

## The Significance of Articular Hand Manifestations in Chronic HCV Patients

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Received: July 3, 2014 Revised: September 10, 2014

Accepted: September 11, 2014

Published online: November 21, 2014

### ABSTRACT

**AIM:** To evaluate the significance of rheumatic hand manifestations in chronic HCV patients.

**METHODS:** Two hundred and ninety seven HCV patients were subjected to history taking, clinical examination, laboratory investigations including erythrocytic sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), antinuclear antibody (ANA) and anti-cyclic citrullinated peptide (Anti-CCP) and plain X-ray for hands and wrists.

**RESULTS:** The range of patients' age was 18-82 years (43.97±13.56). Their disease duration ranged from 6 months to 25 years (7.3+5.6). Hand affection was present in 137 patients (46.1%). The most frequent hand manifestations were arthralgia (28.6%), tenosynovitis (10.1%), Raynaud's phenomenon (9.1%), and arthritis (5.1%), while laboratory abnormalities were RF in (38.4%), ANA in (6.4%), cryoglobulins in (9.4%) and Anti-CCP in (1.3%). Female gender was the most important risk factors for hand manifestations. The patterns

of arthritis in chronic HCV patients were non deforming polyarticular arthritis that affected the small joints of the hands and oligoarthritis.

**CONCLUSION:** Our study strongly supports a direct role of HCV in inducing rheumatic hand manifestations and autoantibodies in chronic HCV patients, but it is mostly non-deforming and non-significant. Surveillance is needed for the detection of rheumatic manifestations and autoantibodies with occasional multidisciplinary team (hepatologist and rheumatologist) approach to HCV patients for early diagnosis and treatment. A long term follow up study for rheumatological manifestations in HCV patients is recommended to reduce health disparities.

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**Key words:** HCV; Rheumatoid factor; CRP; ANA; Arthritis

Bassyouni HM, El Dahan MA, Zaky KA, El Aziz AAA, El-Atrebi KA, Saad AMA, El-Bassyouni HT. The Significance of Articular Hand Manifestations in Chronic HCV Patients. *Journal of Gastroenterology and Hepatology Research* 2014; 3(11): 1344-1348 Available from: URL: <http://www.ghrnet.org/index.php/joghr/article/view/921>

### INTRODUCTION

Hepatitis C virus (HCV) is the second most common chronic viral infection in the world, with over 180 million cases worldwide and a global prevalence of about 3%<sup>[1]</sup>. Egypt has the highest prevalence of HCV that is estimated to be as high as 22%<sup>[2]</sup>. In addition to hepatic complications, hepatitis C virus (HCV) infection is reported to predispose to extrahepatic disorders involving renal, dermatologic, hematologic and rheumatologic systems<sup>[3,4,5]</sup>.

Articular involvement in HCV infection is a frequent complication varying from 4 to 23% and the clinical picture of HCV related arthropathy varies widely, ranging from polyarthralgia to monoarticular or oligoarticular intermittent arthritis and symmetric chronic polyarthritis<sup>[4,5,6]</sup>. HCV associated arthritis in contrast to RA has a benign course, typically not deforming and not associated with

articular bony erosions involving predominantly small joints of the hands (metacarpo-phalangeal, proximal interphalangeals, and ankles) [7].

Mixed cryoglobulinaemia (MC) among all rheumatic manifestations is the most common in HCV infection, it presents clinically as mononeuropathy or polyneuropathy, is mostly sensory and is characterized by numbness, burning skin crawling and pruritus, predominantly in the hands and feet<sup>[8,9]</sup>. Mixed cryoglobulinaemic vasculitis may also lead to Raynaud's Syndrome<sup>[10]</sup> and Sicca Syndrome<sup>[11]</sup> and glomerulonephritis<sup>[12]</sup>.

Many rheumatologic manifestations associated with HCV infection include arthralgia, myalgia, arthritis, vasculitis, sicca symptoms, mixed cryoglobulinemia (MC) and fibromyalgia and associations have been reported between HCV infection and other autoimmune diseases including systemic lupus erythematosus, Sjogren's syndrome, and antiphospholipid antibody syndrome (APS)<sup>[13-16]</sup>.

Musculoskeletal pain is the most frequently described complaint among HCV patients, with descriptions of arthralgia, myalgia, fibromyalgia, and arthritis<sup>[17]</sup>.

The most common cause of arthritis in HCV patients is the coexistence of inflammatory [Rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and Sjögren syndrome (SS)] or non-inflammatory rheumatic disorder such as fibromyalgia. Some of these rheumatic disorders often share clinical manifestations and laboratory findings with chronic HCV infection without articular manifestations such as sialadenitis, generalized fatigue, positive Rheumatoid factor (RF) (40% to 65%), cytopenias, antinuclear antibodies (ANAs) (10%), or low C4 levels<sup>[18-20]</sup>. Certain laboratory findings such as anti-cyclic citrullinated peptide (anti-CCP) for RA, anti-dsDNA for SLE, and anti-Ro/La for SS and radiological (erosive changes in RA) findings are helpful for the differential diagnosis<sup>[21-23]</sup>.

## METHODS

### Patients

Two hundred and ninety seven patients with HCV were recruited randomly from the outpatient's clinic of hepatitis C, National Hepatology and Tropical Medicine Research Institute (NHTRI), Egypt. Consents were taken from all the patients enrolled in the study. All patients were subjected to a thorough history taking, meticulous clinical examination with special emphasis on hand examination, laboratory and radiological examination. HCV antibodies and HCV RNA PCR positive patients for more than 6 months duration were included in the study. Patients less than 18 years old, hepatitis B virus or HIV infection, patients treated with interferon, thyroid dysfunction, diabetics, high serum uric acid and history of alcohol intake were excluded.

Laboratory testing included: Anti-HCV antibodies (Anti-HCV Ab) tested in human serum by using ELISA technique (Sunrise basic Techan, GmbH, Austria) also AST, ALT, bilirubin level and albumin were measured by autoanalyser. C-reactive protein (CRP) and Rheumatoid factor (RF) were estimated by the latex agglutination method in the serum and titer by dilution with positive samples with titers more than 6 U/ml and titers more than 8 U/mL respectively. Cryoglobulins were identified by the Winfield method<sup>[24]</sup>. Indirect immunofluorescence was used for the detection of antinuclear antibody (ANA). Polymerase chain reaction (PCR) was done with COBAS AmpliPrep/COBAS TaqMan system which is an in vitro nucleic acid amplification test for the quantitation of hepatitis C viral RNA in human plasma or serum of HCV-infected individuals using the COBAS AmpliPrep instrument for automated

specimen processing and the COBAS TaqMan 48 Analyzer (USA) for automated amplification and detection with threshold detection of 10 IU/ml and reagents was version 2 of Cobas Amplicore HCV monitor<sup>[25]</sup>. Anti-CCP antibody kit was based on an ELISA method using the immunoscan CCPlus test kit 3rd generation (Euro diagnostica AB, Malmö, Sweden, 2011). Plain radiography of the hands and wrists (X-ray) were conducted for all patients.

### Statistical

Statistical Analysis of data was done by computer using Epi-info. Software, version 6.04. A word processing, data base and statistics program (WHO, 2004). The tests used were  $\chi^2$  test (Chi square test) to test statistical significant relation between different variable or grades, Z test to test statistical significant difference between two percentages and Pearson's correlation test (correlation coefficient r) to test a positive or negative linear relationship between two variables (one dependent and the other is independent variable).

## RESULTS

A total of 297 chronic HCV patients were studied, 161 (54.2%) were males and 136 (45.8%) females. Their ages varied between 18 to 82 years with a mean $\pm$ SD (43.97 $\pm$ 13.56). Classification was done using PCR and was as followed; patients with low viremia <100.000 IU/mL (1) were 96 (32.3%), those with moderate viremia  $\geq$ 100.000 (2) and <1,000.000 IU/mL were 112 (37.7%) and those with high viremia  $\geq$ 1,000.000 IU/mL (3) were 89 (29.9%).

Hand abnormalities were recognized in 137 patients (46.1%) while 160 (53.9%) HCV patients showed no hand abnormalities. The most frequent hand manifestations were arthralgia 85(28.6%), followed by tenosynovitis (10.1%) in the flexor tendons of the hands, Raynaud's phenomenon (9.1%), and finally arthritis (5.1%) as shown in table 1.

**Table 1** Clinical manifestations in the hands of patients.

	Negative (%)	Positive (%)
Arthritis	282 (94.9%)	15 (5.1%)
Arthralgia	212 (71.4%)	85 (28.6%)
Tenosynovitis	267 (89.9%)	30 (10.1%)
Raynaud's	270 (90.9%)	27 (9.1%)

Patients who had arthritis in their hands had the rests of their joints examined as well. From the 15 patients with hand arthritis 3 were oligoarticular and 12 patients had polyarthritis; 7 of whom had a non-erosive symmetrical polyarthritis while, only 5 patients out of the 12 had rheumatoid arthritis that fulfilled the 1987 ACR classification criteria.

As shown in table 2, Rheumatoid factor (RF) was positive in 114 (38.4%) patients and negative in 186 (61.6%) patients. Also, cryoglobulins was found in 28 patients (9.4%). Anti-CCP was positive in 4 patients of the whole study (1.3%) who proved to have RA and it was negative in HCV related polyarthritis and cryoglobulinemia. Furthermore, ANA was positive in 19 patients (6.4%).

**Table 2** Laboratory abnormalities in studied patients.

	Negative (%)	Positive (%)
RF	183 (61.6%)	114 (38.4%)
anti-CCP	293 (98.7%)	4 (1.3%)
ANA	278 (93.6%)	19 (6.4%)
Cryoglobulin	269 (90.6%)	28 (9.4%)

There was no significant correlation between the level of viremia by PCR and the rheumatic manifestations in the hands except in case of Raynaud's where the relation was significant ( $p < 0.05$ ) as shown in table 3. Female predominance in both clinical manifestations and laboratory findings, some of this differences were highly significant (arthralgia and Raynaud's phenomena as well as RF and cryoglobulin) or only significant (ANA), others were non-significant (arthritis, tenosynovitis and anti-CCP) table 4. Arthralgia was the most common symptoms in both female (39.7%) and male (19.3%), Raynaud's phenomena was the lowest clinical manifestation in male HCV patients (1.9%) and was in 17.6% of females as a second common manifestations in females, tenosynovitis was in 11% in females and 9.3% in males while, arthritis was in 7.4% of females and in only 3.1% of males. The arthritis was positive in 7.4% of the females and in only 3.1% of the males. On the other hand, RF was highest in both females (51.5%) and males (27.3%), while the lowest laboratory investigation in both males was anti-CCP in only 0.6% and in just 2.2% of females. ANA and cryoglobulins were in only 3.1% and 3.7% in males and in 10.3% and 16.2% of females. The relation between clinical manifestations and laboratory findings was shown in table 5. The RF was positive in all cases having arthritis (15 cases), but in arthralgia was found in 58.8% of all cases, these two relations were highly significant. In tenosynovitis and Raynaud's the RF was found in only 13.2% of the cases for each, but the only difference was significant relation with Raynaud's and non-significant relation with tenosynovitis. The anti-CCP was positive in only 4 (100%) cases out of the 15 patients who had arthritis, similarly was positive in 4 (100%) cases out of the 85 patients who had arthralgia (those 4 cases were the cases who had arthritis), these relations were highly significant. On the other hand, anti-CCP was positive in only one case (25%) of Raynaud's and was negative in all patients with tenosynovitis, these relations were non-significant. The ANA was negative in all patients who had arthritis, but positive in arthralgia, tenosynovitis and Raynaud's with non-significant relation in 4 patients (21.1%), 1 (5.3%) and 2 (10.5%) respectively. Cryoglobulin was positive non-

**Table 3 Hand manifestations in relation to different levels of HCV viremia.**

	PCR = 1(9%) Number (%)	PCR = 2 (112) Number (%)	PCR = 3 (89) Number (%)	Total	P
Arthritis	4 (26.7%)	5 (33.3%)	6 (40.0%)	15	>0.05
Arthralgia	28 (32.9%)	34(40.0%)	23 (27.1%)	85	>0.05
Tenosynovitis	10 (33.3%)	16 (53.3%)	4 (13.3%)	30	>0.05
Raynaud's	9 (33.3%)	5 (18.5%)	13 (48.1%)	27	<0.05*

$P < 0.05$  Significant\*

**Table 4 The difference between males and females in both laboratory findings and clinical manifestations.**

		Male (161)	Female (136)	P
RF	Negative	117 (72.7%)	66 48.5%	<0.001**
	Positive	44 (27.3%)	70 51.5%	
anti-CCP	Negative	160 (99.4%)	133 97.8%	> 0.05
	Positive	1 (0.6%)	3 2.2%	
ANA	Negative	156 (96.9%)	122 89.7%	<0.05*
	Positive	5 (3.1%)	14 10.3%	
Cryoglobulin	Negative	155 (96.3%)	114 83.8%	< 0.001**
	Positive	6 (3.7%)	22 16.2%	
Arthritis	Negative	156 (96.9%)	126 92.6%	>0.05
	Positive	5 (3.1%)	10 7.4%	
Arthralgia	Negative	130 (80.7%)	82 60.3%	< 0.001**
	Positive	31 (19.3%)	54 39.7%	
Tenosynovitis	Negative	146 (90.7%)	121 89.0%	> 0.05
	Positive	15 (9.3%)	15 11.0%	
Raynaud's	Negative	158 (98.1%)	112 82.4%	< 0.001**
	Positive	3 (1.9%)	24 17.6%	

$P < 0.05$  Significant\*,  $P < 0.01$  Highly Significant\*\*.

significant relation in only 2 (7.1%) cases, 15 (53.6%) cases, 4 (14.3%) cases and 18 (64.3%) cases of arthritis, arthralgia, tenosynovitis and Raynaud's respectively as a clinical manifestations in HCV patients. Twelve cases (4%) had x-ray abnormalities in the form of hand erosions and narrow joint spaces, while (96%) were normal. Table 6 showed highly significant relation between hand erosions and arthritis ( $p < 0.001$ ) and significant relation between it and arthralgia ( $p < 0.01$ ), while no significant relation with tenosynovitis or Raynaud's.

Radiographic abnormalities in the form of hand erosions and hand joint space narrowing were present in only 4 cases (1.3%) who also were positive anti-CCP, importantly, the same 4 cases of arthritis had arthralgia and were diagnosed as RA, while isolated joint space narrowing were found in 6 patients (2%).

**Table 5 The relation between hand manifestations and laboratory findings.**

		RF - (183)	RF+ (114)	P
Arthritis	Negative	183 (100.0%)	99 (86.8%)	< 0.001**
	Positive	0 (0.0%)	15 (13.2%)	
Arthralgia	Negative	165 (90.2%)	47 (41.2%)	<0.001**
	Positive	18 (9.8%)	67 (58.8%)	
Tenosynovitis	Negative	168 (91.8%)	99 (86.8%)	> 0.05
	Positive	15 (8.2%)	15 (13.2%)	
Raynaud's	Negative	171 (93.4%)	99 (86.8%)	≈ 0.05*
	Positive	12 (6.6%)	15 (13.2%)	
		Anti-CCP -(293)	Anti-CCP + (4)	
Arthritis	Negative	282 (96.2%)	0 (0.0%)	< 0.001**
	Positive	11 (3.8%)	4 (100.0%)	
Arthralgia	Negative	212 (72.4%)	0 (0.0%)	< 0.01*
	Positive	81 (27.6%)	4 (100.0%)	
Tenosynovitis	Negative	263 (89.8%)	4 (100.0%)	> 0.05
	Positive	30 (10.2%)	0 (0.0%)	
Raynaud's	Negative	267 (91.1%)	3 (75.0%)	>0.05
	Positive	26 (8.9%)	1 (25.0%)	

$P \approx 0.05$  almost Significant\*,  $P < 0.01$  Highly Significant\*\*.

**Table 6 The relation between hand manifestations and X-ray findings in the study group.**

	No Hand erosion (293) Number (%)	Hand Erosion (4) Number (%)	P
Arthritis	11 (73.3%)	4 (26.7%)	<0.001**
Arthralgia	81 (95.3%)	4 (4.7%)	<0.01**
Tenosynovitis	30 (100.0%)	0 (0.0%)	>0.05
Raynaud's	26 (96.3%)	1 (3.7%)	>0.05

$P < 0.01$  Highly Significant\*\*.

## DISCUSSION

Hepatitis C virus is a worldwide major health problem. Patients infected with HCV might develop at least one extrahepatic manifestation in 40-74% of cases during the course of the disease<sup>[26]</sup>, rheumatologic manifestations are among the most frequent. Many rheumatologic manifestations associated with HCV infection include arthralgia, myalgia, arthritis, vasculitis, sicca symptoms, mixed cryoglobulinemia (MC), and fibromyalgia<sup>[27,28]</sup>. Hand manifestations in the form of arthralgia and arthritis are the main extrahepatic manifestations in patients with HCV affecting mainly the metacarpophalangeal joints, wrists and proximal interphalangeal joints<sup>[29]</sup>. However, the decision of treatment may be difficult and hazardous as patients with RA require more aggressive therapy<sup>[30]</sup>.

In this study, arthralgia was detected in 85 patients (28.6%), Sené *et al*<sup>[31]</sup> similarly found that 24% of patients had arthralgia as one of the rheumatologic manifestations in HCV patients and Gonzalez-Lopez *et al*<sup>[32]</sup> found that arthralgia was present in 42.2% of his study.

In contrast, El-Attar *et al.*<sup>[28]</sup> studied 40 HCV patients and documented arthralgia in 65% of their patients, this high percentage may be explained by the small number of the study and arthralgia is considered a symptom rather than sign.

In our study, arthritis was present in 5.1% with symmetric polyarthritis affecting the small joints of the hands and wrists in 80% of those patients while waxing and waning oligoarthritis was found in 20%. Buskila *et al.*<sup>[27]</sup> reported arthritis in 4% of the chronic HCV patients. However, Nissen and colleagues<sup>[33]</sup> noted that arthritis was found in 12.2% of HCV patients. In this study, the pattern of arthritis was symmetric polyarthritis resembling RA in two thirds of polyarthritis patients (4 of them were diagnosed as RA and HCV), while oligoarthritis was present in the remaining third. This finding was confirmed in a previous study by Rosner<sup>[34]</sup> who found that rheumatoid-like arthritis was present in two thirds of the HCV patients. Similarly Agarwal<sup>[6]</sup> emphasized that HCV can induce arthritis mimicking RA and that symmetric arthritis is the most common affecting almost 70-80% of the patients.

In our series, Raynaud's phenomenon was found in (9%) of patients. This is in consistence with the study of Stefanova-Petrova *et al.*<sup>[35]</sup> and Nissen *et al.*<sup>[33]</sup> who observed similar results.

It was found in this study that cryoglobulins was present in 9.8% that is similar to some reports who found that cryoglobulinemia was present in 11% but less than others<sup>[9,24,35,36]</sup>. This may be ascribed to differences in ethnicity and geographic distribution.

Rheumatoid factor positivity was found in 38.4% of patients, and only 4 cases were proved to be Rheumatoid arthritis, a finding similarly found by Sené *et al.*<sup>[31]</sup> in which 33% of chronic HCV patients were RF positive and the same results were also found in another study<sup>[35]</sup> with 44% of their patients were RF positive. A lower prevalence (14%) was found by Lee *et al.*<sup>[10]</sup> and this has been attributed to the small number of patients in their study and the difference in ethnicity and genetics.

Furthermore, the prevalence of anti-CCP antibodies was 1.3% which agrees with another study in which the prevalence was 3.3%<sup>[35]</sup>. This is in accordance with the findings of Sené *et al.*<sup>[31]</sup>, who found anti-CCP to be positive in 1.4% of their patients, similarly Al-Dahshan reported anti-CCP in 2% of 100 HCV patients<sup>[37]</sup>. Zeynel *et al.*<sup>[38]</sup> declared that anti-CCP antibodies are a better diagnostic laboratory marker present in 4.5% of patients in whom HCV-related arthritis is diagnosed.

Female sex was the most frequent risk factor for hand affection in HCV patients especially polyarthralgia, Raynaud's phenomena, and RF which came confirmatory to two previous studies were female gender was regarded as one of the risk factors for extrahepatic manifestations<sup>[11,37,39]</sup>. It was found in the study that erosive changes in the hand and joint space narrowing detected by hand X-ray was found in 4% of the studied patients, but it was restricted to RA patients.

In two previous studies by Rosner *et al.*<sup>[34]</sup> and Zuckerman *et al.*<sup>[40]</sup>, it was concluded that HCV-RA is non-erosive and non-deforming in contrast to patients with co-existent RA. In contrast to this, an Italian study by Fadda and colleagues<sup>[41]</sup> delineated that erosive arthritis was present in 30.4% of the detected arthritis patients.

Our study shows that the viral load had no impact on the hand manifestations confirming previous studies who found that there was no correlation between viral load and extrahepatic manifestations<sup>[11,41,42]</sup>.

In conclusion, the study emphasizes the important role of HCV in inducing rheumatic hand manifestations and autoantibodies in chronic HCV patients, but it is mostly non-deforming and non-significant. Therefore, surveillance for the occurrence of the rheumatic mani-

festations as well as testing for the autoantibodies with occasional multidisciplinary team (hepatologist and rheumatologist) approach to HCV patients for early diagnosis and treatment is needed. A long term follow up study for rheumatological manifestations in HCV patients is recommended.

## CONFLICT OF INTEREST

The authors have no conflicting financial interests.

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