Lack of Association of Fibromyalgia with Hepatitis C Virus Infection

JAVIER NARVÁEZ, JOAN M. NOLLA, and JOSÉ VALVERDE-GARCÍA

ABSTRACT. ***Objective.*** An association between chronic hepatitis C virus (HCV) infection and fibromyalgia (FM) remains controversial, mainly because previous studies were based on prevalent case series or comparisons with less than optimal control groups. We investigated whether there might be an association between chronic HCV infection and FM.

Methods. We prospectively investigated the prevalence of HCV infection in a series of 115 patients with FM and compared it with the prevalence in the general population of our community reported in the same period. Anti-HCV antibodies were determined by ELISA. In positive cases, infection was confirmed by recombinant immunoblot assay and HCV-RNA was detected by PCR using sera samples. Differences between prevalence rates were assessed by chi-square test.

Results. HCV infection was confirmed in 3 of 115 patients with FM (2.6%). Two of these patients (1.74%) had active HCV infection shown by the presence of viral RNA in serum, whereas HCV RNA was undetectable in the third patient. In these cases, liver disease had previously been undiagnosed and HCV infection manifested itself by extrahepatic symptoms. Although the prevalence of HCV infection was slightly higher in patients with FM than in the general population in the age groups 25–44 and 45–64 years, when we compared prevalence rates in the total group and the different age groups, no statistically significant differences were found.

Conclusion. From our results, it seems unlikely that HCV infection plays a pathogenic role in FM. (J Rheumatol 2005;32:1118–21)

Key Indexing Terms:
HEPATITIS C VIRUS INFECTION FIBROMYALGIA

Fibromyalgia (FM) is a common condition characterized by chronic diffuse musculoskeletal pain, fatigue, sleep disturbances, and a number of palpation tender points. Its etiology and pathogenesis are still poorly understood. Different theories have been proposed and besides genetic, neuroendocrine, psychological, and traumatic causes, a precipitating infectious factor has also been hypothesized based upon the observed similarities between FM and the chronic fatigue syndrome[1,2]. In recent years FM has been associated with different infectious agents such as human immunodeficiency virus (HIV), herpesvirus 6, coxsackie B virus, enterovirus, human parvovirus B19, Lyme disease, and hepatitis C virus (HCV)[1,2].

Among the several infections discussed, the association of FM with HCV infection has been the object of multiple studies[3-10]. However, it is critical to know if the reported associations with HCV infection are due to chance or if they indicate a cause-effect association. Since chronic HCV is relatively common, particularly in some subsets of the population, it might coexist with FM simply by chance alone. Thus, to show convincingly that FM is linked with HCV, studies that include control populations matched for age, sex, race, and other demographic variables are required. To our knowledge, no studies reporting linkage between HCV and FM have had that kind of ideal control population. Information that supports a causal relationship between HCV and FM comes basically from studies of the prevalence of FM in selected populations of patients with HCV infection, revealing a higher prevalence of this condition in HCV-positive patients compared to healthy controls[5-9]. By contrast, reports of systematic investigation of the seroprevalence for HCV in epidemiologically defined FM populations are scarce; at present only one study addressing this issue has been published, although that study used a series of patients with rheumatoid arthritis as a control group[10].

We investigated whether there might be an association between chronic HCV infection and FM; we prospectively determined the prevalence of HCV infection in a series of 115 patients with FM, in comparison with the prevalence of HCV infection in the general population of our community, Catalonia, an autonomous region in northeast Spain. Information on the extent of HCV in Catalonia comes from 2 major community based seroepidemiological surveys performed in the same period[11,12].

MATERIALS AND METHODS

Over an 8 year period (1996 to 2003), 115 patients with FM were prospec-

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tively studied. All patients met the 1990 American College of Rheumatology classification criteria for the diagnosis of FM[13]. Patients were excluded if they had disease other than HCV infection that could explain the presence of FM. All patients were evaluated at an outpatient rheumatology clinic. Demographic, clinical, and laboratory data were collected prospectively according to a specific protocol. Anti-HCV antibodies were tested using a commercial third-generation ELISA. In cases found to be positive, infection was confirmed by a third-generation recombinant immunoblot assay (RIBA), and the HCV RNA was detected in serum samples by polymerase chain reaction (PCR).

The prevalence of HCV infection in patients with FM was compared with the prevalence of HCV infection in the general population of our community reported in the same period. Information on the extent of HCV in Catalonia comes from 2 recent community based seroepidemiological surveys[11,12]. Both studies were performed on a representative sample selected at random from different Catalonian counties. In these studies the age and sex standardized prevalence of anti-HCV in the general population ranges from 2.5% (95% confidence interval 1.8–3.2)[11] to 2.64% (95% CI 2.53–2.75)[12]. Since the prevalence of HCV in the general population increases with age, the comparative study was performed on the total population and on different age groups (ages 25–45 and 45–65 yrs).

Statistical analysis. Continuous data were described as mean ± standard deviation and categorical variables as percentages. Differences between prevalence rates were assessed by the chi-square test. Statistical significance was defined as $p \leq 0.05$. The binomial proportion test was also calculated for completeness.

RESULTS

The series included 105 women and 10 men with a mean age at time of diagnosis of 45 ± 10 years (range 25–64). The mean duration of symptoms prior to the diagnosis was 5 ± 3 years (range 15 months–8 yrs). The main clinical features and laboratory data of these patients are summarized in Table 1. Nineteen of the 115 patients (17%) recalled an acute onset of the disease with "flu-like" symptoms.

Anxiety and/or depression were present in 85% of cases. Other associated findings less frequently observed were paresthesias (not in a dermatomal distribution), headaches (either tension or migraine), sicca symptoms with no evidence of underlying connective tissue disease, irritable bowel syndrome, subjective cognitive dysfunctions (concentration and minor memory deficits), atypical chest pain, and temporomandibular joint dysfunction. Of interest, 37% of the patients in our series were housemaids.

Laboratory studies (acute phase reactants, blood cell counts, coagulation tests, complete biochemical studies, and thyroid hormones) were normal in all patients, except in 2 cases who presented mildly elevated serum transaminases.

Anti-HCV antibodies were detected by ELISA in 3 of the 115 patients with FM (2.6%). The presence of HCV antibodies was confirmed by RIBA in all cases. Two of these patients had active infection by HCV, as shown by the presence of viral RNA in serum (with a viral load $< 0.2 \times 10^6$/ml), whereas in the others, HCV RNA was undetectable. In these cases, liver disease was previously undiagnosed and HCV infection manifested itself by extrahepatic symptoms. During followup in these patients, HCV infection remained paucisymptomatic, with clinically minimal liver disease (normal or mildly elevated serum transaminases on serial laboratory evaluations) and with no cirrhotic complications. Rheumatoid factor was positive in 2 of these patients and antinuclear antibodies (ANA) were positive at low titers in one, but none of them fulfilled diagnostic criteria for rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE). Anti-SSA and anti-SSB antibodies were negative in all cases.

Data for the age and sex standardized prevalence of HCV infection in the patients with FM and in the general population from the same geographic area are summarized in Table 2. Although the prevalence of HCV infection was slightly higher in patients with FM than in the general population in

Table 1. Clinical and laboratory data of patients with FM. Results are presented as mean ± standard deviation or number of cases with prevalence rates.

No. of patients	115
Age, yrs	45 ± 10
Women/men, n	105/10
Mean disease duration, yrs	5 ± 3
Associated findings, n (%)	
Anxiety and/or depression	98 (85)
Paresthesias, numbness, and tingling sensation	70 (61)
Headaches	58 (50)
Temporomandibular joint dysfunction	15 (13)
Sicca symptoms	23 (20)
Atypical chest pain	17 (15)
Vestibular dysfunction	4 (3)
Irritable bowel syndrome	22 (19)
Subjective cognitive dysfunctions	30 (26)
Restless-legs syndrome	7 (6)
Laboratory data, n (%)	
Elevated acute phase reactants	0 (0)
Hematological cytopenias	0 (0)
Elevated transaminases*	2 (3)
Elevated alkaline phosphatase	0 (0)
Positive rheumatoid factor	2 (3)
Positive ANA	1 (1)
Anti SSA/SSB antibodies	0 (0)

* Both patients had HCV infection.

Table 2. Comparative study of prevalence of HCV infection between patients with FM and the general population.

	Patients with FM, % (n)*	General Population, % (95% CI)	p
Age group			
25–44 yrs	2.22 (1/45)	1.74 (1.62–1.86)**	NS
45–64	2.85 (2/70)	2.54 (2.37–2.71)**	NS
Total	2.6 (3/115)	2.5 (1.8–3.2)† 2.64 (2.53–2.75)**	NS

* Results are presented as percentages (number of patients with HCV infection/number of patients of the group). When we considered only those FM patients with active HCV infection, the prevalence results were: age 25–44 years, 2.22% (1/45), 45–64 years, 1.42% (1/70), and total population, 1.74% (2/115). ** Age and sex standardized prevalences from Sola, *et al*[12] and † Dominguez, *et al*[11]. NS: not significant.

age groups 25–44 and 45–64 years, when we compared prevalence rates in both the total group and the different age groups, no statistically significant differences were found ($p > 0.05$, chi-square test; using the binomial proportions test, $p = 0.747$).

DISCUSSION

Given that chronic infection with HCV is relatively frequent, patients with many different diagnoses will be found who have coexistent HCV infection. In this way, numerous extrahepatic disease manifestations, mainly autoimmune disorders, have been reported to be associated with HCV infection[14-17]. However, there are conflicting reports for most of these associations, and definitive validation is lacking for all except for the association with mixed cryoglobulinemia and, probably, with membranoproliferative glomerulonephritis, porphyria cutanea tarda, lymphocyte sialadenitis, and B cell non-Hodgkin's lymphomas[14-17]. In the remaining reported extrahepatic manifestations, the critical determination of a specific role for HCV in the pathogenesis was not confirmed, and no evidence has been presented that this association is more frequent than might be expected by chance alone.

The possible association between chronic HCV infection and FM[3-10] provides an example. The possibility that HCV might be involved in the pathogenesis of FM is supported by several studies of the prevalence of FM in selected HCV infected patient populations[5-9]. In these reports, a moderate increase in the prevalence of FM was observed in HCV-positive patients (ranging from 5% to 19%) compared with healthy controls, which may support the impression of an apparent infectious disease relationship[7]. The majority of patients with FM associated HCV infection in these series had clinically minimal liver disease, with normal or mildly elevated liver enzymes. In these patients, the HCV infection remained undiagnosed, probably because of the low grade of liver disease. However, it should be noted that some authors suggest that FM-like symptoms were more common in patients with chronic HCV hepatitis who have higher liver transaminase levels[3]. The main limitation of these studies is a problem with patient selection bias that can produce false associations, particularly in endemic regions where coincidental disease is more likely to be observed. Moreover, we must remember that HCV infection can frequently present with fatigue and musculoskeletal symptoms, including arthralgias and myalgias[5,18]. Fatigue is present in 53% of patients, and is severe in 17% of cases, impairing activity[19]. Thus, HCV infection can mimic FM in the same way that it can mimic some connective tissue diseases, particularly SLE[20]. On the other hand, some of these reports had a relatively small number of patients and an inadequate number of controls, or lacked a control group.

Reports on systematic investigation of the seroprevalence of HCV in epidemiologically defined FM populations are scarce. To our knowledge there is only one study, conducted in another area of Spain, in which the authors also analyzed the prevalence of HCV infection in a series of patients with FM, although they used a series of patients with RA as a control group[10]. In that study, they found a higher prevalence of HCV infection in patients with FM (15%) in comparison with the patients with RA (5.3%). However, in contrast with these preliminary data, we found that the seroprevalence of HCV infection in patients with FM was not significantly increased compared to the general population of our region. According with our data, it seems unlikely that HCV infection plays a pathogenic role in FM. These conflicting results may be partly explained by variations in study design, particularly regarding the control population. Longer prospective studies with larger numbers of patients are necessary to confirm these results.

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