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Hepatitis C virus infection and biological false-positive syphilis tests

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Abstract

Background—The diagnosis of syphilis requires two-step serological testing. Not infrequently, sensitive screening tests are reactive but are not confirmed by more specific confirmatory tests yielding a biological false positive (BFP). This study sought to describe the prevalence of BFP in a large population of hepatitis C virus (HCV)-infected and uninfected women.

Methods—A cross-sectional serosurvey of HIV-seropositive and HIV-seronegative women enrolled in the Women's Interagency HIV Study, a multicentre collaborative study of the natural history of HIV in women.

Results—Among HCV-infected women 4% had a BFP compared with 1% among those who were HCV uninfected (odds ratio (OR) 3.3, 95% CI 2.1 to 5.1). Controlling for both HIV infection and a history of intravenous drug use among all tests for syphilis a BFP also occurred more commonly in HCV-infected women compared with HCV-uninfected women (6% vs 1%, OR 7.62, 95% CI 1.9 to 12.5).

Conclusion—HCV infection is associated with various effects on immune function including alterations in serological test results. Women with HCV are more likely to have a BFP syphilis test than women without HCV.

Non-specific screening tests for syphilis can yield a biological false positive (BFP), which is associated with lupus, intravenous drug use (IDU) and HIV.1 2 Hepatitis C virus (HCV) has

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also been linked with a BFP.3 4 We demonstrate this association in a large cohort of HIV-infected and uninfected women.

METHODS

The Womens Interagency HIV Study (WIHS) is a prospective study of HIV infection in women and includes both HIV-seropositive and HIV-seronegative participants.[5] All enrollees were screened for antibodies to HCV using a second-generation enzyme immunoassay (HCV EIA 2.0; Abbott Laboratories, Abbott Park, Illinois, USA). When HCV EIA 3.0 (Ortho-Clinical Diagnostics, Raritan, New Jersey, USA) became available, testing was repeated on stored sera. A total of 3666 women underwent HCV testing. HCV-seropositive women were tested for HCV RNA using the COBAS Amplicor Monitor 2.0 (Roche Diagnostics, Branchburg, New Jersey, USA) and the Amplicor 2.0 HCV (Roche Diagnostics). Study enrollees underwent syphilis testing using the rapid plasma reagin (RPR) test, the fluorescent treponemal antigen-absorption test, the microhaemagglutination-*Treponema pallidum* test or the *T pallidum* particle agglutination test depending on the local laboratory protocol. A BFP was defined as a reactive syphilis screening test unconfirmed by the fluorescent treponemal antigen-absorption test, the microhaemagglutination-*T pallidum* test or the *T pallidum* particle agglutination test. A stratified analysis using χ^2 tests, odds ratios (OR) and 95% CI were determined using SPSS (version 11.0). Data were reviewed retrospectively.

RESULTS

A total of 1256 women (33%) was HCV seropositive. [6] Most of the women were over 35 years of age, African-American and high school graduates. More than 90% of the women admitted to IDU and/or other forms of drug use in the past. Pregnancy at enrollment was rare.

One hundred and eighty (14%) of those who were HCV seropositive and 174 (7%) of those who were HCV seronegative were RPR reactive (OR 2.15, 95% CI 1.7 to 2.7; table 1). Fifty-five (31%) of those who were HCV positive/RPR positive and 33 (19%) of those who were HCV negative/RPR positive had non-reactive treponemal-specific serological tests (OR 1.9, 95% CI 1.1 to 3.1). These represented 4% of all HCV-positive and 1% of all HCV-negative women (OR 3.3, 95% CI 2.1 to 5.1).

A BFP was more common among those who were HCV seropositive controlling for IDU history. A total of 378 HCV-seropositive and 2365 HCV-seronegative women reported no IDU. Fifty-eight (15%) of the HCV-seropositive women with no IDU history and 163 (7%) of the HCV-seronegative women with no history of IDU had a reactive RPR (OR 2.5, 95% CI 1.8 to 3.4). Fourteen (24%) of these HCV-positive/RPR-positive women had a BFP. Thirty-one (19%) of the non-IDU HCV-negative/RPR-positive women had a BFP (NS). Among all HCV-seropositive and all HCV-seronegative women without an IDU history a BFP occurred in 4% and 1%, respectively (OR 3.1, 95% CI 1.6 to 5.9).

There were 933 HIV-seronegative women whose HCV serostatus was available. Of these, 185 (20%) were HCV seropositive and 748 (80%) were HCV seronegative. Both a reactive RPR and a BFP were more common for those HIV-uninfected women who were HCV seropositive.

Among HCV-positive/HIV-negative women without a history of IDU, 30% of reactive RPR were a BFP compared with 17% of those who were HCV negative/HIV negative without a history of IDU (NS). The prevalence of a BFP for all those who were HCV positive/HIV negative and non-IDU was 6% compared with 1% for those who were HCV negative/HIV negative, non-IDU (OR 7.6, 95% CI 1.9 to 12.5). RPR specificity for syphilis in this select group was 92.9% among HCV-seropositive women and 99.1% among HCV-seronegative women.

Of 1070 HCV-seropositive women, 860 (80%) were positive for HCV RNA. RPR were reactive in 16%, of which 28% were BFP. Two hundred and forty-two HCV-seropositive women were negative for HCV RNA. RPR were reactive in 11%, of which 12% were BFP. A trend was suggested but was not significant.

DISCUSSION

In this cohort a BFP was associated with HCV infection controlling for IDU and HIV. Patients with HCV attending the Baltimore City sexually transmitted disease clinic were found to have a fourfold higher incidence of BFP than uninfected patients.[3] The impact of HIV or IDU history was not clarified. A similar observation was made in a study from Turkey.[4] Our large cohort permits the observation of BFP in HCV independent of HIV and IDU. The reason for this association is unclear. It may relate to the association of other extrahepatic, autoimmune phenomena reported in HCV.

This study has several drawbacks. It was retrospective and limited to women. Syphilis testing was done in local laboratories under unique conditions. IDU history was ascertained by self-report. The reliability of self-reported drug use may be good.[7] Recent data suggest that the transmission of HCV through non-IDU means (ie, sexual) may be more common than appreciated.[8]

HCV needs to be conclusively considered a cause of BFP. It makes an already non-specific treponemal test less specific. HCV might alter the operational parameters of other treponemal-specific serological tests or serological tests used for other non-syphilis clinical conditions.

Key messages

Non-treponemal serological tests (eg, RPR) are frequently reactive in individuals with HCV infection.

In patients with evidence of HCV infection reactive non-treponemal serological tests are often not confirmed by reactive treponemal-specific tests and therefore should be considered less specific for detecting true disease.

Discordant treponemal serological tests in HCV-infected individuals appear to occur independently of a history of IDU or HIV infection.

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Table 1

BFP results as a proportion of reactive syphilis serological tests by HCV serostatus

	HCV antibody +	HCV antibody −	OR (95% CI)
All	1256	2410	
RPR reactive	180 (14%)	174 (7%)	2.15 (1.7 to 2.7)
BFP	55	32	
Of all reactive RPR	(31%)	(19%)	1.9 (1.1 to 3.1)
Of all syphilis tests	(4%)	(1%)	3.3 (2.1 to 5.1)
No history of IDU	378	2365	
RPR reactive	58 (15%)	163 (7%)	2.5 (1.8 to 3.4)
BFP	14	31	
Of all reactive RPR	(24%)	(19%)	NS
Of all syphilis tests	(4%)	(1%)	3.1 (1.6 to 5.9)
HIV seronegative	185	748	
RPR reactive	21 (11%)	37 (5%)	2.5 (1.4 to 4.3)
BFP	10	7	
Of all reactive RPR	(48%)	(19%)	3.9 (1.0 to 15.2)
Of all syphilis tests	(5%)	(1%)	6.0 (2.1 to 15.0)
HIV seronegative/no history of IDU	48	692	
RPR reactive	9 (19%)	35 (5%)	4.3 (2.0 to 9.7)
BFP	3	6	
Of all reactive RPR	(33%)	(17%)	NS
Of all syphilis tests	(6%)	(1%)	7.6 (1.9 to 12.5)

BFP, biological false positive; HCV, hepatitis C virus; IDU, intravenous drug use; NTST, non-treponemal serological test; OR, odds ratio; RPR, rapid plasma reagin.