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Prevalence of Rheumatoid Arthritis and Hepatitis C in Those Age 60 and Older in a US Population Based Study

FLORENCE C. HSU, GORDON STARKEBAUM, EDWARD J. BOYKO, and JASON A. DOMINITZ

ABSTRACT. ***Objective.*** A positive association between rheumatoid arthritis (RA) and hepatitis C virus (HCV) infection has been reported in clinic based cross sectional studies. We investigated if RA and HCV are associated in a population based survey.

Methods. Using data from the National Health and Nutrition Examination Survey III, hepatitis C and RA status were determined for subjects ≥ 60 years of age. RA was defined to be present when 3 of 6 American College of Rheumatology (ACR) criteria were met.

Results. Of 6596 subjects, 1827 (27.7%) were excluded due to missing data. Of the remaining 4769, 196 subjects (4.1%) met our modified ACR criteria for probable RA: 63 tested positive for anti-HCV antibodies (1.3%) while 35 were HCV RNA positive (0.7%). Two subjects had both HCV antibodies and RA, while one subject was both HCV RNA positive and had RA. HCV antibody positivity was not associated with RA (OR 0.44, 95% CI 0.07–2.80). Similarly, HCV positivity by polymerase chain reaction was not associated with RA (OR 0.77, 95% CI 0.10–6.19).

Conclusion. These results argue against a potential role for HCV in the etiology of RA in the US population aged 60 years and over. (J Rheumatol 2003;30:455–8)

Key Indexing Terms:
HEPATITIS C VIRUS RHEUMATOID ARTHRITIS RHEUMATOID FACTOR

Hepatitis C virus (HCV) seropositivity has been estimated to occur in 1.8% of the US population, or roughly 3.9 million persons, of whom 2.7 million have chronic infection with HCV[1]. The peak prevalence is highest among Americans aged 30–39 years (3.9%), with a prevalence of 0.9% in those 60–69 years of age and 1.0% in persons age 70 and older[1]. Hepatitis C infection is a leading cause of chronic liver disease and the most common etiology of endstage liver disease resulting in liver transplantation[2]. Rheumatologic complications of HCV infection have been reported and include mixed cryoglobulinemia, vasculitis, sicca symptoms, myalgias, and arthritis[3,4]. The presence of rheumatoid factor (RF) in viral diseases and hepatitis has also been well established[3,4].

The prevalence of rheumatoid arthritis (RA) in the general population is estimated at 1%, with increased prevalence with increasing age and among females[5,6]. RA is estimated to occur in 2% of men age 55 and older, 3% of women age 55–64, and 5% of women ≥ 65 years of age[5].

Arthritis associated with hepatitis C has been reported to be a mimic of RA[3]. Also, a potential association between RA and hepatitis C infection has been reported[7]. Rivera, *et al* tested 303 patients with RA in Southern Europe for HCV antibodies and found that 23 (7.6%) were positive. However, only 0.95% of the control group of first-time blood donors were positive for HCV antibodies ($p < 0.001$). Given that the patients with RA came from a clinic based population and the control subjects may have been prescreened for risk factors for hepatitis C, selection bias likely played a role in determining these results. To overcome this methodological problem, we used information gathered from a cross sectional population based survey of the general United States population to determine if there is an association between RA and HCV.

MATERIALS AND METHODS

The National Health and Nutrition Examination Survey (NHANES) is conducted periodically by the National Center for Health Statistics for the Centers for Disease Control and Prevention to obtain nationally representative data on the health and nutritional status of the noninstitutionalized civilian population by means of household interviews, standardized physician's physical examinations, and the collection and testing of blood samples in special mobile examination centers[8]. NHANES III was conducted between 1988

From the Seattle Epidemiologic Research and Information Center and the Arthritis and Gastroenterology Sections, VA Puget Sound Health Care System; and the Division of Rheumatology, University of Washington, Seattle, Washington, USA.

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F.C. Hsu, MD; G. Starkebaum, MD, VA Puget Sound Health Care System and Department of Medicine, Division of Rheumatology, University of Washington School of Medicine; E.J. Boyko, MD, MPH, Seattle Epidemiologic Research and Information Center, VA Puget Sound Health Care System, Department of Medicine, Division of General Internal Medicine, University of Washington School of Medicine; J.A. Dominitz, MD, MHS, Northwest Hepatitis C Resource Center, Seattle Epidemiologic Research and Information Center, VA Puget Sound Health Care System, Department of Medicine, Division of Gastroenterology, University of Washington School of Medicine.

Address reprint requests to Dr. J.A. Dominitz, VA Puget Sound Health Care System, 111-Gastro, 1660 South Columbian Way, Seattle, WA 98108-1532. E-mail: jason.dominitz@med.va.gov

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and 1994, and included a sample of roughly 34,000 persons aged 2 months and older in 89 randomly selected locations throughout the US. All participants provided informed consent, and no personal identifiers are included. We limited our analysis to the 6596 individuals age 60 and older as survey questions, physical examinations, and laboratory data focusing specifically on arthritis were directed only within this subset of participants.

NHANES III was based on a complex, stratified, multistage, probability-sample design[9]. Persons less than 5 years of age or 60 years of age and older, non-Hispanic blacks, and Mexican-Americans were sampled at a higher frequency than other persons. After weighting on the basis of age, sex, level of education, and race or ethnic group, the distribution of the participants was similar to that of the US population as a whole.

Laboratory methods. Serum samples were tested for anti-HCV by a second generation enzyme immunoassay and a supplemental test (EIA 2.0 and HCV Matrix, Abbott Laboratories, North Chicago, IL, USA) as described[1,9]. Patients with serum samples that were positive according to HCV Matrix results were considered positive for anti-HCV.

Testing for HCV RNA by reverse transcriptase-polymerase chain reaction (RT-PCR) amplification of the 5' noncoding region was performed on anti-HCV positive samples as described[1,9]. Samples found to be negative for HCV RNA were extracted a second time by the same procedure, with an additional incubation at 50°C for 45 min with 25 units of reverse transcriptase (Boehringer Mannheim, Indianapolis, IN, USA) and 10 units of RNAsin (Boehringer Mannheim).

Specimens for RF analysis were initially screened by latex enhanced nephelometry (Behring Nephelometer Analyzer System, OVCI11, Behring Diagnostics Inc., Somerville, NJ, USA)[9]. RF concentrations are calculated using a calibration curve. For quantification, all samples having nephelometric measurements > 13 IU/ml are titered in a 12 tube titer sequence in the Singer-Plotz agglutination procedure to determine reportable results. Positive tests from tube titer are reported to the last dilution showing visible agglutination. All samples with concentrations ≤ 13 IU/ml are run at 1:20 and 1:400 in the same procedure.

Ascertainment of RA. The most recent classification of RA is based on the revised 1987 American College of Rheumatology (ACR) criteria in which RA is defined as fulfilling 4 of 7 criteria[10]. The ACR criteria include morning stiffness lasting ≥ 1 h, arthritis of ≥ 3 joints, arthritis of hand joints, symmetry of arthritis, rheumatoid nodules, positive serum RF titer, and radiographic changes typical of RA. These criteria have been shown to have a sensitivity of 91% and specificity of 89%[10,11]. RF was considered positive if agglutination titer was ≥ 1:20. While radiographs of hands, wrists, and knees were done on all NHANES III subjects age 60 and older (about 10,400 radiographs total), these results are not yet available. Given the lack of radiographic information, only 6 of the 7 ACR criteria were available for analysis. Therefore, we defined probable RA as the presence of 3 of 6 ACR criteria, and defined possible RA as the presence of 2 of 6 ACR criteria. In all, there were 28 variables included to determine the presence or absence of RA. If a subject did not have data for at least 22 of these variables, they were excluded from the analysis.

Analysis. All analyses were conducted using statistical methods that took into account the complex design of this survey (Stata 7.0, Stata Corp., College Station, TX, USA). Each analysis incorporated subject selection design features (primary sampling unit, stratum) and appropriate sample weights based on the subsample employed in the analysis[12]. Proportions were compared using a design based F test. Mean values were compared using linear regression analysis, which is also used to assess the association between measures of RA in relation to HCV serology and covariates[13]. The relative odds of RA in relation to HCV serology and covariates were estimated using a design based logistic regression procedure[13].

RESULTS

The subset of 6596 NHANES III participants age 60 and older was evaluated for RA and HCV infection. Of the 6596 eligible persons, 1827 were excluded from the analysis because of missing HCV serology (n = 1634), indeterminate HCV status (n = 20), or missing variables for the determination of RA (n = 173). Rates of participation for anti-HCV testing were lower for subjects in the younger and older age groups[1]. Rates of participation were no different when persons who reported engaging in high risk behavior were compared with those who did not[1]. In our study, excluded subjects tended to be female, slightly older, and were more likely to be of black or white racial groups than those included in the analysis. Subject demographics, RA status, and hepatitis C status are shown in Table 1.

Of the 4769 participants, 196 (4.1%) met our definition of probable RA and 313 (6.6%) fulfilled the less strict criteria of possible RA (Table 1). Of the 196 subjects with probable RA, 113 (57.6%) were women. Subjects who met the criteria for probable RA tended to be older compared to those who did not meet these criteria (p = 0.02) and were also more likely to be female (p = 0.02). Mean duration of disease reported in subjects with probable RA was 15.2 years.

Of the 4769 subjects, 63 were anti-HCV positive (1.3%) and 35 (0.7%) were HCV RNA positive. Subjects with probable RA had similar proportions with HCV antibody positivity (p = 0.32) and HCV RNA positivity (p = 0.77) to those without evidence of RA. Subjects with possible RA also had similar proportions with HCV antibody positivity (p = 0.41) and HCV RNA positivity (p = 0.92) to those without evidence of RA.

Criteria for RA were analyzed in relation to HCV serology using logistic regression analysis. There was no significant association between probable RA and HCV status in a bivariate analysis and in a multivariate analysis adjusted for age, sex, and race (Table 2). Similarly, no significant association was seen with our less strict criteria of possible RA and either HCV seropositivity or HCV RNA positivity in bivariate and multivariate logistic regression analyses.

Among this subset of participants age 60 and older, men were less likely to have RA compared with women (OR 0.61, 95% CI 0.39–0.94), while increasing age was associated with higher odds of RA [OR 1.03 per year, 95% confidence interval (CI) 1.00–1.05]. There was no significant association between race and either probable or possible RA. The odds ratio (OR) for RA in relation to HCV serology showed a negative, but nonsignificant association between our definition of probable RA and HCV antibody positivity (OR 0.44, 95% CI 0.07–2.80). HCV RNA positivity was not associated with probable RA (OR 0.77, 95% CI 0.10–6.19). Similarly, no association was found in our definition of possible RA with respect to HCV antibody positivity (OR 0.66, 95% CI 0.20–2.15) or HCV RNA positivity (OR 0.90, 95% CI 0.20–4.12).

The independent associations between each ACR criterion with HCV status showed that only RF positivity had a strong association with anti-HCV and HCV RNA positivity (Table 3).

Table 1. Characteristics of subjects with RA and HCV antibody (AB) or PCR positivity.

Characteristics	No Evidence of RA, n = 4456	Probable RA, n = 196	Possible RA, n = 313	HCV Ab +, n = 63	HCV PCR +, n = 35
Age, median yrs (interquartile range)	71 (65–78)	71 (65–80)	72 (65–80)	70 (65–78)	73 (66–78)
Female, n (%)	2250 (50.5)	113 (57.7)	194 (62.0)	24 (38.1)	18 (51.4)
Non-Hispanic white, n (%)	2619 (58.8)	113 (57.7)	178 (56.9)	30 (47.6)	14 (40.0)
Non-Hispanic black, n (%)	843 (18.9)	32 (16.3)	56 (17.9)	18 (28.6)	13 (37.1)
Mexican-American, n (%)	851 (19.1)	50 (25.5)	76 (24.3)	12 (19.1)	5 (14.3)
Other race, n (%)	143 (3.2)	1 (0.5)	3 (1.0)	3 (4.8)	3 (8.6)
HCV Ab +, n (%)	58 (1.3)	2 (1.0)	5 (1.6)	—	35 (100)
HCV PCR +, n (%)	32 (0.7)	1 (0.5)	3 (1.0)	35 (55.6)	—

Table 2. Unadjusted and adjusted odds ratio and 95% confidence intervals for predictors of RA.

	Probable RA		Possible RA	
Variable	Unadjusted OR (CI)	Adjusted OR (CI)*	Unadjusted OR (CI)	Adjusted OR (CI)*
Age, per year	1.03 (1.00–1.05) p = 0.02	1.03 (1.00–1.05) p = 0.05	1.04 (1.02–1.06) p = 0.0002	1.03 (1.01–1.05) p = 0.001
Male, vs female	0.59 (0.38–0.91) p = 0.02	0.61 (0.39–0.94) p = 0.03	0.48 (0.33–0.72) p = 0.0006	0.50 (0.34–0.74) p = 0.001
HCV antibody +	0.40 (0.06–2.60) p = 0.33	0.44 (0.07–2.80) p = 0.37	0.62 (0.19–1.99) p = 0.41	0.66 (0.20–2.15) p = 0.48

*Adjusted for age, sex, and race.

Table 3. Association between American College of Rheumatology criteria for RA and hepatitis C (HCV) status.

Criteria	HCV Antibody Negative, n = 4706 (%)	HCV Antibody Positive, n = 63 (%)	HCV PCR Negative, n = 4734 (%)	HCV PCR Positive, n = 35 (%)
Morning stiffness ≥ 1 h	248 (5.3)	2 (3.2)	248 (5.2)	2 (5.7)
Arthritis of > 3 joints	259 (5.5)	3 (4.8)	261 (5.5)	1 (2.9)
Arthritis of hands	293 (6.2)	4 (6.3)	294 (6.2)	3 (8.6)
Symmetric arthritis	254 (5.4)	3 (3.2)	256(5.4)	1 (2.9)
RF titer ≥ 1:20	307 (6.5)	21 (33.3)*	314 (6.6)	14 (40.0)†
Rheumatoid nodules	30 (0.6)	0 (0)	30 (0.6)	0 (0)

* $p < 0.0001$ compared to HCV antibody negative subjects. † $p < 0.0001$ compared to HCV PCR negative subjects.

Of the 63 persons who were anti-HCV positive, 21 (33.3%) were RF positive compared with 307 of the 4706 (6.5%) anti-HCV negative persons who were RF positive ($p < 0.0001$). Similarly, 14 of the 35 (40.0%) patients with HCV RNA positivity were RF positive, while their HCV RNA negative counterparts were RF positive in only 314 (6.6%) persons ($p < 0.0001$).

DISCUSSION

This analysis of the NHANES III national survey data does not support a higher prevalence of hepatitis C infection among persons aged 60 and older with features of chronic inflammatory arthritis, which would include RA. Due to the design of the study, the information analyzed is dependent upon the completeness and accuracy of the cross sectional data collection in the NHANES III database. As this analysis of arthritis prevalence is based on surveying the civilian, noninstitutionalized population, certain excluded groups (e.g., the institutionalized elderly, active duty military) may have different rates of hepatitis C infection and RA. Nevertheless, the prevalence of both hepatitis C and RA in the database are consistent with previous estimates for both these disorders in similar populations[1,5,6].

The epidemiologic study of RA and most rheumatic diseases is a great challenge because there is no diagnostic "gold standard"[6]. Diagnostic criteria for the classification of RA were originally developed for clinical and epidemiological investigations to ensure uniformity among cases[6]. The clinical course of RA can often evolve insidiously and slowly. The median time between onset of symptoms and diagnosis can often take more than 6 months[6]. Those with inactive, mild, or early RA may not have demonstrated enough disease activity during the survey's physical examination to fulfill the criteria for RA. Potentially, these participants may only be identified by serial examinations over time, resulting in underestimation of the number of patients with RA.

In considering this potential underestimation of RA, we analyzed participants who fulfilled less strict criteria of possible RA (2 of 6 ACR criteria) according to HCV status. By using these less strict criteria, and in the absence of radiographic findings, patients with chronic arthritis other than RA, such as calcium pyrophosphate dihydrate deposition disease or polymyalgia rheumatica (PMR), may have been included. The clinical features of elderly onset RA (onset after age 60) may overlap with PMR[14,15]. Compared to patients whose RA begins after age 60, younger onset RA patients tend to have disease that more closely resembles "classic" RA, with small joint disease, subcutaneous nodules, positive RF, and a relatively long duration of disease[15-17]. The mean duration of disease reported in our participants was over 15 years, which is a pattern more consistent with those having younger onset, more "classic" RA. The long duration of disease would also make their arthritis unlikely to be confused with PMR. Even taking these factors into account, the prevalence of HCV seropositivity in the participants without arthritis was not different than in those with arthritis, which would include the participants with RA.

It is known that the prevalence of RA increases with age while the prevalence of HCV infection is lower among older persons[1,5,6]. The low prevalence of HCV infection in the older age groups is thought to be most likely due to the cohort effect, with the risk of acquiring HCV infection lower in the distant past than in the recent past[1]. The observation that the prevalence of RA increases in those over age 60, while the prevalence of HCV infection decreases in this particular population, could argue that there is no effect of HCV infection on the development of RA in this age group. Despite these observations, the older population included in this study allowed us to validly test whether an association exists between RA and HCV with perhaps greater power than in a younger population, due to the higher prevalence of RA with advanced age.

In this study, about one-third of patients with prior or current HCV infection were RF positive, reconfirming that RF positivity and HCV infection are associated[3,4]. The mechanism leading to formation of RF after HCV infection remains obscure. Direct infection of lymphocytes by HCV, as well as effects from chronic immune complex stimulation leading to increased RF production, have been postulated[18].

These results differ from previous studies suggesting an association of hepatitis C virus infection with RA[3,7]. Given that our results are based on a sample assembled using methods to achieve general representation of the US population, we believe that our results represent a more valid measure of this association in an older subset of the population in this country. Previous clinic based comparisons may have been susceptible to selection biases that might have caused spurious associations[19].

We conclude that there is no evidence to support an association between HCV and RA in the US population aged 60 years and over, arguing against a potential role of HCV in the etiology of RA in this particular age group.

REFERENCES

1. Alter MJ, Kruszon-Moran D, Nainan OV, et al. The prevalence of hepatitis C infection in the United States, 1988 through 1994. N Engl J Med 1999;341:556-62.
2. Seeff LB. Natural history of hepatitis C. Hepatology 1997;26: 21S-28S.
3. Lovy MR, Starkebaum G, Uberoi S. Hepatitis C infection presenting with rheumatic manifestations: a mimic of rheumatoid arthritis. J Rheumatol 1996;23:979-83.
4. McMurray RW, Elbourne K. Hepatitis C virus infection and autoimmunity. Semin Arthritis Rheum 1997;26:689-701.
5. Lawrence RC, Hochberg MC, Kelsey JL, et al. Estimates of the prevalence of selected arthritic and musculoskeletal diseases in the United States. J Rheumatol 1989;16:427-41.
6. Chan KA, Felson DT, Yood RA, Walker AM. Incidence of rheumatoid arthritis in central Massachusetts. Arthritis Rheum 1993;36:1691-6.
7. Rivera J, Garcia-Monforte A, Pineda A, Nunez-Cortes JM. Arthritis in patients with chronic hepatitis C virus infection. J Rheumatol 1999;26:420-4.
8. National Center for Health Statistics. Plan and operation of the Third National Health and Nutrition Examination Survey, 1988-1994. Vital and health statistics. Series 1. No. 32. Washington, DC: Government Printing Office, July 1994. DHHS publication no. (PHS) 94-1308.
9. US Department of Health and Human Services. National Center for Health Statistics. Third National Health and Nutrition Examination Survey, 1988-1994, NHANES III laboratory data file (CD-ROM). Public Use Data File Documentation Number 76200. Hyattsville, MD: Centers for Disease Control and Prevention; 1996.
10. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-24.
11. Hulsemann JL, Zeidler H. Diagnostic evaluation of classification criteria for rheumatoid arthritis and reactive arthritis in an early synovitis outpatient clinic. Ann Rheum Dis 1999;58:278-80.
12. US Department of Health and Human Services. National Center for Health Statistics. Third National Health and Nutrition Examination Survey, 1988-1994, NHANES III analytic and reporting guidelines (CD-ROM). Public Use Data File Documentation Number 76200. Hyattsville, MD: Centers for Disease Control and Prevention; 1996.
13. Kahn HA, Sempos CT. Statistical methods in epidemiology. New York: Oxford University Press; 1989.
14. Healy LA, Sheets PA. The relation of polymyalgia rheumatica to rheumatoid arthritis. J Rheumatol 1988;15:750-2.
15. Deal CL, Meenan RF, Goldenberg DL, et al. The clinical features of elderly-onset rheumatoid arthritis. Arthritis Rheum 1985; 28:987-94.
16. Terkeltaub R, Esdaile J, Decary F, Tannenbaum H. A clinical study of older age rheumatoid arthritis with comparison to a younger onset group. J Rheumatol 1983;10:418-24.
17. Ehrich GE, Katz WA, Cohen SH. Rheumatoid arthritis in the aged. Geriatrics 1970;25:103-13.
18. Wener MH, Johnson RJ, Sasso EH, Gretch DR. Hepatitis C virus and rheumatic disease. J Rheumatol 1996;23:953-9.
19. Strassburg CP, Obermayer-Straub P, Manns MP. Autoimmunity in hepatitis C and D virus infection. J Viral Hepatol 1996;3:49-59.