

# Prevalence and Characteristics of Sjögren's Syndrome or Sicca Syndrome in Chronic Hepatitis C Virus Infection: A Prospective Study

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**ABSTRACT. Objective.** To describe the prevalence and clinical and laboratory characteristics of sicca syndrome and Sjögren's syndrome (SS) in chronic hepatitis C virus (HCV) infection.

**Methods.** Forty-five consecutive HCV infected patients referred for liver biopsy were enrolled in a prospective study. Subjective and objective criteria of xerophthalmia or xerostomia were systematically investigated and the patients classified according to 3 sets of criteria (European, Manthorpe, and Fox criteria) for the diagnosis of SS.

**Results.** Sicca syndrome was present in 28 (62%) patients; all had oral dryness and 14 had both oral and ocular dryness. Twenty-four (53%) patients had SS by the European criteria, 25 (56%) by Manthorpe criteria, and 4 (8%) by Fox criteria. Salivary gland biopsy was positive for SS (grade III or IV by Chishom classification) in 21 samples (47%); 9 samples (21%) were classified grade 0, and 15 (32%) grade I or II. No patient had anti-SSA or anti-SSB antibodies. The presence of SS or sicca syndrome was associated with older age and liver disease activity according to the METAVIR scoring system, but not with the presence of other extrahepatic manifestations or with HCV genotype. A high METAVIR activity score was only statistically associated with primary SS.

**Conclusion.** HCV infection appears to account for a subgroup of patients with sicca syndrome in which half the cases meet the definition for SS according to European and Manthorpe criteria. This subgroup is characterized by the constant finding of xerostomia, the absence of classical systemic manifestations observed in primary SS, and the absence of anti-SSA or anti-SSB antibodies. Such characteristics delineate a distinctive, virus associated entity that differs from primary SS. (J Rheumatol 2001;28:2245–51)

## Key Indexing Terms:

HEPATITIS C VIRUS  
AUTOIMMUNE DISEASES

SICCA SYNDROME

SJÖGREN'S SYNDROME  
EXTRAHEPATIC MANIFESTATIONS

Hepatitis C virus (HCV) has been associated with various immunological disorders that can be confirmed using virological techniques, as in mixed cryoglobulinemia<sup>1,2</sup>, or based on epidemiological data<sup>3</sup>, as in the case of porphyria cutanea tarda. Others are presumed to be of autoimmune origin. Autoantibody production (antinuclear, anti-smooth-muscle, anti-liver-kidney microsomal antibodies) generally has no pathological significance<sup>4</sup>. However, true autoimmune diseases such as type 1 or 2 autoimmune hepatitis<sup>5</sup>, Sjögren's syndrome<sup>6</sup>, lichen planus<sup>7</sup>, and autoimmune thyroiditis<sup>8,9</sup> have been described in association with HCV related liver disease.

Sjögren's syndrome (SS), a chronic inflammatory autoimmune disease of the exocrine glands, involving salivary and lacrimal glands in particular, is probably the most frequently encountered connective tissue disease<sup>10</sup>. The immune disorder involves a progressive lymphocytic infiltration of the salivary and lacrimal glands, with polyclonal B lymphocyte activation and autoantibody production, especially antinuclear antibodies, autoantibodies to SSA or SSB antigen, and rheumatoid factor. The most salient sign and basic diagnostic criterion for SS is the presence of focal lymphocytic sialadenitis on minor salivary gland biopsy. The progression of periductal lymphocytic foci parallels that of acini cell destruction, lobular duct dilatation, and myoepithelial cell hyperplasia. The glands are infiltrated by T cells, predominantly of the helper-inducer (CD4) phenotype. SS can occur alone (the so-called primary SS) or in association with other connective tissue diseases (secondary SS). Although xerostomia and xerophthalmia are by far the most prominent symptoms of primary SS, a broad spectrum of systemic manifestations can occur, complicating the disease or leading to its discovery.

Several viruses such as Epstein-Barr virus<sup>11</sup>, cytomegalo-

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virus, herpesvirus, and retroviruses have recently been implicated in the pathogenesis of primary SS. Viruses residing in the salivary glands<sup>12</sup> could initiate the inflammatory process. Human immunodeficiency virus (HIV) has been found to produce parotid enlargement, sicca syndrome, and CD8 T cell infiltration in glands of US Black patients bearing the HLA-DR5 phenotype<sup>13</sup>. Human T cell leukemia virus type I could be implicated in primary SS in Japan<sup>14</sup>. Finally, a possible role of HCV in primary SS has recently been suggested<sup>6</sup>, since HCV has been recognized as the major etiologic agent of essential mixed cryoglobulinemia, in which the prevalence of SS has been shown to be as high as 20%<sup>1</sup>.

The prevalence of sicca syndrome (SS) and sialadenitis in chronic HCV infection has been diversely estimated since the first report of the association in 1992<sup>6</sup>. However, to our knowledge, no published study to date has systematically and prospectively investigated sicca syndrome and SS according to current criteria for the diagnosis of primary SS in an unselected population of consecutive patients with chronic hepatitis C. We conducted a prospective study of 45 patients with chronic HCV liver disease to assess the prevalence and characteristics of SS and primary SS in this population. We also searched for significant associations between the presence of SS or primary SS and epidemiological, clinical, laboratory, and pathological features of the liver disease.

## MATERIALS AND METHODS

Forty-five consecutive outpatients with chronic HCV infection referred to the Department of Internal Medicine for liver biopsy as a prerequisite before the initiation of therapy were prospectively studied. Inclusion criteria were the following: (1) positive serological markers of HCV infection (2nd or 3rd generation ELISA) or recombinant immunoblot assay (Deciscan Sanofi Diagnostic Pasteur, Marne-La Coquette, France); (2) positive combined reverse transcription polymerase chain reaction (RT-PCR; Amplicor, Roche Diagnostics, Meylan, France); (3) biochemical active disease demonstrated by increased serum aminotransferase activity; and (4) liver biopsy, with hepatic lesions quantified using Knodell's score<sup>15</sup> and the METAVIR scoring system<sup>16</sup> defined by a semiquantitative reproducible evaluation of elementary lesions, with a grading score of "activity" (necrosis and inflammation) and a staging score of "fibrosis." Exclusion criteria were the following: (1) other causes of chronic liver disease, (2) other causes of sicca syndrome (preexisting lymphoma, acquired immunodeficiency syndrome, sarcoidosis or graft-versus-host disease, or other connective tissue disease), and (3) patients currently or previously treated with interferon- $\alpha$ .

HCV genotypes were determined in 37 cases. Sera stored at  $-80^{\circ}\text{C}$  were studied using a PCR technique (LIPA; Inno-LIPA HCV; Immunogenetics, Antwerpen, Belgium)<sup>17</sup>. The consensus nomenclature proposed by Simmonds, *et al* was used to classify the genotypes and subtypes<sup>18</sup>.

Ocular and oral dryness was systematically investigated, irrespective of the patient's complaints. After giving informed consent, all patients followed the same protocol. A questionnaire validated by the European Community<sup>19</sup> was administered, and then objective tests were systematically performed. Schirmer's test (pathologic when  $\leq 5$  mm in 5 min) and rose Bengal score (pathologic when  $\geq 4$  according to Van Bijsterveld's scoring system) were used for the identification and scoring of ocular

involvement, while unstimulated salivary flow (pathologic when  $\leq 0.1$  ml/min), salivary radionuclide scintigraphy, and labial salivary gland biopsy were used for identification and scoring of oral involvement. The 45 biopsy samples were fixed in Bouin's fluid, embedded in paraffin, and stained with hematoxylin-eosin-safranin. All the sections were examined twice by the same pathologist and graded according to Chisholm and Mason's classification<sup>20</sup>. Ocular dryness was defined by a positive response to the questionnaire and at least one positive objective test. Oral dryness was confirmed by at least 2 positive objective tests. The salivary gland biopsies were examined for the presence of lymphocytic infiltration, one focus being defined as an agglomeration of at least 50 mononuclear cells. To accurately assess the focus score, at least 4 lobules were evaluated in each biopsy. Only grades III and IV, which correspond to one focus/4 mm<sup>2</sup> and more than one focus/4 mm<sup>2</sup>, respectively, according to Chisholm's classification, were considered positive.

The diagnosis of primary SS was established using the European criteria<sup>19</sup>, validated in 1996<sup>21</sup>. Six items were studied: I, ocular symptoms; II, oral symptoms; III, ocular objective signs; IV, objective signs of salivary gland involvement; V, positive minor salivary gland biopsy with a focus score  $\geq 1$ ; VI, presence in the serum of antibodies to Ro (SSA) or La (SSB) antigens; or antinuclear antibodies or RF. Primary SS was defined as probable with 4 items (sensitivity 97.5% and specificity 90.5%) and certain with at least 5 items (sensitivity 76.9% and specificity 98.3%).

These results were compared to those obtained using criteria published by Manthorpe, *et al*<sup>22</sup> and by Fox, *et al*<sup>23</sup>.

A search was carried out to identify extrahepatic involvement (commonly observed in primary SS or in chronic hepatitis C), including routine blood count abnormalities, rheumatologic symptoms, thyroid abnormalities (on the basis of clinical findings and measurements of thyrotropin and antiperoxidase antibodies), peripheral nerve involvement (clinical examination and if abnormal, electrophysiologic investigations), dermatologic signs, kidney involvement (dipstick urinalysis; Multistix, Bayer Diagnostics, Puteaux, France), and lung involvement (clinical examination and chest roentgenogram).

Antinuclear, anti-smooth-muscle, type 1 anti-liver-kidney microsomal (LKM1), and antimitochondrial antibodies were detected by indirect immunofluorescence using HEp2 cells and air dried cryostat sections of rat kidneys, liver, and stomach. Antibodies to double stranded DNA, autoantibodies to SSA and SSB antigens were detected by ELISA (BMD, Marne La Vallée, France). Rheumatoid factor was measured using sheep cell agglutination (Fumouze, Levallois Perret, France) and a nephelometer analyzer (Behring, Rueil-Malmaison, France). Antithyroid peroxidase antibodies were detected by ELISA (DynotestR, BRAHMS, Sartrouville, France). A search for cryoglobulinemia was carried out by drawing venous blood that was centrifuged at  $37^{\circ}\text{C}$ . The supernatant was incubated at  $4^{\circ}\text{C}$  for 8 days and examined daily for cryoprecipitation.

**Statistical analysis.** We defined the populations to compare according to the presence or absence of SS (ocular and/or oral dryness) and the presence or absence of primary SS defined by the European criteria<sup>19</sup>. Categorical variables were compared using the chi-square test or Fisher's exact test. Quantitative variables were compared by Mann-Whitney U test and Kruskal-Wallis test. A value of  $p < 0.05$  indicated statistical significance. As numerous statistical tests were done in the comparison of the populations, we fixed the level of significance to 0.005 using Bonferroni's correction.

## RESULTS

**Epidemiological data.** The epidemiological data are shown in Table 1. Patients whose probable cause of HCV infection was transfusion were older than intravenous drug abusers ( $p < 0.001$ ) and had a longer duration of chronic liver disease ( $p = 0.01$ ). A higher Knodell score was found in patients with blood-borne HCV liver disease compared to

Table 1. Epidemiological data. Data in parentheses are percentages.

Number of patients	45
Men	23
Women	22
Sex ratio	1
Mean age(yrs)	49.6 ± 1.2
Range (yrs)	25 to 80
Cause of infection	
Blood transfusion	24 (53)
IV drug user	14 (31)
Other (sexual transmission or tatooing)	2 (5)
Unknown	5 (11)
Mean duration of liver disease (evaluated for 38 patients) (yrs)	11.1 ± 8.3
Range (yrs)	2.8 – 19.4
Mean Knodell score	8.2 ± 3.1
Knodell score > 6	27 (66)
METAVIR scoring system	
Activity minimal or moderate (A1 or A2)	33 (80)
Fibrosis with septa and without cirrhosis (F3)	7 (15)
Cirrhosis (F4)	9 (20)
Genotypes (37 patients)	
1b	23 (62)
1a	3 (8)
2b	1 (3)
3a	5 (13.5)
4a	5 (13.5)

other sources of contamination, but the difference was of borderline significance ( $p = 0.06$ ). A history of transfusion was associated with the degree of activity ( $p = 0.02$ ), but with neither the degree of fibrosis nor the presence of cirrhosis, according to the METAVIR scoring system. Patients with genotype 1b were older than patients with other genotypes ( $p < 0.01$ ), and had a longer disease duration ( $p = 0.05$ ) and a higher rate of contamination by transfusion ( $p = 0.01$ ), as reported<sup>24</sup>. The liver lesions (Knodell, METAVIR, and presence of cirrhosis) did not differ significantly with respect to the genotype (1b versus other genotypes).

**Prevalence of SS and primary SS.** The preestablished questionnaire allowed identification of subjective oral dryness in 23 patients and subjective ocular dryness in 20. It is noteworthy that some of these patients complained spontaneously of ocular dryness (9 cases) or oral dryness (12 cases) before answering the questionnaire. Sicca syndrome was present in 28 patients (62%); 14 had ocular and oral dryness and 14 had isolated oral dryness, as defined by Vitali, *et al*<sup>19</sup>. The diagnosis of SS in our population with HCV according to the 3 sets of criteria is shown in Table 2. The salivary gland biopsy was suggestive of SS in 21 (47%) samples: 19 samples (39%) were grade III and 2 samples (8%) were grade IV. Nine (21%) samples were classified grade 0 and 15 (32%) were classified grade I or II.

**Immunological studies.** Antinuclear and anti-smooth-muscle antibodies were present at significant levels in 5 (11%) and

Table 2. Diagnosis of Sjögren's syndrome in our population with HCV according to 3 sets of criteria.

	Certain %	Diagnosis of SS Probable %	Total %
European criteria <sup>21</sup>	38 (n=17)	15 (n=7)	53 (n=24)
Manthorpe criteria <sup>22</sup>	18 (n=8)	38 (n=17)	56 (n=25)
Fox criteria <sup>23</sup>	8 (n=3)	2 (n=1)	10 (n=4)

4 patients (9%), respectively. No doublestranded DNA antibodies, anti-LKM1, or antimitochondrial antibodies were found in any patient. Moreover, no patient had anti-SSA or anti-SSB antibodies suggestive of SS. RF was present in 9 patients (20%), 5 of whom had a positive result with the nephelometric method. Mixed type II or type III cryoglobulinemia was detected in only 3 patients.

**Other extrahepatic manifestations.** Routine blood count abnormalities were found in 23 patients (51%). Thrombocytopenia was present in 19 patients (42%), in whom only 7 had cirrhosis, and was classified as mild (platelet count 100 to 150 g/l) in 12, moderate (50–100 g/l) in 5, and severe ( $< 30$  g/l) in 2 patients. Of the patients with severe thrombocytopenia, one had symptomatic autoimmune thrombocytopenic purpura, which resolved upon treatment with corticosteroids and relapsed when interferon was administered. The other case was associated with severe portal hypertension. Neutropenia ( $< 2$  g/l) was present in 9 patients (20%) and was associated with thrombocytopenia in 5. Symmetrical inflammatory joint involvement was found in 10 patients (22%), affecting principally the hands (9 cases), wrists, ankles, and knees bilaterally. No patient complained of joint swelling and no synovitis was observed. There were no bone erosions on radiographs or signs of rheumatoid arthritis. No patient with rheumatological symptoms had detectable cryoglobulinemia. Thyroid dysfunction was found in 3 patients (6.7%) and consisted of hypothyroidism without antithyroid peroxidase autoantibodies in 2 and Graves' disease in one. Isolated antithyroperoxidase antibodies were found at a significant level in 2 other patients. A peripheral sensorimotor polyneuropathy affecting the lower limbs was suspected clinically and confirmed by electrophysiological studies in 3 patients (6%); none of them had detectable cryoglobulinemia. Miscellaneous manifestations included Raynaud's phenomenon associated with arthralgia in 2 patients, prurigo in one, and oral lichen planus in one patient. No lung or kidney involvement was recorded in any patient.

**Statistical analysis.** The presence of immunological abnormalities and extrahepatic manifestations was not statistically different among genotypes.

The presence of SS or primary SS (Table 3) according to Vitali's criteria was not associated with sex or duration of

**Table 3.** Characteristics of chronic HCV infection and prevalence of extrahepatic manifestations in patients with or without primary SS.

Epidemiological Factors	Patients with pSS (n=24)	Patients without pSS (n=21)	Statistical Test, p
Mean age (yrs)	55.5	43	0.017*
Male sex	12	11	NS**
Duration of liver disease (yrs)	12	10	NS*
Blood transfusion (%)	78	50	NS**
Knodell score (mean)	9.2	7.1	0.017*
Metavir A2, A3, (%)	82	32	0.001***
Metavir F3, F4 (%)	50	16	0.021***
Cirrhosis (%)	21	14	NS**
Immunological abnormalities (%)	50	14	0.011**
Extrahepatic manifestations (%)	46	28	NS**

\* Mann-Whitney U test, \*\* chi-square test, \*\*\* Pearson chi-square.

HCV infection ( $p < 0.05$ ). Patients with SS or primary SS were older (mean ages 55 and 55.5 yrs, respectively) than patients with no oral or ocular involvement or primary SS (mean ages 40 and 43 years;  $p = 0.006$  and  $p = 0.02$ , respectively). Knodell score was higher in patients with SS or primary SS compared with patients with no oral or ocular involvement ( $p = 0.03$ ,  $p = 0.02$ , respectively). Patients with SS and primary SS were associated with higher METAVIR activity ( $p = 0.01$ ,  $p = 0.001$ , respectively) and fibrosis ( $p = 0.03$ ,  $p = 0.002$ , respectively) scores, but not with cirrhosis ( $p > 0.05$ ). Sicca syndrome or primary SS were associated with antinuclear antibodies ( $p = 0.02$ ) and RF ( $p = 0.01$ ) but not with HCV genotype or extrahepatic manifestations, except thrombocytopenia ( $p < 0.01$ ).

Finally, using Bonferroni correction METAVIR activity was the only variable significantly associated with the presence of primary SS.

A high Chisholm score was associated with older age ( $p = 0.002$ ), transmission by transfusion ( $p = 0.005$ ), a higher Knodell score ( $p = 0.01$ ), and higher METAVIR activity ( $p = 0.004$ ) and fibrosis scores ( $p = 0.05$ ), but not with cirrhosis or HCV genotype.

## DISCUSSION

**Autoimmunity and extrahepatic manifestations.** In our prospective and unselected sample of patients with untreated chronic hepatitis C infection, serum immune disturbances were more frequent in patients with SS or primary SS than in patients unaffected by both syndromes (50% versus 14%;  $p = 0.011$ ). Extrahepatic manifestations were also more frequent in patients with SS or primary SS compared with the rest of the series (46% versus 14%). But the difference was not statistically significant using the Bonferroni correction. The prevalence of extrahepatic mani-

festations in our series compares with other studies<sup>25,26</sup>, except for the rate of mixed cryoglobulinemia, which is markedly lower (6.7%) than the reported rate of 36% to 54%<sup>26,27</sup>. Technical problems may at least partially explain such a discrepancy, but not entirely.

**Seroprevalence of HCV in populations with primary SS.** With the currently used 2nd or 3rd generation HCV tests confirmed by RIBA or PCR, the prevalence ranged from 4% to 19%<sup>28,29</sup>, which remains significantly higher than the 1.1% prevalence of HCV seropositivity observed in the general population in France<sup>30</sup>.

**Prevalence of SS and primary SS in populations with HCV.** To our knowledge, only one study has searched for SS in a population of 12 unselected Swedish patients with chronic hepatitis C<sup>31</sup>. In this series<sup>31</sup>, only 2 cases (16%) fulfilled Manthorpe's criteria. In our series, the prevalence of SS was high (53%) and xerostomia was more frequent than xerophthalmia, in accord with Haddad's study<sup>6</sup>. However, we found substantial differences in the prevalence of primary SS according to which set of criteria was applied: 53% when applying the European criteria validated in 1996<sup>21</sup>, 47% according to the recently revised and unpublished European criteria<sup>32</sup> that require either a characteristic minor salivary gland biopsy (focus score  $\geq 1$ ) or antibodies to SSA or SSB antigen, 56% according to Manthorpe<sup>22</sup>, but only 8% by the Fox criteria<sup>23</sup>. It is notable that the observed discrepancy in the incidence of primary SS depends entirely on the value attributed to the immunological criteria, which are mandatory in Fox's classification. Indeed, no anti-SSA or anti-SSB antibodies were found in our patients, similar to most previous studies of patients with HCV<sup>25,26,31</sup>, except one<sup>33</sup>. An explanation could be that Ramos-Casals, *et al*<sup>33</sup> selected a population of patients with HCV in whom the diagnosis of primary SS was made before the diagnosis of HCV in 70% of the cases<sup>33</sup>. Finally, our results emphasize the significant differences between the Fox, Manthorpe, and European criteria for classification of primary SS, underlining the need for an international consensus.

**Systemic manifestations of primary SS in populations with HCV.** In our patients with a definite diagnosis of primary SS, no systemic complication could be attributed to primary SS. In particular, no chronic interstitial lung disease or renal tubular acidosis was observed in any patient. Moreover, the prevalence of joint pain and limb sensorimotor polyneuropathy was similar in patients with or without primary SS. These results contrast sharply with the 64% incidence of systemic manifestations in our series of 48 patients with primary SS in the absence of HCV<sup>34</sup> and in other comparable series<sup>35,36</sup>. In those studies, interstitial lung disease and kidney involvement were present, at some point in the disease, in 27% and 12.5% of patients, respectively. Further, Jorgensen, *et al*<sup>37</sup> compared 2 populations of patients with primary SS with or without HCV infection and found fewer



systemic manifestations, except polyneuropathy, in the HCV positive group. Ramos-Casals' study<sup>33</sup> alone did not agree with these results; only parotidomegaly was significantly more frequent in patients with primary SS but without HCV infection.

*Pathology of minor salivary glands in HCV disease.* Data on the pathological involvement of the minor salivary glands in patients with chronic hepatitis C are scanty and contradictory, the prevalence of grade III and IV focus scores (by Chisholm and Mason classification) ranging from 14% to 57%<sup>6,25</sup>. In our study, a systematic survey of lip involvement yielded a rate of positive grade III or IV biopsies of 47%. It is notable that only 2 biopsies (8%) would have been classified as positive according to Daniels' focus score method, which requires grade IV histology to classify a biopsy as positive<sup>38</sup>. In our opinion, using grade III as the threshold of positivity in the classification of lip biopsy strikes the best balance between sensitivity and specificity<sup>19,21</sup>.

Subtle differences may be observed in the appearance of the lymphocytic infiltration in patients with HCV related SS compared with other SS. Pawlowsky, *et al*<sup>25</sup> described in half of their patients a specific pattern of lymphocytic infiltration that they called "lymphocytic capillaritis," in which the cell infiltrate surrounded capillaries rather than ducts and never destroyed duct walls. In our series, a similar appearance was found more frequently in HCV positive patients compared with 44 patients with primary SS but without HCV infection and 17 patients with secondary SS<sup>39</sup>. Nonetheless, in patients with HCV infection, lymphocytic infiltration may be located within intralobular salivary duct epithelium, destroying the duct walls and leading to duct ectasia and acinar depletion, as characteristically seen in patients with isolated primary SS. Scott, *et al*, comparing the morphological characteristics of lymphocytic sialadenitis in chronic HCV infection and isolated primary SS, found a similar degree of tissue damage but a lesser extent of inflammation in patients with HCV<sup>40</sup>. More recently, Koike, *et al*<sup>41</sup> developed an interesting animal model of transgenic mice carrying the HCV envelope genes. Mice developed an exocrinopathy involving the salivary and lacrimal glands that resembled SS in 84% of cases, with subsequent cell aggregation around the intralobular ducts, thus closely resembling Chisholm and Mason's grade III or IV focus scores. Notably in this model the lymphocytic infiltration first involved the capillaries and later the lacrimal glands. Lymphocytic capillaritis may therefore represent an early stage of sialadenitis in patients with SS due to chronic HCV infection. The slow course of the disease would possibly account for the discrepant findings that are reported.

A recent immunohistochemical study of lip biopsies from patients with SS showed a CD4 to CD8 T cell ratio of 2/1 within the lymphocytic infiltrate, irrespective of the presence or absence of chronic HCV infection. This finding suggests that chronic HCV infection induces sialadenitis

similar to that observed in primary SS<sup>42</sup>, but different from the predominantly CD8 T cell infiltration induced by HIV infection<sup>43</sup>. Moreover, Jorgensen, *et al*, using immunohistological techniques, revealed HCV viral proteins in minor salivary gland biopsies of patients with chronic HCV infection<sup>44</sup>.

*Factors associated with the presence of SS and primary SS in populations with HCV.* We found no relationship between HCV associated SS or primary SS and sex, disease duration, the presence of cirrhosis, and genotype. On the other hand, SS or primary SS was associated with older age, METAVIR activity, and fibrosis scores, but after Bonferroni correction, only METAVIR activity was significantly associated with primary SS. Chisholm and Mason focus score of at least grade III was also statistically associated with older age and METAVIR activity.

These findings suggest that lymphocytic infiltration on lip biopsy may represent a marker of liver disease activity. It is unlikely that the degree of lymphocytic infiltration could be attributed solely to the aging process. De Wilde, *et al* found a similar frequency of lymphoplasmocytic infiltrates in the sublabial salivary glands throughout different age groups of 68 healthy volunteers, with only 9% of cases corresponding to grades III or IV<sup>45</sup>.

In summary, chronic HCV infection may account for the pathogenesis of a subgroup of patients with Sjögren's syndrome characterized by the constant findings of oral dryness, the absence (or rarity) of systemic manifestations such as those frequently observed in primary SS, especially pulmonary and kidney involvement, and the lack of suggestive autoimmunity, e.g., autoantibodies against SSA or SSB antigens. Salivary glands of patients with primary SS with and without chronic hepatitis C probably share similar pathological changes. Discrepancies that have been reported concerning HCV related SS may be due to the lack of recognition that there are different stages in the same pathologic process (early disease inducing a pericapillary infiltrate and later stages inducing damage resembling primary SS). They could also be related to the mean age of patients, and finally, to genetic and environmental differences. Moreover, a relationship between lymphocytic infiltration on lip biopsy and liver disease activity is suggested. It is possible that HCV related SS represents an entity to be differentiated from isolated primary SS. Our data may be helpful in revising the criteria for the diagnosis of primary SS. In everyday practice, testing for HCV should be routinely performed in patients with primary SS and SS. This would lead to detection of additional cases of chronic hepatitis C and provide helpful prognostic information for Sjögren's syndrome.

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