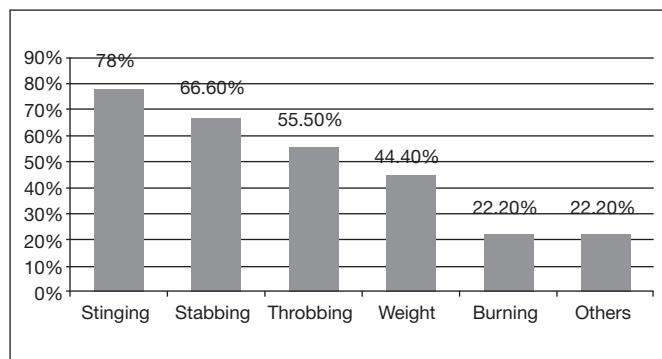


Figure 1. Percentage of widespread pain quality in infected fibromyalgia patients treated at HUPD Liver Nucleus, São Luís-MA, 2009

DISCUSSION

Although not having a well-defined etiological factor, FM has an established association with infectious diseases such as chronic Lyme disease, hepatitis C, *coxsackievirus*, parvovirus, and human immunodeficiency virus^{9,12}.

This study examined 118 chronically HCV-infected patients, with an average age above 50 years. Of the sample, 35.6% were women. The route of contamination was unknown in 40% of cases, followed by blood transfusion, similar to that described in the literature for developing countries^{30,31}. Several studies with a similar design in different parts of the world have found a positive association between HCV infection and FM. Buskila et al.¹⁵ observed a significant prevalence of FM (16%) in the infected group when compared to the group without HCV (3%). Rivera et al.¹⁶, in a study conducted in Spain, found 10% of those infected with FM compared to 1.72% of the group without infection. Kozanoglu et al.¹⁹, in Turkey, observed that 18.9% in the group with hepatitis C had FM, compared to 5.3% without the syndrome. In a similar study, Goulding, O'Connell and Murray¹⁷ found 5% of FM in infected individuals, considering a frequency of almost twice the local population and statistically significant compared to the control group. In Brazil, a non-comparative cross-sectional study by Loureiro et al.²⁴ showed a prevalence of FM in infected individuals of 12%. In this study, a positive association was found between C virus infection and FM, with results of 7.6% of HCV positive

patients with FM compared to 0.9% of HCV negative group. As can be seen, a lower percentage when compared to the other studies already described. This result could be explained by the different proportions of women who composed each study. The study with FM prevalence of 18.9% had 65% of the sample consisting of women¹⁸. As for the 16% prevalence of FM in infected patients, 46% of the study population was women. The reflection of female significance in the genesis of the relationship between FM and HCV was observed in this study and reinforced by several authors^{1,5,14,18,20}.

In addition to FM, it is known that other extrahepatic symptoms may be observed in patients with hepatitis C. Musculoskeletal pain complaints are common, with a prevalence of 50-81%³². In a study by Poynard et al.³⁴, fatigue was highlighted in 53% of patients, followed by arthralgia (23%), paresthesia (17%), and myalgia (15%). In this study, the most reported symptoms among infected people were arthralgia (45.8%), fatigue (39%) and myalgia (36.4%). In the group of HCV patients with FM, it was observed that pain complaints were significantly more frequent.

Dry syndrome, also known as *sicca*, is characterized by complaints of dry eye and/or mouth that can be objectively observed with specific tests such as Schirmer's. This syndrome may be part of the Sjögren's syndrome (SS), which makes up the picture of rheumatologic manifestations associated with the C virus. The diagnosis of SS is given along with specific patterns in serological and histopathological exams of the salivary glands. Experimental and epidemiological studies have already found a high prevalence of such histological patterns in HCV-positive salivary glands^{34,35}. Lormeau et al.³⁵ found a positive association between *sicca* and HCV infection in 10 to 20% of patients. In this study, only the presence of *sicca* and the ST were evaluated. Significant changes were found for ST in HCV patients, but there were no significant differences regarding dryness complaints. When comparing the number of patients who reported *sicca* with the number of positive ST, a discrepancy was observed between such numbers in the uninfected group, in which 14 reported *sicca* and only eight had a positive ST; while in the infected, 22 reported *sicca* and 25 had positive ST. The results found in this study were similar to those obtained by Goulding, O'Connell and Murray¹⁷, who observed a degree of dry eye by ST in patients with HCV. As found by other authors, there was no association between the positivity of ST for infected fibromyalgia^{16,18}. However, complaints of dry eye were significant. Thus, the association of FM with this extrahepatic manifestation was not established to estimate a common pathophysiological mechanism. It is believed that dryness complaints, restricted only to the subjectivity of the patient, could contain an association with the psychological characteristics of this population with such significant degrees of anxiety, depression and pain complaints.

Several theories have been proposed to explain extrahepatic complaints in patients with C virus infection. Thompson and Barkhuizen³⁷ suggested that changes in cytokine dynamics could be involved in these extrahepatic manifestations. Other theories for the causes of such manifestations would be the

patient's emotional state at the news of a chronic infection, influence of the viral genotype^{14,37}, or the reduction of liver-produced substances (IGF-1), the lack of which would be responsible for musculoskeletal injuries¹⁴. Another element to consider is the difference in the design of the studies used for discussion. All studies with a similar design were in agreement to find a relationship between FM and HCV^{14-16,18}. However, those who researched HCV infection in patients known to have FM had different results^{12,20,21,38}.

Few studies address the evaluation of the role of anxiety and depression in patients with hepatitis C and FM. Rivera et al.¹⁶ put the emotional factor on a secondary level, since when researching the C virus infection in patients with FM, they observed that this infection is more prevalent in this group than in the control group. This points to the viral role in the genesis of pain syndrome. It is important to note that most patients did not know about the infection and/or that it would have a chronic course. Therefore, they would not have the emotional impact established by this news¹⁵. A similar conclusion was found in a study conducted in Paraná by Silva et al.⁴⁰.

Goulding, O'Connell and Murray¹⁷ present a study that evaluates the degree of anxiety and depression in HCV and FM patients, revealing higher anxiety in this group when compared to healthy patients. They also show that the high degree presented by these patients is independent of the presence or absence of circulating viral RNA in the blood and the route of infection. In this study, there was a tendency for a higher prevalence of depression in HCV patients than in those without HCV. There was no significant difference between anxiety levels. When comparing those infected with and without FM, it was observed that 78% of FM had anxiety and 66.7% depression compared to 23 and 13% for anxiety and depression infected without FM. This difference, being statistically significant, supports the emotional influence on the genesis of FM. However, one cannot rule out the role of the infection itself in the generation of FM, since in this group it is not known what the initial event was: pain or depression.

Two studies evaluating the quality of life presented by fibromyalgic patients with HCV according to the FIQ showed an average of 52.1²³ and 85.9 points¹⁶. These values are considered moderate and severe, respectively⁴⁰. In the study in question, the impact was more intense in patients with virus C, with an average of 59.77 points, a value considered moderate. Unfortunately, it was not possible to make a comparison with the group without infection, as it presented only one fibromyalgia patient with mild impact (43.58 points).

When the items were discriminated, the ones with the highest score were related to difficulties in performing tasks and work, pain intensity, fatigue, alteration of well-being, alteration in functional capacity, work absences, anxiety, depression, stiffness and morning fatigue. Given the relevance of pain and fatigue in the worsening of quality of life in positive HCV and, knowing that these are common extrahepatic manifestations, C virus infection is now considered an important factor in FM genesis. Other evidence supporting this theory is that when comparing the group with and without HCV, there are similar

degrees of anxiety and depression, but more prominent pain complaints in the group that has the infection as a differential. Among those infected, pain complaints become more prevalent in those patients with FM, as well as a higher number of anxiety and depression cases.

Different neurotransmitters have been related to the genesis of the symptoms presented by patients with HCV and FM. Wallace et al.⁴¹ demonstrated elevated levels of IL-8, IL-1 and IL-6 in patients with FM. Thompson et al.³⁷ established a connection between cytokine alterations as a consequence of infection and the origin of pain. High levels of alpha tumor necrosis factor have been observed in infected patients, also related to a worse prognosis. In a study by H. Marotte et al.⁴², an improvement in pain and a decrease in FM pain points were observed with the use of an alpha tumor necrosis factor antagonist. Other substances also participate in the genesis of FM as substance P and serotonin. Increasing substance P, or reducing serotonin levels and its precursor, tryptophan, are believed to contribute to the development of this disease⁸⁻¹⁰. This finding corroborates the theory of viral genesis in this pain syndrome. This thinking is the basis of the theory of cytokine release as an etiological factor for FM, which would be directly or indirectly due to HCV infection³⁷.

Given these studies and the high levels of anxiety and depression found in this population, it is thought that there is an association of different factors in the etiology of FM in patients with HCV. Elements that predispose pain, such as HCV infection and individual characteristics in dealing with the news of being a chronic disease, are believed to contribute to higher pain intensity and suffering in this group of patients.

The most prevalent genotype in the HCV population was 1, present in 67.6% of known cases and all patients in the FM and infected group. When analyzing only the group composed of women infected with and without FM, the results were similar. The dissociation between hepatic impairment and the development of pain syndrome was also a concern of the authors of this study, as well as that of Buskila et al.¹⁵. When comparing cirrhotic that had C virus infection as their differential, they initially noticed a significant prevalence of FM in those infected. However, considering that FM is more frequent in females, and that there was an unequal gender distribution between HCV groups with and without cirrhosis, they reviewed the results obtained. In a second moment, they evaluated only females and definitively ruled out the association between cirrhosis and FM¹⁴. In order to avoid such bias, this study analyzed only the variables of the female population infected with and without FM, and no association was considered between the degree of inflammation, the degree of liver fibrosis, and FM.

CONCLUSION

This study demonstrated, in females, a positive relationship between HCV, FM infection and extrahepatic symptoms, which translates into a higher prevalence of anxiety and depression, consequently a compromise in the quality of life of these individuals.

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