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Anti Cyclic Citrullinated Peptide and Rheumatoid Factor in Patients with HCV Arthropathy

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Abstract

Background: HCV related arthritis is not uncommon and both diagnosis and treatment is challenging and the role of anti cyclic citullinated peptide (Anti CCP) in the diagnosis of HCV arthropathy is unknown.

Materials and methods: A case control Prospective study conducted on 60 patients known to have chronic hepatitis C infection with arthropathy (Study group) and 20 healthy subjects as control group.

Results: The most frequent affected joint in the study was PIPs 32 (53.3%) followed by MCPs joint in 26 (43.3%) while the least frequent joint was the elbow that was affected in only one patient (1.7%). Ten patients (16.6%) had picture of arthritis while 50 (83.4%) had arthralgia. Serum RF in our study it was positive in 16 (26.6%) with low titre with mean 77.01 ± 11.05 (nine of these patients had arthralagia with mean 68.09 ± 13.44, and seven patients had arthritis with mean 80.77 ± 11.45).The prevelance of total cases with positive cryoglobulinemia had estimate about 26 (43.33%). The Anti ccp among HCV arthropathy and we found that about (8 patients 13.33%) have low positive titer for Anti ccp with mean 15.77 ± 5.05.

Conclusion: Anti cyclic citrunated peptide can be detected among patients with HCV arthropathy with positive low titer.

Keywords: Hepatitis c virus; Arthropathy; Anti cyclic citrunated peptide; Rheumatoid factor; Cryoglobulinemia

Introduction

About 3% of the world population has been infected with HCV and this according to world health organization. The highest prevalence has been reported from Egypt where the main HCV genotype is type IV [1].

Joint manifestations in patients with chronic HCV infection can be encountered in four different forms: a coexistent arthropathy (not related to HCV), arthritis in the setting of mixed cryoglobulinemia, arthritis directly related to HCV (HCV associated arthritis), and arthritis induced by antiviral therapy [2]. Cryoglobulinemia which associated with HCV increase the risk of joint affection and may have role in its pathogenesis [3].

RFs can be found in 40-50% of patients with HCV infection.Their production is probably due to chronic stimulation of the immune system by HCV, also RFs are frequently detected in patients with systemic autoimmune diseases, such as systemic lupus erythematosus, mixed connective tissue disease [4].

Citrulline antibody is an immune protien that bind with non standard amino acid citrulline. Anti cyclic citrullinated peptide (Anti ccp) antibodies have high specificity for RA. In addition to their diagnostic properties, anti-CCP antibodies have also been shown to be good prognostic markers, as they help predict the erosive or non-erosive progression of the disease and anti-CCP antibodies are usually present early in the course of RA [5].

Recent studies have shown that anti-CCP antibodies are present in 4.5% to 7% of patients in whom HCV-related arthritis is diagnosed [6].

Materials and Methods

Study design

Prospective study included 60 patients known to have chronic hepatitis C infection with arthropathy (Study group) and 20 healthy subjects as control group. From January 2016 and January 2017 at Rheumatology unit, Internal Medicine department, Assiut University Hospitals.

Patients

Inclusion criteria: All HCV patients with arthropathy.

Exclusion criteria : Rheumatoid arthritis patients previously diagnosed and fulfilling American collage criteria 2010. Deformed joint affection.

Clinical data

Thorough medical history and clinical examination of 60 HCV patients with arthropathy, with special focus on rheumatologic manifestation.

- onset, course and duration of joint affection.

-pain site, character, timing. Relation to movement.

- Number and sequence of joint involvement.

-presence of myalgia, lower limb vasculitic rash.

-presence of morning stiffness for more than one hour.

Laboratory investigation

After taking the acceptance of the patients, Venous samples were withdrown to do the following investigations at assuit university:

Liver Function Test (LFT) (albumin, liver enzymes, prothrombine time, prothrombine concenteration).

HCV Antibody.

Patients with HCV infection were diagnosed by the presence of HCV antibodies.

Polymerase Chain Reaction for HCV (PCR HCV).

C Reactive Protein (CRP), Erythrocyte Sedimentation Rate (ESR).

Serum cryo globulins.

Detection of cryoglobulinemia Venous blood was taken from fasting patients. It was collected in pre-warmed tubes, immediately transferred to 37°C, and allowed to clot at this temperature. The serum was separated by centrifugation at 37°C. The supernatant was removed from the serum. The serum was stored at 4°C for 8 days and examined daily for cryoprecipitation.

Rheumatoid factor

The Sera obtained from 60 patients with hcv arthropathy and 20 control group previously stored at -80°C evaluated for RF.

Anti cyclic citrullinated peptide

The Sera obtained from 60 patients with hcv arthropathy and 20 control group previously stored at -80°C were evaluated for anti-CCP antibodies Table 1.

	All patients (n=60)	Control group (n=20)
Age (years)		
Range	29-64	33-63
Mean ± SD	48.56 ± 7.9	50.09 ± 8.1
Gender		
Male	25 (41.7%)	11 (55%)
Female	35 (58.3%)	9 (45%)
Blood pressure (mmHg)		
Systolic (mean ± SD)	130 ± 15	130 ± 20
Diastolic (mean ± SD)	70 ± 20	80 ± 10
Comorbidities		
Diabetes mellitus	8 (13.33%)	3 (15%)
Hypertension	4 (6.67)	2 (10%)
Ishaemic heart disease	1 (1.7%)	0
Chronic kidney disease	0	0
Continuous data was expressed in form of mean SD while nominal one in form of frequency (%).		

Table 1: Demographic data of studied subjects.

Patients were considered to be anti-CCP positive when the absorbance was higher than the cutoff value of the kit (10 U/mL). Values <10 U were considered negative, while values between 10 and 19 U were considered "weakly" positive, 20-39 U "moderately" positive, and >40 U "strongly" positive.

Statistical analysis

Data from the results will be collected, stored and suitable stastistical analysis will be done. Analysis of the data was performed and statistical analysis using the SPSS software (version 16).

Results

It was noted that the most frequent affected joint in the study was PIPs -32 (53.3%) followed by MCPs joint in 26 (43.3%) while the least frequent joint was the elbow that was affected in only one patient (1.7%). Laboratory data of studied patients with chronic HCV infection and arthropathy (Table 2 and Figure 1). It was noticed that patients HCV infection and arthropathy had significant higher level of anti-CCP, ESR, RF, CRP, ALT and AST in compared with controls where P was <0.05. Patient with arthritis -10 (16.7%) had significant higher level of anti-CCP, ESR, RF and CRP than those with arthralgia-50 (83.3%) where P was <0.05.

Discussion

Rheumatological manifestations are relatively uncommon in HCV patients and until now the association between HCV and arthropathy is puzzling. Also the management is challenging because of the joint manifestations among HCV arthropathy are similar to RA, so HCV arthropathy can be misdiagnosed as early RA.

On the other hand, the presence of highly specific RA biomarkers such anti CCP is very helpful in the diagnosis of RA. Sixty patients with HCV arthropathy were included in this study from Assuit university hospital and to our knowledge this number is relatively large. We focus on the Rheumatological manifestation of HCV syndrome.

The mean age of study group was 48.56 ± 7.92 years, 35 (58.3%) of them were females in agreement with what was reported in the study conveyed by Stefanova-Petrova et al. [7], where they conclude that: female sex is one of the risk factors for developing extrahepatic manifestations Chronic HCV infection. Arthralgia was the commonest presentation in our study affecting fifty patients (83.3%), while arthritis was found only in ten patients (16.7%)

It was noted that the most frequent affected joint was PIP (53.3%) patient followed by MCPS (43.3%) while the least frequent joint was the elbow (1.6%) Table 2.

Joint	Number (%)
PIPs	32 (53.3%)

MCPs	26 (43.3%)
Knees	25 (41.6%)
Wrists	24 (40%)
Ankles	20 (33.3%)
Shouldrs	2 (3.3%)
Elbow	1 (1.7%)
Data was expressed in from frequency (%). PIP: Proximal Interphalangeal Joint; MCP: Meta Carpophalangeal Joint.	

Table 2: Joint inection in chronic hepatitis C infection and arthropathy.

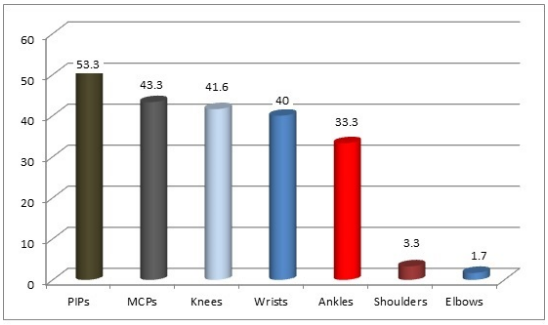

Figure 1: Frequency of joint affection in chronic HCV infection with arthropathy.

Myalgia was a common rheumatological presentation among our patients (8 patients 13.3%) having myalgia .in agreement with previous study carried out by Cacoub et al. [8] reported only 15% of 1614 patients with chronic HCV had mialgia Table 3 and Figure 2.

Clinical characteristics	Frequency (%)
Morning stiffness more than one hour	
Yes	9 (15%)
No	51 (85%)
Arthritis	10 (16.6%)
Arthralgia	50 (83.4%)
Vasculitic skin lesions	
Yes	55 (91.7 %)
No	55 (8.3%)
Myalgia	
Yes	8 (13.3%)
No	52 (86.7%)
Data was expressed in from frequency (%).	

Table 3: Specific Clinical Characteristics among the Studied Group.

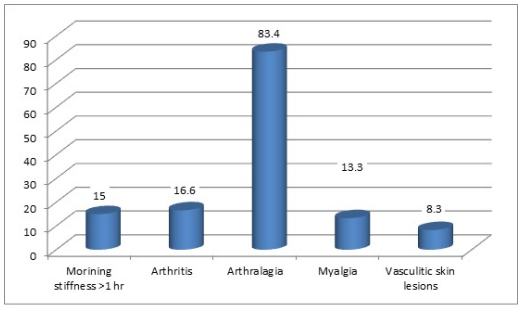

Figure 2: Specific Clinical characteristics among the studied cases.

Serum RF in our study it was positive in 16 (26.6%) with low titre with mean 77.01 ± 11.05 (nine of these patients had arthralgia with mean 68.09 ± 13.44, and seven patients had arthritis with mean 80.77 ± 11.45). The other 44 (73.3%) patients shows negative RF. there is significant difference between patient and control group (p value =0.04) also there is significant difference in RF titre between patients with arthralgia and arthritis (p value =0.03).

According to Toubi et al. [4] RF can be positive in HCV patients even without joint manifestation SO this results can give us the guidance that the positive low titer of RF can be associated with HCV arthropathy and not against its diagnosis, on the other hand we suggest the presence of high titer of RF may favor the diagnosis of RA.

We had found that 8 patients with hcv arthritis had positive serum cryoglobulins and and they had estimate about (80%) of total patients with hcv arthritis, on the other hand hcv arthralgia patients with positive serum cryoglobulin had estimate about 18 (36%) of total hcv patients with arthralgia, while the prevelance of total cases with positive cryoglobulinemia had estimate about 26 (43.33%) Table 4 and Figure 3.

Parameters	All patients	Patients with arthralgia	Patients with arthritis	Control group	P1 value	P2 value
No.	60	50	10	20		
ESR (ml/h)						
1st hour	28.5 ± 5.19	24 ± 5.09	31.34 ± 9.01	12 ± 2.01	0	0
2nd hour	40.11 ± 12.04	34.1 ± 8.11	50.56 ± 16.11	22 ± 3.11	0.01	0
AST (U/L)	79.99 ± 11.14	76.99 ± 12.94	80.11 ± 13.04	34.08 ± 5.53	0.04	0.99
ALT (U/L)	85 ± 10.42	84.11 ± 12.09	86 ± 11.23	37.16 ± 7.11	0.02	0.54
CRP					0	0
No. (%) of +ve cases	49 (81.67%)	41 (82%)	8 (80%)	0 (0%)		
Mean ± SD	8.48 ± 2.57	9.48 ± 2.57	15.98 ± 2.33	2 ± 1.33		

RF					0.04	0.03
No. (%) of +ve cases	16 (26.6%)	9 (18%)	7 (70%)	0 (0%)		
Mean ± SD	77.01 ± 11.05	68.09 ± 13.44	80.77 ± 11.45	6.1 ± 1.15		
ACCP					0	0.02
No. (%) of +ve cases	8 (13.33%)	3 (6%)	5 (50%)	0 (0%)		
Mean ± SD	13.77 ± 5.05	12.36 ± 4.04	14.01 ± 6.04	4.01 ± 0.04		
Cryoglobulin					0.04	0
No. (%) of +ve cases	26 (43.33%)	18 (36%)	8 (80%)	0 (0%)		

Table 4: Laboratory Data of Studied Cases and Controls.

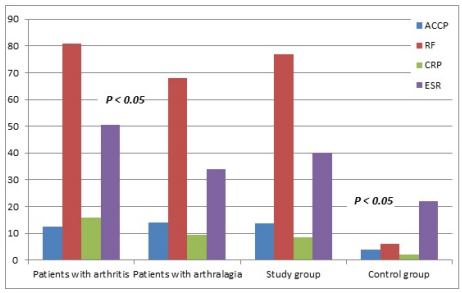

Figure 3: Laboratory Data of both Studied Groups where data expressed in form of mean.

The main corner stone of our study is to evaluate the Anti ccp among HCV arthropathy and we found that about (8 patients 13.33%) have low positive titer for Anti ccp with mean 15.77 ± 5.05.

On the other hand five positive cases for AntiCCP (mean 14.01 ± 3.04) have arthritis, While the other three positive patient for anti CCP have arthralagia (mean 12.36 ± 2.04) and this was agreement with Bombardieri et al., where anti-CCP positivity in patients with HCV was borderline [9].

Ethical aspects

This study was approved by the Ethical Committee of Assiut University Hospital.

Funding

No fund has been received.

Conflict of interest

No Conflict of interest could be declared.

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