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BRIEF REPORT

Frequency of hepatitis C in patients with rheumatoid arthritis

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ABSTRACT

Background: Hepatitis C virus (HCV) infection has been explained as a disease that sometimes present with rheumatic manifestations indistinguishable from rheumatoid arthritis. This study has been performed to evaluate the frequency of hepatitis C virus infection in a group of patients with rheumatoid arthritis.

Patients and methods: In this study, during one year, serum samples collected from two hundred consecutive patients with rheumatoid arthritis in all affiliated hospitals of Shaheed Beheshti University, M.C., were examined for anti-HCV antibody and HCV-RNA by ELISA and RT-PCR method, respectively. Using a questionnaire, the frequency of HCV infection, age and sex distribution, duration of rheumatoid arthritis, associated immune mediated disorders and risk factors for hepatitis C virus infection were assessed.

Results: A total of 200 patients (M/F=26/174) who were mainly aged 51-70 years were studied. The frequency of HCV was found to be 2% (95%CI: 0.6-7%). All of the infected persons have had a low risk occupation in terms of exposure to the virus and none of them had HCV risk factors. No associated immune mediated disorder was found in HCV infected patients.

Conclusion: Our results did not support any contribution of HCV infection in the pathogenesis of rheumatoid arthritis.

Keywords: *Hepatitis C, Rheumatoid arthritis, HCV-RNA, RT-PCR.*
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INTRODUCTION

Hepatitis C virus (HCV) infection has been found to be strikingly associated with autoimmune phenomena (1). Meanwhile, it may also be involved in the pathogenesis of some lymphoproliferative disorders such as monoclonal gammopathies and B-cell lymphomas (2,3). Since HCV infection can be accompanied by or be the cause of a number of autoimmune disorders (1,4), it is suggested that HCV infection should be included as one of the causes in patients with unexplained rheumatological symptoms (5). Arthropathy is a common extrahepatic manifestation associated with HCV infection, affecting up to 20% of HCV-infected individuals (6). Some authors suggest that there is an etiologic association between arthritis and hepatitis C antigenaemia (7). Serological markers of autoimmunity and clinically apparent immune-mediated nonhepatic syndromes may be present in up to 70% of patients with chronic hepatitis C infection. HCV arthritis usually runs a relatively benign course that, in contrast to 'true' rheumatoid arthritis (RA), is typically non-deforming and is not associated with articular bony erosions (6).

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Consequently, HCV infection should be considered in the differential diagnosis of patients with atypical arthritis (8).

Although a high prevalence of HCV antibodies is suspected in patients with RA, some authors believe that its occurrence may be coincidental and the interpretation of this coincidence is difficult (9,10). HCV can induce immune-complex production and also cryoglobulinemia (11); these events can explain the HCV-related arthropathy via essential type II mixed cryoglobulinemia (ECM) (3). Some investigators propose that direct invasion of synovial cells by HCV elicits local inflammatory response, particularly in genetically susceptible individuals (6).

According to great importance of HCV infection in producing rheumatologic manifestations and its non-deniable effect on disease progression in RA patients and non-identified role of HCV in pathogenesis of RA, We determined the prevalence of HCV in patients with rheumatoid arthritis.

PATIENTS and METHODS

During one-year period (2001), we collected 200 consecutive patients attending the medicine clinics of Shahid Beheshti University, M.C., hospitals. We selected the patients who fulfilled the American College of Rheumatology (ACR) criteria for RA.

All patients were counseled about the study and requested to sign an informed consent. Thereafter, all patients were given a careful physical examination and their serum samples were screened for the presence of anti-HCV antibodies. The serum samples were tested using an Amicroplate ELISA (Monolisa anti-HCV Plus version 2, Bio-Rad). All positive samples were rechecked using another ELISA technique, called Ortho HCV 3.0 ELISA test system with enhanced save. In order to confirm the reactive samples, they were checked for the second time using HCV-RNA reverse transcriptase polymerase chain reaction (RT-PCR) within the NS 5'NC gene (Amplicor HCV, Roche). Samples revealed to be positive through all three techniques were considered as HCV-positive cases. We also determined erythrocyte sedimentation rate (ESR), serum aminotransaminase, alkaline phosphatase concentrations, IgM RF and ANA titres.

We assessed the distribution and frequency of HCV-infection in different subgroups, including: age, sex, occupation, duration of RA disease, accompanying autoimmune disease(s), risk factors for hepatitis C, and family history of RA.

Consequently, we determined the prevalence of HCV-infection with definite confidence interval.

Data were analyzed using SPSS software (version 11.5, SPSS Inc., USA) and chi square and t-test were used, when appropriate.

RESULTS

Two hundred patients (174 women and 26 men), fulfilling inclusion criteria, were investigated, among whom 22 patients (11%) were <30 years old, 66 (33%) between 31 and 50, 82 cases (41%) between 51 and 70, and (15%) 30 cases >71 years old. Totally, 141 (70.5%) patients were positive for RFs and 68 (34%) for ANAs. The mean ESR was 41.3±26.2 mm/1st h (normal <10 mm). Serum aminotransaminases, and alkaline phosphatases were increased in 8 (4%), and 3 (1.5%) patients, respectively.

HCV-infection was detected in four patients (2%, 95%CI: 0.6-7) (table 1). Although, there were seven positive cases among serum samples tested by ELISA technique for the first time, this amount declined to five cases after the first confirmatory ELISA test. After the second confirmatory test (RT-PCR), HCV-infection was confirmed only in four cases (out of five). The characteristics of the four HCV-positive cases are summarized in table 1. In this study, we categorized patients' occupation as high-risk and low-risk occupations. Totally, 40

patients (20%) had high-risk occupations and 160 patients (80%) had low-risk occupations. The four HCV-infected patients were in low-risk occupation group. With respect to the duration of RA disease, patients were assigned in four groups; 10 patients suffered RA (5%) <1 year, 7 (35%) between 1 and 5 years, 74 (37%) between 6 and 10 years, and 46 patients (23%) more than 11 years. Among 4 HCV-infected patients, 2 had RA for 1-5 years and the others for 6-10 years.

Positive family history for RA was detected in 106 patients (53%). The same was true for two of the four HCV-infected patients. All HCV-RNA positive patients had active hepatitis and serum aminotransaminases were increased. None of the four HCV-infected patients had risk factors for hepatitis C infections. Similarly, none of them had accompanying autoimmune disease.

Table 1. Characteristics of the HCV-infected patients found among patients with RA

Case	**1**	**2**	**3**	**4**
Age	62	54	59	45
Sex	Male	Male	Female	Female
Occupation	L *	L	L	L
Duration of RA (year)	1-5	6-10	1-5	6-10
Family history of RA	-	+	-	+
Risk factors for HCV	-	-	-	-
Accompanying autoimmune disease	-	-	-	-

* Low-risk group, RA: Rheumatoid arthritis

DISCUSSION

Presence of anti-HCV antibody in serum of individuals indicates the old infection and/or recent active infection (12). HCV viraemia as assessed by RT-PCR is a much more powerful indicator of chronic hepatitis due to the virus (12). In this investigation the prevalence of old HCV-infection in patients with rheumatoid arthritis was 2%, which does not differ significantly from the prevalence of HCV-infection in general population (13). Consequently, this investigation does not support the participation of HCV infection in the pathogenesis of rheumatoid arthritis. Rivera et al noted that HCV-RNA was detected in two RA patients out of 112 patients (14). Hsu and colleagues investigated HCV in the pathogenesis of RA, and reported that this virus has probably no role in the etiology of RA in a study based on a US population (15). In Hungary, where the prevalence of anti-HCV positivity in the adult population is less than 1%, HCV did not seem to be a relevant factor in the induction or perpetuation of RA (16). Cacoub et al did not find any patient with RA in a sample of 1614 patients with chronic HCV infection (17).

Two major hypotheses can be proposed to explain these results: HCV infection is not participated in the pathogenesis of RA; or HCV infection could play a major role in pathogenesis of RA, at least in some RA subgroups, but this study failed to show a significant association. We believe that the first hypothesis is true. Because in our study, we used the second generation ELISA tests which are more sensitive than the first generation tests. Meanwhile, for detection of chronic HCV infection, assessment of viremia by RT-PCR is more sensitive than serology (12). Therefore, using this method, we could accurately prove the presence of HCV infection in our patients. Although, we did not measure the level of viremia (using quantitative PCR) in our RA patients, the RT-PCR test is sensitive enough to detect HCV infection even if it is low. Finally, we found no significant association between HCV infection and RA, which may be in part explained by insufficient number of patients contributing in our study.

According to the first published report (18) on the association between rheumatoid arthritis and HCV-infection, interferon therapy may precipitate subclinical rheumatoid arthritis in an individual

without pre-existing clinical arthritis. Regarding this claim, it seems beneficial to evaluate the history of interferon therapy, in a patient with HCV infection and subclinical RA. In our study, none of the patients had received interferon before participation in our study. Thus, their RA disease could not be associated to interferon administration.

As mentioned above, HCV-infection is dramatically related to some immunologic disorders (19). In regard to the importance of definite differentiation between HCV-related polyarthritis and rheumatoid arthritis (20), we examined our patients using the diagnostic criteria for rheumatoid arthritis. We found that none of the HCV-infected patients showed evidence of immunologic disorders.

Patients with HCV-infection contributed to our study suffered from rheumatoid arthritis at the age of 45 and 62 years. Thus we found no significant association between age and rheumatoid arthritis in HCV-infected cases.

In previous studies, most of the infected patients had positive history of close contact with risk factors (21). This is in contrast to ours in which none of the patients had positive history. It seems that this controversy is due to the differences between sampling methods of the two studies and insufficient number of patients contributing in our study.

These results indicate that the prevalence of HCV among patients with RA is not higher than the general population, and may raise the idea that HCV infection participate in the pathogenesis of RA. However, additional studies on larger samples and on different RA populations are needed to confirm the validity of such a conclusion for any RA subgroup. Meanwhile, we recommend conducting diagnostic tests for detection of hepatitis C virus in rheumatoid arthritis patients in countries with high prevalence of HCV infection or highly suspicious patients for HCV infection.

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