CONCISE REPORT

Prevalence of hepatitis C virus infection in patients with rheumatoid arthritis

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Background: Various viruses have been implicated in the cause and pathogenesis of rheumatoid arthritis (RA). Hepatitis C virus (HCV) infection, which has been recognised as a cause of some autoimmune diseases, and which has been described as sometimes presenting with rheumatic manifestations indistinguishable from RA, might be a candidate.

Objective: To evaluate the prevalence of HCV infection in patients with RA.

Methods: Consecutive patients with RA admitted to hospital in two departments of rheumatology were prospectively studied. Patients' serum samples were screened for the presence of anti-HCV antibodies. Patients with positive serology were further evaluated for the presence of HCV ribonucleic acid by reverse transcriptase polymerase chain reaction (RT-PCR).

Results: 309 patients (232 women, 77 men, mean age (SD) 54.1 (14.8) years) were studied. Their mean (SD) disease duration was 74.1 (91) months. Tests for rheumatoid factors and antinuclear antibodies were positive in 213 (69%) and 114 (37%) of the patients respectively. Systemic vasculitis was found in 12 (4%) of the patients. Mean erythrocyte sedimentation rate was 36.4 (SD 30.5) mm at the first hour (normal <10 mm) and C reactive protein was 36.8 (SD 45.8) mg/l (normal range <5 mg/l), respectively, with 181 (58.6%) of patients considered as having active disease. Aspartate transaminases were increased in 14 (4%) patients, and alkaline phosphatase in 14 (4%). A positive anti-HCV serology was found in two (0.65%) patients, including one with a previously diagnosed HCV infection. HCV RNA was positive by RT-PCR in one of those two patients.

Conclusion: A 0.65% prevalence of past or active HCV infection was found in patients with RA, which did not differ from the prevalence of HCV in the general French population. This result does not support the participation of HCV infection in the pathogenesis of RA.

Although much progress has been made in understanding the pathogenesis of rheumatoid arthritis (RA), its cause remains unclear. The disease might result from the interaction between a susceptible host and an environmental trigger.¹ Among the latter, implication of bacterial or viral infections has been proposed.^{2–4} However, there is no definite evidence to confirm such a hypothesis, possibly owing to the fact that several environmental factors, rather than a single one, might be capable of triggering RA.¹

With a seroprevalence of hepatitis C virus (HCV) close to 1% in the French population, 81% of seropositive subjects being also positive for HCV ribonucleic acid (RNA), and cirrhosis occurring in 20 to 25% of seropositive patients, HCV infection

seems to be a major public health concern.^{5–7} This infection is often associated with systemic clinical and laboratory manifestations, such as arthralgia, which occurs in more than 20% of patients, and serum positivity for rheumatoid factors (RFs) and antinuclear antibodies (ANAs).^{8,9} Moreover, HCV infection is associated with some immune mediated disorders, such as mixed cryoglobulinaemia^{6,7} and sicca syndrome, although its association with defined Sjögren's syndromes is much rarer.^{7,9–11} Additionally, although arthritis is less commonly associated with HCV infection than arthralgia,^{8,9} several authors described patients affected with HCV infection and chronic polyarthritis who fulfilled the American College of Rheumatology (ACR, formerly, the American Rheumatism Association) criteria for RA.^{12,13} Finally, serum anti-HCV antibodies were detected in 5.2% and 7.6% of patients with RA.^{14,15} Thus a causal link might exist between HCV and RA in some patients.

The objective of this study was to consider this question by evaluating the prevalence of HCV infection among patients with RA.

METHODS

Patients

Consecutive patients fulfilling the ACR criteria for RA and admitted to hospital between 1999 and 2001 in two rheumatology departments were prospectively studied.

Evaluation

All patients were given a careful physical examination, which systematically recorded the number of painful and swollen joints and the presence or absence of vasculitis. Routine laboratory investigations included determination of erythrocyte sedimentation rate (ESR), serum C reactive protein (CRP) concentration, serum aminotransaminase, gammaglutamyl transferase, and alkaline phosphatase concentrations, and IgM RF and ANA titres.

Additionally, patients' serum samples were screened for the presence of anti-HCV antibodies. Serum samples from the first department of rheumatology were tested using a microparticle enzyme immunoassay (AxSYM HCV version 3.0, Abbott). For confirmation of reactive specimens, an amicroplate ELISA (Monolisa antiHCV Plus version 2, BioRad) was used. Serum samples from the second department of rheumatology were tested using an amicroplate ELISA (Monolisa antiHCV Plus version 2, BioRad), with confirmation using another ELISA technique (Ortho HCV 3.0 ELISA test system with enhanced save). Samples positive by both techniques were considered as positive. Cases with positive serology were further evaluated

Abbreviations: ACR, American College of Rheumatology; ANA, antinuclear antibodies; ESR, erythrocyte sedimentation rate; CRP, C reactive protein; HCV, hepatitis C virus; RF, rheumatoid factor; RT-PCR, reverse transcriptase polymerase chain reaction

for HCV-RNA with a reverse transcriptase-polymerase chain reaction (RT-PCR) based method within the NS 5' NC gene (Amplicor HCV, Roche) followed by a reverse hybridisation for genotyping (Innolipa HCV II, Innogenetics).

Searches for serum antikeratin antibodies (indirect immunofluorescence on rat oesophagus) and HLA-DR typing, were not systematically performed but the results were recorded when available. An active disease was defined by the presence of at least three of the items: ≥ 6 painful joints; ≥ 3 swollen joints; ≥ 45 minutes of morning stiffness; ESR ≥ 28 mm/1st h.

RESULTS

Three hundred and nine patients (232 women, 77 men, mean age (SD) 54.1 (14.8) years) were included. The mean (SD) disease duration was 74.1 (91) months. Systemic vasculitis was seen in 12 (4%) patients. Sixty nine per cent of patients were positive for RFs and 37% for ANAs. A serological testing for antikeratin antibodies was performed in 146 patients, and was positive in 57 (39%). HLA-DR typing was carried out in 86 patients, and showed the following distribution of shared epitope: DR4/-X in 29 (34%), DR1/-X in nine (10%), DR4/-DR4 or DR4/-DR1 in 13 (15%), absence of DR1 and DR4 in 35 (41%). The mean ESR was 36.4 (SD 30.5) mm/1st h (normal < 10 mm), and mean CRP was 36.8 (SD 45.8) mg/l (normal range < 5 mg/l); 181 (58.6%) of the patients were considered to have active disease. Serum aminotransaminases, gamma-glutamyl aminotransferase, and alkaline phosphatases were increased in 14 (4%), 43 (14%), and 14 (4%) of the patients, respectively, most of the increased transaminases being due to therapy. A positive HCV serology was detected in two patients (0.65 %; 95% confidence interval (95% CI) 0.08% to 2.3%, exact binomial method). These two patients were women 39 and 79 years old with typical RF positive erosive RA of 96 and a 70 months' duration, and with no systemic vasculitis or Sjögren's syndrome. HCV infection had been previously diagnosed in the first. Serum aminotransaminases and alkaline phosphatases were in the normal range in both, whereas serum gamma-glutamyl aminotransferase was increased two-fold in one, and was in the normal range in the other. HCV RNA RT-PCR was positive in the first patient (the one with previously diagnosed hepatitis C virus infection), but was negative in the second (0.32%; 95% CI 0.008% to 1.8 %, exact binomial method).

DISCUSSION

Detection of serum anti-HCV antibodies is indicative of past or active infection. HCV viraemia as assessed by RT-PCR is a much more powerful indicator of chronic hepatitis due to the virus.⁵ Thus, we found a 0.85% prevalence of past or active, and a 0.42% prevalence of active HCV infection in patients with RA. Such prevalences do not differ from those in the general French population.⁵ These results do not support the participation of HCV infection in the pathogenesis of RA.

Two major hypotheses can be proposed to explain these results: HCV could be implicated in the cause of RA, at least in some RA subgroups, but this study failed to show a positive association; or HCV infection is not implicated in the pathogenesis of RA.

This study could have failed to show a positive association between HCV infection and RA for several reasons. Firstly, the sample of patients might not be representative of the RA population. However, all studied characteristics—that is, the sex ratio, the prevalence of shared epitope, the proportion of RFs, antikeratin antibodies, and ANA seropositivity, were comparable with those obtained in other RA populations. Nevertheless, the method of inclusion of our patients—through admission to hospital in rheumatology departments—might have introduced a selection bias, by recruiting patients with more severe RA than average.

However, the bias introduced by the recruitment of patients in hospital could have overestimated, rather than underestimated, the prevalence of HCV infection. Furthermore, although the size of the studied sample was large, it may not have been sufficient to eliminate an association of HCV infection in a subgroup of patients with RA. Regarding this point, we should highlight that the two HCV positive patients in this study had seropositive erosive RA. Finally, viraemia assessed by RT-PCR is a more sensitive indicator of chronic HCV infection than serology.⁵ Hence, some patients infected with HCV could have been missed in this study, because patients were systematically screened for anti-HCV antibodies with a search for HCV RNA only in cases of seropositivity. However, this methodology was used because the prevalence of patients negative for HCV by serology, but positive by RT-PCR seems to be very low.⁵ Some previous results, in which serum anti-HCV antibodies were detected in 5.2% and 7.6% of patients with RA,^{14,15} suggests that this study failed to show a true positive association between HCV infection and RA. However, the first study had only a few patients with RA (76).¹⁴ Moreover, in the second work, with 303 patients with RA, the confirmatory serological test performed in the 23 patients with positive HCV antibodies on ELISA was positive in only 13, indeterminate in three, negative in four, and not done in three, leading to a non-significant difference between patients with RA and controls in anti-HCV antibody positive proportions of patients.¹⁵ Moreover, the mean age of the control group was younger than the RA group (33.4 v 58.3 years). Finally, the recruitment through rheumatology clinics might have overestimated the prevalence of HCV infection in these previous studies.

As an alternative interpretation of our results, HCV infection might truly not be associated with RA. Thus, the reported cases of association between HCV infection and chronic polyarthritis fulfilling the ACR criteria for RA could be fortuitous, or correspond to a disease entity different from RA. The results by Cacoub *et al* support this hypothesis, as these authors did not find any patient with RA in a sample of 1614 patients with chronic HCV infection.⁸ In another study, most patients presenting with both HCV infection and polyarthritis, and fulfilling the ACR criteria for RA had mild non-erosive joint manifestations, responding to hydroxychloroquine and low doses of prednisone (≤ 5 mg/day).¹³ Thus, some patients infected with HCV might develop a non-erosive non-deforming polyarthritis mimicking RA. The confusion, increased by the cryoglobulinaemia induced high prevalence of RF in hepatitis C infection,⁶ might be of clinical importance as arthritis occurring in HCV infected patients might be cured by antiviral treatment.

These results indicate that the prevalence of HCV is not increased among patients with RA compared with the general population, and do not support the idea of participation of HCV infection 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.

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