CONCISE REPORTS

Hepatitis C virus infection in 'primary' Sjögren's syndrome: prevalence and clinical significance in a series of 90 patients

Mario García-Carrasco, Manel Ramos, Ricard Cervera, Josep Font, Josep Vidal, Francisco J Muñoz, Carles Miret, Gerard Espinosa, Miguel Ingelmo

Abstract

***Objectives*—To determine the prevalence and clinical significance of hepatitis C virus (HCV) infection in a large cohort of patients with 'primary' Sjögren's syndrome (SS).**

***Methods*—90 consecutive patients (83 female and seven male) were included, with a mean age of 62 years (range 31-80) who prospectively visited our unit. All patients fulfilled the European Community criteria for SS and underwent a complete history, physical examination, as well as biochemical and immunological evaluation for liver disease. Serum from all patients was tested for antibodies to HCV by third generation enzyme linked immunoassay and positivity was confirmed by polymerase chain reaction.**

***Results*—Antibodies to HCV were present in 13 (14%) patients with 'primary' SS. When compared with patients without HCV infection, patients with HCV infection presented a higher prevalence of hepatic involvement (100% *v* 8%, p < 0.05). Transcutaneous liver biopsy was performed in five patients with HCV infection, and specimens obtained showed in all cases a chronic active hepatitis with varying degrees of portal inflammation.**

***Conclusion*—HCV infection is frequent in patients with 'primary' SS and liver involvement is present in all these patients. The possible pathogenic role of HCV infection in these patients is still unclear.**

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Systemic Autoimmune Diseases Unit
M García-Carrasco
M Ramos
R Cervera
J Font
FJ Muñoz
C Miret
G Espinosa
M Ingelmo

and the Department of Microbiology
J Vidal

Hospital Clínic, Barcelona, Catalonia, Spain

Correspondence to:
Dr R Cervera, Unitat de Malalties Autoimmunes Sistèmiques, Hospital Clínic, C/Villarroel, 170, 08036 Barcelona, Catalonia, Spain.

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Sjögren's syndrome (SS) is a systemic autoimmune disease that mainly affects exocrine glands and usually presents as a persistent dryness of the mouth and the eyes caused by functional impairment of the salivary and lacrimal glands. The histological hallmark is a focal lymphocytic infiltration of the exocrine glands. In the absence of an associated systemic autoimmune disease, patients with this condition are classified as having 'primary' SS. Viral infection has long been suspected as a potential cause of SS.[1] Specifically, a possible relation between hepatitis C virus (HCV), which is a virus that can be excreted in saliva, and SS has recently been postulated.[2] However, information on the prevalence of HCV infection in 'primary' SS is scarce and reported prevalences show a wide range of variation depending on the technique to detect HCV infection.[3]

The aim of this study was to determine prospectively the prevalence and clinical significance of HCV infection in a large cohort of patients with 'primary' SS by means of a third generation enzyme linked immunosorbent assay (ELISA 3) and a polymerase chain reaction (PCR) assay.

Methods

PATIENTS

We included 90 consecutive patients (83 female and seven male; mean age 62 years; range 31-80) who attended the Systemic Autoimmune Diseases Unit from March 1993 until April 1996. All patients were white and fulfilled four or more of the diagnostic criteria for SS proposed by the European Community Study Group in 1993.[4] None of these patients presented clinical or immunological evidence of other systemic autoimmune disease and no patient had been previously diagnosed as having primary biliary cirrhosis or autoimmune hepatitis.

All patients underwent a complete history and physical examination, as well as diagnostic tests for SS applied according to the recommendations of the European Community Study Group.[4] All were systematically questioned on documented risk factors for hepatitis virus infection. No patient had previously received interferon therapy.

LABORATORY STUDIES

Detection of antibodies to HCV

Serum from all patients was tested for HCV antibodies by a third generation ELISA (Ortho 3.0 Diagnostic Systems, Neckargemund, Germany). Positivity for HCV infection was confirmed by second generation recombinant immunoblot assay (RIBA-2;Ortho). In

anti-HCV positive serum samples, presence of HCV-RNA was analysed by PCR (Amplicor HCV, Roche Diagnostic System). Reverse transcription and cDNA synthesis were carried out in a single step reaction using 10 µl of RNA with specific oligonucleotides NCR1 and NCR2 [5] derived from the well conserved 5'NC region of HCV.

Other laboratory tests

Hepatitis B surface antigen (HBsAg) was determined by ELISA. The immunological tests included antinuclear antibodies (ANA) (indirect immunofluorescence using mouse liver as substrate), antimitochondrial antibodies (AMA), antismooth muscle antibodies (SMA) and antiliver kidney microsome antibodies type-1 (LKM-1) (indirect immunofluorescence), precipitating antibodies to the extractable nuclear antigens Ro-SSA and La-SSB (counterimmunoelectrophoresis), and rheumatoid factor (latex fixation and Waaler-Rose tests).

STATISTICAL ANALYSIS

For analysing qualitative differences we used a χ^2 test or the Fisher's exact test when appropriate. For comparison of quantitative parameters, Student's test was used in large samples of similar variance, and non-parametric Mann-Whitney U test for small samples. p Values < 0.05 were considered to indicate statistical significance. When several independent variables appeared to have statistical significance in the univariate analysis, a logistic regression test was performed for multivariate analysis to rule out possible confounding variables. In this case, only those variables showing statistical significance in the multivariate analysis were considered as significant in the results of the study.

Results

Antibodies to HCV (ELISA-3 and RIBA-2) were present in 13 (14%) of our patients with 'primary' SS. They all were positive for HCV-RNA by PCR. Risk factors for HCV infection were identified in nine of these patients (past blood transfusions or surgical procedures). In four patients no obvious source of infection was found. When compared with patients without HCV infection, patients with this infection presented a higher prevalence of hepatic involvement (100% *v* 6%, p<0.05) (table 1).

Table 1 Clinical and immunological manifestations of patients with 'primary' SS and HCV infection compared with patients without HCV infection

	SS with HCV infection (n=13)	*SS without HCV infection (n=77)*
Dry mouth	11 (85)	76 (99)
Dry eyes	12 (92)	72 (95)
Parotidomegaly	3 (23)	31 (40)
Splenomegaly	6 (46)	3 (4)
Articular involvement	7 (54)	36 (47)
Raynaud's phenomenon	4 (31)	10 (13)
Cutaneous vasculitis	3 (23)	8 (10)
Pulmonary involvement	1 (8)	12 (16)
Hepatic involvement	13 (100)*	5 (6)
Peripheral neuropathy	3 (23)	7 (9)
Autoimmune thyroiditis	3 (23)	9 (12)
Thrombocytopenia	6 (46)	7 (9)
Cryoglobulins	6/11 (55)	5/37 (14)
Hypocomplementaemia	4 (31)	9 (12)
ANA (+)	10 (77)	57 (74)
SMA (+)	3 (23)	22 (29)
AMA (+)	2 (15)	0 (0)
RF (+)	8 (62)	29 (38)
Ro-SSA (+)	6 (46)	22 (29)
La-SSB (+)	4 (30)	11 (14)

* p < 0.05. ANA = antinuclear antibodies; SMA = antismooth muscle antibodies; AMA = antimitochondrial antibodies; RF = rheumatoid factor. Figures in parentheses are percentages.

Of the 13 patients with 'primary' SS and HCV infection, 12 were female and one male. Mean age at the onset of clinical manifestations of the dry syndrome was 55 years (range 40-77) and at the time of protocol was 65 years (range 53-80). Liver involvement was detected in all these patients. Nine patients had both clinical and biochemical features of liver disease, while the remaining four had raised liver enzyme activities but were asymptomatic and without clinical signs of hepatopathy. The most common clinical manifestation of liver disease was hepatomegaly, which was present in eight patients and jaundice, which was seen in two patients. Biochemical tests showed increased aminotransferase activities in nine patients, increased γ-glutamyltransferase in nine, raised bilirubin in six, and increased alkaline phosphatase in three patients. Anti-SMA antibodies were observed in three patients, AMA were detected in two, and no patient had positive anti-LKM-1 antibodies. All patients were negative for HBsAg.

Abdominal ultrasound was performed in all patients. Diffuse change in liver structure was detected in seven patients, homogeneous hepatomegaly in four, and no alteration was demonstrated in three patients. Transcutaneous liver biopsy was performed in five patients after informed consent. Specimens obtained showed in all cases a chronic active hepatitis with varying degrees of portal inflammation. Other associated histological features were steatosis in one patient and parenchymal nodules with loss of normal architecture (cirrhosis) in another patient.

Mean age at detection of liver alteration in these 13 patients with HCV infection was 61 years (range 46-79) and the follow up of liver involvement was four years (range 1-18). Only two patients presented during this follow up period with clinical manifestations of hepatic descompensation (ascites, encephalopathy, peripheral oedema or gastrointestinal bleeding), and diagnosis of hepatocellular carcinoma was finally diagnosed in both.

Discussion

Our study shows that HCV infection is present in 14% of the patients with a previously considered 'primary' SS. This prevalence is significantly high when compared with the prevalence of HCV infection that has been found in the general population in Catalonia (1.2%)[6 7] and raises the possibility of a link between HCV infection and SS. Several authors[8–11] have previously analysed the prevalence of HCV in SS and this ranges between 0 and 19% using a RIBA-2 technique. This wide range of variation may result from a

disparity in selection criteria for patient inclusion or may reflect ethnic or geographical differences.

Dryness of the mouth and the eyes (with positive ocular and salivary tests),[12] lymphocitic infiltration of salivary glands,[2] and positivity of autoantibodies, such as the ANA, anti-Ro/SS-A, and anti-La/SS-B,[13] have previously been described in patients with HCV infection. In this study, we describe 13 patients with HCV infection that met at least four of the six criteria proposed by the European Community Study Group for the diagnosis of SS,[4] and had no evidence of other systemic autoimmune disease, thus being considered as having a 'primary' SS. Moreover, in our group of patients with SS, we have found an association between HCV infection and hepatic involvement. Taken these findings together, it is conceivable that chronic infection by HCV may originate a 'secondary' SS in some patients, although most of these patients could be in our clinics with a diagnosis of 'primary' SS. It is possible to postulate that chronic infection by HCV could remain subclinical during many years, and may be clinically expressed with features of liver disease (hepatomegaly or raised aminotransferase activities) or with the appearance of dryness of the mouth and the eyes.

The relation between HCV infection and SS might also have therapeutic implications. Interferon therapy has been used in patients with HCV infection to treat not only the liver disease but also extrahepatic manifestations related to this virus, for example cryoglobulinaemia.[14] Shiozawa *et al*[15] recently reported a beneficial effect of interferon alfa on the xerostomia of SS. However, the possible benefits of interferon in patients with SS associated to HCV infection has not been evaluated.

In conclusion, HCV infection is frequently detected in patients with SS and liver involvement is present in all these patients. The possible pathogenetic role of HCV infection in the extrahepatic manifestations of SS is still unclear, and potential therapeutic implications for this combination of diseases remain to be determined.

1 Flescher E, Talal N. Do viruses contribute to the development of Sjögren's syndrome? Am J Med 1991; 90:283-4.
2 Haddad J, Deny P, Munz-Gotheil C, *et al*. Lymphocytic sialadenitis of Sjögren's syndrome associated with chronic hepatitis C virus liver disease. Lancet 1992;339:321-3.
3 Kaplan G. Hepatite virale, VHC et syndrome de Gougerot-Sjögren. *L'Actualité Rhumatologique 1993*. Paris: Expansion Scientifique Française, 1993:11-8.
4 Vitali C, Bombardieri S, Moutsopoulos HM, *et al.* Preliminary criteria for the classification of Sjögren's syndrome. Arthritis Rheum 1993;36:340-7.
5 Garson JA, Ring C, Tuke P, Tedder RS. Enhanced detection by PCR of hepatitis C virus RNA. Lancet 1990; 336:878-9.
6 Sanchez-Tapias JM, Barrera JM, Costa J, *et al*. HCV infection in patients with nonalcoholic chronic liver disease. Ann Intern Med 1990;112:921-4.
7 Esteban JL, Esteban R, Viladomiu L, *et al.* Hepatitis C antibodies among risk groups in Spain. Lancet 1989;ii:294-6.
8 Loustaud-Ratti V, Vidal E, Delaire L, *et al*. Gougerot-Sjögren, syndrome sec et hépatite C. Rev Méd Interne 1992;13:S346.
9 Vitali C, Sciutto M, Neri R, *et al.* Anti-hepatitis C virus antibodies in primary Sjögren's syndrome: false positive results are related to hypergammaglobulinaemia. Clin Exp Rheumatol 1992;10:103-4.
10 Perney P, Jorgensen C, Legouffe MC, *et al.* Syndrome de Gougerot-Sjögren et infection virale C: caracteristiques cliniques, immunologiques, génétiques et génotypiques. Rev Med Int 1995;16 (suppl 3):390s.
11 García-Carrasco M, Ramos M, Cervera R, *et al.* Liver involvement and hepatitis C virus infection in patients with primary Sjögren's syndrome. Br J Rheumatol 1996;35 (suppl 1):15.
12 Almasio A, Provenzano G, Scimeni M, *et al.* HCV and Sjögren's syndrome. Lancet 1992;339:989-90.
13 Lobreglio G, Salerno L, Ciullo A, *et al.* SSA/SSB autoantibodies in patients with chronic HCV liver disease. (Abstract). J Hepatol 1993;17 (suppl):32.
14 Misiani R, Bellavita P, Fenili D, *et al.* Interferon alfa-2a in cryoglobulinemia associated with hepatitis C virus. N Engl J Med 1994;330:751-6.
15 Shiozawa S, Morimoto I, Tanaka Y, Shiozawa K. A preliminary study on the interferon-alpha treatment for xerostomia of Sjögren's syndrome. Br J Rheumatol 1993;32:52-5.