

Prevalence of Hepatitis C Virus Infection in Patients with Systemic Lupus Erythematosus: A Case-Control Study

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Background and Aims: Viruses might be one of the causes that trigger systemic lupus erythematosus (SLE). Steroid therapy may influence the natural history of virus infections. Reports on the association between SLE and hepatitis C virus (HCV) infection are scarce. We conducted a study to investigate the prevalence and clinical significance of HCV infection in patients with SLE.

Methods: In a prospective study (2003-2005) we evaluated the prevalence and clinical significance of chronic HCV infection in patients who met the diagnostic criteria of the American College of Rheumatology for SLE. The blood samples of 124 patients were tested for HCV antibodies by an enzyme-linked immunosorbent assay (ELISA). Anti-HCV reactive samples were retested for confirmation by Abbott MATRIX Immunoblot assays and also for HCV-RNA detection by the polymerase chain reaction (PCR). The control group consisted of first time blood donors referred to the regional blood transfusion organization.

Results: Six of 124 (4.8%) patients were seropositive for anti-HCV by ELISA; of these only 3 cases (2.4%) were positive by PCR. Both ELISA and the Immunoblot assays may be falsely positive for ongoing HCV infection in patients with SLE. A 2.4% prevalence of active HCV infection was found in patients with SLE, which did not differ significantly from the prevalence of HCV in the general population (less than 1%). In the few positive cases, we observed no adverse influence of this infection on the clinical features of the systemic lupus erythematosus.

Conclusions: Our results do not support the participation of HCV infection in the pathogenesis of SLE.

Keywords: Hepatitis C Virus, Autoimmunity, Systemic Lupus Erythematosus

Introduction

Hepatitis C virus (HCV) infection has become a major public health problem, with 170 million people considered to be infected worldwide. The disease progresses slowly and a chronic infection develops in 85% of the cases. Among patients with chronic hepatitis, 20 to 30% develop cirrhosis that, once established, carries a poor prognosis, with a high risk of developing hepatocarcinoma ⁽¹⁾.

Autoimmune manifestations are common in patients chronically infected by HCV ⁽²⁾. These manifestations can be dominant, while the hepatic disease can be quiescent or mild. More recently, there has been growing interest in the relationship between HCV and Sjogren's syndrome (SS), rheumatoid arthritis (RA) and systemic lupus

erythematosus (SLE) ⁽³⁻⁵⁾. Although most of the data are based on small series and case reports, awareness and recognition of these manifestations are important in facilitating early diagnosis and in offering treatment. Several authors described

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patients affected with HCV infection and SLE who fulfilled the American College of Rheumatology (ACR) criteria for SLE (6, 7).

Finally, serum anti-HCV antibodies were detected in 1 to 11% of patients with SLE (8, 9). Thus a causal link might exist between HCV and SLE in some patients. The objective of this study was to determine if there is a possible link between SLE and HCV infection by evaluating the prevalence of this infection among patients with SLE.

Materials and Methods

Study population

In a prospective study we evaluated the prevalence and the clinical significance of chronic HCV infection in 124 consecutive patients who met the diagnostic criteria of the American College of Rheumatology for SLE. The patients were referred to Ahwaz Jundishapur University Hospitals (AJSUH) and Rheumatology Clinics from May 2003 to September 2005. A standard form was used to collect socio-demographic data, medical history, physical examination, diagnosis, time of evolution, hospital admissions, and use of immunosuppressive drugs and pulse therapy.

Laboratory studies

Patients were tested for HCV antibodies (anti-HCV) by an enzyme-linked immunosorbent assay (ELISA). Anti-HCV reactive samples were retested for confirmation by Abbott MATRIX Immunoblot assays and also for HCV- RNA detection by the polymerase chain reaction (PCR). Sera from all 124 patients were provided for the following liver function tests at the patients' first visit to our outpatient clinic: serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), g-glutamyl transpeptidase (G-GTP), total bilirubin (T Bil), total protein (TP), albumin (Alb), and G-globulin (g-glob). Ultrasonographic examination was performed in all patients to investigate hepatic shape and lesions occupying the hepatic space.

Immunologic tests included antinuclear antibodies (ANA) (indirect immunofluorescence using mouse liver/kidney as substrates), antibodies to double-stranded DNA (positive if > 7 U/mL), precipitating antibodies to the extractable nuclear antigens Ro/SS-A, La/SS-B, Sm and RNP (ELISA) and rheumatoid factor (RF) (ELISA). IgG and IgM anticardiolipin antibodies were estimated by an ELISA technique and lupus anticoagulant was measured by coagulation assays. Complement

factors (C3 & C4) were measured. The control group consisted of 125 matched (sex and age) first time blood donors referred to the regional blood transfusion organization.

Statistical analysis

Collected data were coded, analyzed and computed, using the SPSS version 10.0 (SPSS Inc., Chicago, IL, USA). The chi-squared test and the unpaired Student's *t* -test were used for statistical analyses. Differences were judged significant when $P < 0.05$. Informed consent was obtained from all patients after the purpose and methods of the study were explained. The institutional Ethics Review Committee approved the study protocol.

Results

One hundred and twenty four cases with SLE were included in this study (Table 1). One hundred and nine (87.9%) patients were female and 11 (12.1%) were male, age ranged from 17 to 57 years with a mean age at SLE diagnosis of 40.3 ± 1.3 years. The mean disease duration was 64.2 months. There were various lupus manifestations, but none of the patients had used immunosuppressive drugs during the course of the disease, but all were taking chloroquine diphosphate and low doses of prednisolone (<20 mg/day).

Table 1. The comparison of HCV between the healthy controls and patients with SLE.

	Healthy donors (n=125)	patients with SLE (n=124)
Age	39 $\pm$ 0.8	40.3 $\pm$ 1.3
Female sex (%)	110 (88.7%)	109 (87.9%)
HCV-infected cases	1	3
Seropositive for anti-HCV	3	6
HCV positive by PCR	1	3

As shown in Table 1, six of 124 (4.8%) patients were seropositive for anti-HCV by a 2d generation ELISA; of these only three cases were positive by PCR corresponding to a prevalence of (2.4%) for hepatitis C in the study group. All PCR positive samples were genotyped. Two individuals were infected with subtype1, genotype1a and one patient presented genotype 3, subtype 3a. There was no history of blood transfusion, or other risk factors for HCV infection but all of them had a history of hospitalization. These three patients were 39, 42, and 48 years old women with typical SLE

manifestations of 26, 31, and 12 months' duration, respectively. Abdominal ultrasound showed normal liver structure in all HCV positive patients. Serum aminotransaminases and alkaline phosphatases were in the normal range in all three cases. We didn't perform transcutaneous liver biopsy because of patient's rejection.

Discussion

Autoimmunity and viral infections are closely related fields, and viruses have been proposed as possible etiological or triggering agents of autoimmune disorders (ADs). It is reported in the medical literature that in patients with chronic hepatitis more autoimmune disorders like SLE are seen than in patients with other causes of hepatitis virus ⁽¹⁰⁾. A fact also related with the variable geographical prevalence of HCV infection found in the general population ⁽¹¹⁾. Our study was designed to evaluate the prevalence of HCV infection and to analyze the association of HCV with clinical features of systemic lupus erythematosus.

Detection of serum anti-HCV antibodies is indicative of past or active infection. HCV viremia as assessed by PCR is a sensitive indicator of chronic hepatitis due to the virus ⁽¹²⁾. As shown in Table 1, 6 of 124 (4.8%) patients were anti-HCV positive, of these only 3 cases were positive by PCR corresponding to a prevalence of (2.4%) for hepatitis C in the study group. Such prevalence does not differ from those in the general Iranian population. This rate is estimated to be less than 0.2% among Iranian blood donors ^(13, 14). We found no significant difference between healthy population and SLE patients in terms of prevalence of anti-HCV ($P>0.45$). These results do not support the participation of HCV infection in the pathogenesis of SLE.

There were not many studies in our medical literature about the prevalence of anti-HCV in SLE patients. However, two studies have specifically analyzed the existence of Ads in large series of HCV patients ^(15, 16). Michel *et al.* in their study about anti-GOR and HCV in autoimmune liver diseases have reported no anti-HCV in 10 SLE patients ⁽¹⁷⁾. An anti-HCV prevalence of 4.8% was observed in our SLE patients, which was higher than that reported in Israel (1%) which ELISA II was used ⁽⁸⁾; but lower than those obtained in Italy (6%) ⁽⁷⁾, and Spain (11% & 12.5%) ^(9, 18). These differences may be due to the use of different methods for HCV diagnosis, distinct populations, and to the geographical variability in the prevalence of HCV infection observed in different countries. SLE is a

disease known to induce B lymphocyte polyclonal stimulation, with high autoantibody production, raising the possibility of cross-reactions, which can cause false-positive anti-HCV results (4.8% anti-HCV positive versus 2.4% PCR positive).

Our results showed that patients were infected with genotype 1a and 3a. In a study on 13 HCV infected SLE patients (12.5%) being infected with genotype 1a and 3a ⁽¹⁸⁾. This genotype distribution is similar to that found in the present study. In this study, Perlemuter *et al.* ⁽¹⁸⁾ reported a follow-up and observed a serious clinical picture with systemic involvement and concluded that corticoid therapy did not alter the course of chronic hepatitis. In their study, the 3 RA patients had used methotrexate and showed a stable clinical course. Several practical considerations should be kept in mind when dealing with HCV infected SLE patients. The use of corticoid and immunosuppressive drugs in these patients can increase HCV replication. In addition, the interferon used for the treatment of hepatitis C can precipitate and exacerbate SLE and causes several side effects, such as arthralgia, leukopenia and thrombocytopenia ⁽¹⁹⁾, which are common during the active phases of this disease, further impairing the evaluation of patients.

In conclusion, our study demonstrated that the prevalence of the HCV infection in patients with SLE was not higher than that of the general population, and the relation between HCV and SLE could not be established. However, further studies will be necessary for a better understanding of the influence of HCV infection on the clinical course of SLE and vice-versa.

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