Rheumatologic manifestations associated with Hepatitis C virus infection: A cross sectional multicentric study in Cameroon

Doualla BM[1, 2], Luma NH[1, 2], Oudou N[1], Kwedi F[2], Kemta LF[2], Memopi M[2], Temfack E[2], Ngandeu SM[1]

[1]*Faculty of Medicine and Biomedical Sciences, Yaoundé-Cameroon*
[2]*General Hospital Douala-Cameroon*

***Corresponding author**: Dr BM Doualla, General Hospital Douala, P.O. Box 4856, Douala, Cameroon. Email: marie.doualla@gmail.com*

Abstract

Background: Hepatitis C Virus (HCV) infection is a worldwide burden whose seroprevalence is higher in developing countries with Cameroon being the third most affected country in Africa. HCV both a hepatotropic and lymphotropic infection is responsible for a great number of hepatic and extra hepatic disorders some of which are rheumatic in nature. These rheumatologic manifestations though extensively studied in western countries; there is little or no data in sub-Saharan Africa.

Objective: The study was conducted with the aim to describe the musculoskeletal manifestations associated to HCV infection in a hospital setting in Cameroon.

Design: A cross-sectional study.

Setting: Three hospitals in Cameroon: the Douala General Hospital, a tertiary referral hospital with a capacity of 320 beds in Douala, the largest city and economic capital of Cameroon; the University Teaching Hospital of the Faculty of Medicine and Biomedical Sciences of the university of Yaoundé 1, a 240 beds hospital in Yaoundé the political capital of Cameroon and the "Centre Médical de la Cathédrale", a private acceptable standard Gastroenterology clinic also found in Yaoundé.

Patients and methods: From February to June 2009, we did a multicentric cross-sectional study of patients from the Gastroenterology, Rheumatology and Internal medicine outpatient clinics of three hospitals in Cameroon. Patients with HIV or HBV infection and those on antiviral treatment were excluded.

Results: Among 148 patients with HCV infection identified during the study period, only 62 fulfilled eligibility, 15 (24.2%) of whom had musculoskeletal manifestations related to HCV, the commonest of which were myalgia 9/62 (14.5%) , arthritis 6/62 (9.7%), bone pain 6.4% (4/62), sicca syndrome 3/62 (4.8%), and Raynaud's phenomenon 6/62 (9.7%). Among patients with rheumatologic manifestations, 9/15 (60%), had rheumatologic symptoms at HCV diagnosis and in 6/15 (40%). HCV infection was discovered during routine medical check-up. Musculoskeletal manifestations were neither associated with the genotype (*p=0.17*) nor with the viral load (*p>0.98*).

Conclusion: Arthralgia is the most common presenting feature of the symptomatic disease. Musculoskeletal manifestations may be confused with symptoms of common tropical infections, leading to delayed diagnosis and treatment of HCV infection.

Key words: Hepatitis C Virus, Arthralgia, Extra hepatic manifestations; Africa

Introduction

Hepatitis C Virus (HCV) infection which occurs worldwide has a higher seroprevalence in Africa, estimated at 5.3% compared to about 1.03% in Europe[1,2]. Cameroon, the third most affected country in Africa, has a seroprevalence which varies from as low as 0.6% to 4.8% in Pygmy groups and blood donors, to as high as 13% in hospital based studies[4,5]. Hepatitis C virus (HCV) which is a single-stranded, spherical RNA enveloped flavivirus, measuring 38 to 50 nm in diameter has multiple genotypes and quasispecies classified in six major clades. This genetic diversity confers to this virus a difference in pathogenicity, disease severity, and response to treatment with interferon[3]. Though considered a hepatotropic virus, HCV's lymphotropic nature is responsible for a great number of extra hepatic immune system disorders[1]. About 40 to 70% of affected patients will develop an extra hepatic manifestation that can have a rheumatic nature. These

rheumatologic manifestations include arthralgia, arthritis, myalgia, Sicca syndrome, vasculitis, and high prevalence of auto antibodies[6,7]. In western countries with relatively low burden of HCV infection, these syndromes have been extensive[6-9] but in sub-Saharan Africa with the higher burden of HCV, little or no data is available and some of the rheumatologic manifestations may be considered as symptoms of common tropical parasitic infections, thus retarding diagnosis and appropriate medical care. In this light, we opted to carry out this study with the aim of describing the musculoskeletal manifestations in HCV infection in a hospital based setting in Cameroon (Central Africa).

Study setting and patients: From February to June 2009, after prior institutional ethical clearance, we carried out a cross-sectional study in three hospitals in Cameroon: the Douala General Hospital, a tertiary referral hospital with a capacity of 320 beds in Douala, the largest city and economic capital of Cameroon; the University Teaching Hospital of the Faculty of Medicine and Biomedical Sciences of the University of Yaoundé 1, a 240 beds hospital in Yaoundé the political capital of Cameroon and the "Centre Médical de la Cathédrale", a private acceptable standard Gastroenterology clinic also found in Yaoundé. Our study population comprised of consenting adult patients diagnosed to be HCV infected diagnosed either through a routine medical check-up or those who presented with symptoms suspicious of HCV infection. Our study units were the Gastroenterology, Rheumatology and Internal medicine units of these hospitals. HCV infection was defined by positive serum antibodies against HCV detected by Enzyme linked Immunosorbent Assay (Abbot Architect i1000SR immunology analyser, Abbott, France), followed by positive RNA plasma detection of viral particles, quantified by Polymerase Chain Reaction (Cobas Tagman, Roche). Genotype specification was done using Immunoblot Genolipa, Bayer. Patients with Human Immunodeficiency Virus (HIV) or Hepatitis B Virus (HBV) infection and patients on antiviral treatment were not included in this study. For each eligible patient, socio-demographic, clinical and biological data relevant to the study comprising age, sex, past medical history of rheumatologic disease, symptoms relevant to musculoskeletal disease, as well as hepatic tests (transaminases), HCV RNA viral load and genotype, Antinuclear Antibodies (ANA), Rheumatoid Factor (RF), and Anti-Citrullinated Peptide Antibodies (ACPA). HCV RNA viral loads were later stratified: below 800,000 IU/ml were considered low and above 800,000 IU/ml were considered high. Categorical variables were presented as percentages of the total study population and continuous variables presented as mean and standard deviation. Statistical significance was considered at p values < 0.05.

Results

Out of 148 patients with HCV infection seen during the study period, 62 were eligible for the study (Figure 1). Among the studied patients, 37/62 (59.7%) were female (Table 1).

Figure 1: Flow chart of patient selection

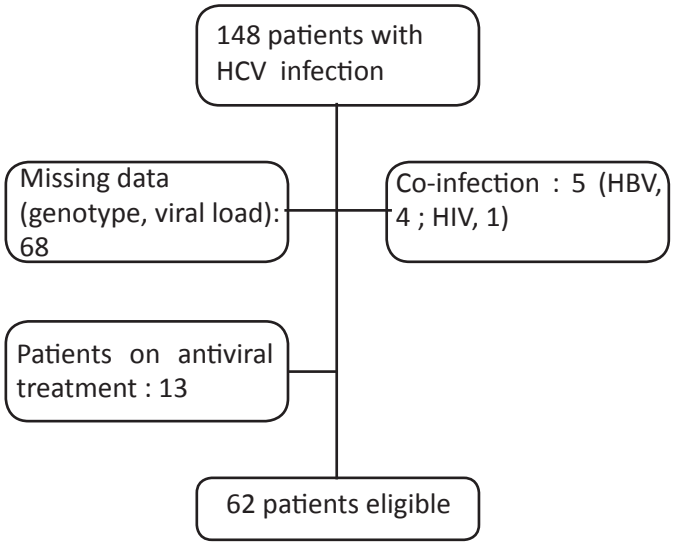

Table 1: Baseline characteristics of patients included in this study

Characteristics	No. (%)
Age, median [Interquartile range]	54 (28 – 76)
Female/male, n (sex ratio)	37/25 (1.7:1)
Viral genotype(n=62)	
Genotype 1,	31(50%)
Genotype 2,	9 (14.6%)
Genotype 3,	1 (1.6%)
Genotype 4,	20 (32.2%)
Genotype 5,	1 (1.6%)
Viral load (n=57)	
< 800,000 IU/mL	34 (59.6%)
≥ 800,000 IU/mL	23 (40.4%)

Fifteen patients (24.2%) had rheumatologic manifestations related to HCV infection all of whom had arthralgia 15/62 (24.2%). The diagnosis of HCV infection in these patients with rheumatologic manifestations was made during routine medical check-up in 6/15 (40%) of patients and in 9/15 (60%) of patients because of symptoms and/or signs that motivated testing for HCV. In the study population, arthritis was 6/62 (9.7%), myalgia was 9/62 (14.5%), bone pain was 4/62 (6.4%), sicca syndrome was 3/62 (4.8%), and Raynaud's phenomenon 6/62 (9.7%) (Figure 2).

Figure 2: Presenting complaints of HVC

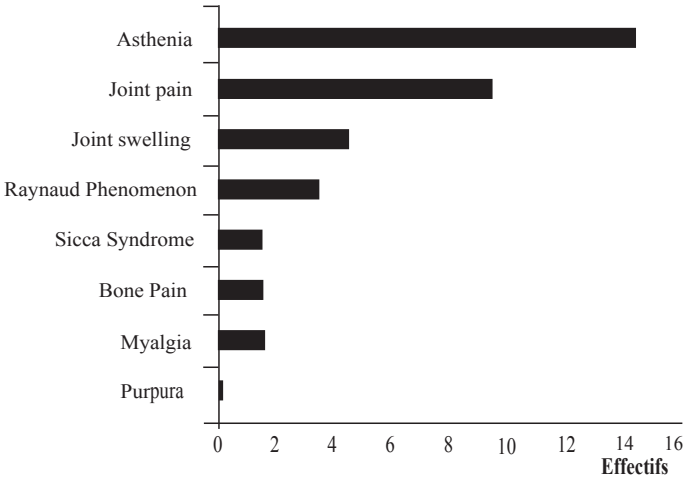

Table 2: Rheumatologic manifestations according to genotype

	Genotype 1 (n=8)	Genotype 2 (n=2)	Genotype 3 (n=2)	Genotype 4(n=3)
Arthralgia	8	1	1	2
Arthritis	3	1	0	0
Myalgia	4	2	0	2
Bone pain	2	0	0	2
Sicca syndrome	1	0	0	1
Raynaud's phenomenon	2	1	0	1

One genotype could present one or more rheumatologic manifestations

Among patients with arthralgia, the joint areas affected included: hands 12/15 (80%), knees 11/15 (73.3%), spine 8/15 (53.3%) and shoulder 7/15 (46.7%). RF, ANA and ACPA were done in some patients among whom RF was found in 4/8 (50%), ANA in 2/4 (50%) and ACPA in 1/3 (33.3%) tested patients respectively. One patient fulfilled the 1987 American College of Rheumatology (ACR) criteria for rheumatoid arthritis and another one the 1997 ACR criteria for systemic lupus erythematous. HCV genotype 1 was the most common in the study population (Table 1). Genotype and viral loads were not statistically significantly associated to presence of rheumatologic manifestations and were not associated with the genotype (p=0.17 and 0.98 respectively).

Discussion

To the best of our knowledge, our study is the first to describe prevalence and characteristics of rheumatologic manifestations in HCV-infected patients in sub-Saharan Africa. Our finding of a prevalence of rheumatologic manifestations in our HCV-infected patients to be 24.2% is not different to those reported in Western countries where it ranges from 19% to 31% [6-9]. In Egypt, a country with the highest burden of HCV infection in Africa, the overall estimated prevalence of rheumatologic manifestations of HCV infection was 16.39%[10]. In our study population, the diagnosis of HCV was made in the presence of nonspecific symptoms in 60% of patients with asthenia and musculoskeletal complains being the leading symptoms which is higher than 25% found in patients with extra-hepatic symptoms described as initial manifestations of HCV infection[9]. Though we found many patients to have symptoms that could be related to HCV, arthralgia, myalgia, arthritis, and Raynaud's phenomenon were the most common musculoskeletal manifestations as described in other studies[6-8]. Inflammatory arthralgia and arthritis were almost exclusively found in small joints of the hand. Two of our patients fulfilled classification criteria of RA and SLE. Rheumatologic manifestations of HCV infection can mimic some chronic inflammatory rheumatic diseases as RA, SLE, polymyositis, and Sjögren syndrome[6,11,12]. More so, the onset of arthritis has been reported in about 2 to 3% of HCV infected patients making the distinction from classical RA difficult. However, the presence of cyclic citrullinated peptide antibody is considered a discriminatory marker between RA and chronic HCV related arthritis[13]. Though patients in our study population were not tested for the presence of cryoglobulins, none was found to have clinical signs of small-vessel vasculitis amongst which purpura, livedo reticularis, distal ulcers and glomerulonephritis which are commonly associated with cryoglobulinemia. Two patients had Raynaud's phenomenon and one a Sicca syndrome.

Genotype 1 was the most common in our patients with rheumatologic manifestations. This could simply be reflecting the prevalence of this genotype in the general population in Cameroon[14]. Though common, this genotype was not statistically associated with rheumatic disorders. Contrary to expectation, this could suggest that rheumatologic manifestations could not be due to the direct effect of the virus; else we should have expected to see more in genotype 1 patients. Though viral load was not associated with an increase in rheumatologic manifestations, more manifestations were found in patients with low viral loads. Our finding is in favour of previous evidence that suggested that viral load or viral replication is not involved in the occurrence of rheumatologic manifestations[15]. Also, interferon reduces the prevalence of rheumatologic manifestations independently to viral response[16].

Our study had some limitations. Being a hospital based hospital study with few patients precludes generalization. Secondly, financial and laboratory limitations rendered it difficult to detect autoantibody profile in all patients (ANA, RF, and ACPA) and these were done only in patients with high suspicion of autoimmune disease, meaning that some patients with autoimmune diseases in our study population might have been missed.

Conclusion

Rheumatologic manifestations are frequent in HCV infection and may even be a diagnostic lead to HCV infection and therefore patients presenting with nonspecific rheumatologic manifestations should also be screened for HCV. HCV infected patients with rheumatologic manifestations should also be worked up for autoimmune antibodies because they could be associated.

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