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Prevalence of Hepatitis C Virus Antibody in Patients With Sexually Transmitted Diseases Attending a Harrisburg, PA, STD Clinic

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ABSTRACT

Objective: The prevalence of hepatitis B and hepatitis C in a sexually transmitted disease (STD) clinic population was studied, along with the prevalence of various STD agents, in an attempt to identify possible STD markers for the hepatitis C virus and help delineate the role of hepatitis C as an STD. The hepatitis C antibody rates found in the STD clinic were also compared with those found among patients attending a local OB/GYN clinic and those enrolled in a blood donor program, all from the same geographical area.

Methods: A total of 150 women attending an STD clinic were examined for each of the following agents: ***Chlamydia trachomatis, Neisseria gonorrhoeae,*** syphilis, hepatitis B surface antigen, hepatitis B core antibody, hepatitis B surface antibody, and hepatitis C virus antibody. Additionally, several patients who signed informed consent to be evaluated for human immunodeficiency virus (HIV) antibody were tested by an enzyme immunoassay (EIA) screen method. The prevalence of each agent was then compared with the other agents.

Results: The overall prevalence rates detected were as follows: hepatitis B 16%, hepatitis C 4%, chlamydia 18.7%, gonorrhea 7.4%, syphilis 0.7%, and HIV 0%. Hepatitis C antibody was detected in 4% of patients in the STD clinic, 0.76% of volunteer blood donors from central Pennsylvania, and 0% of patients studied from the Harrisburg Hospital (Harrisburg, PA) prenatal population.

Conclusions: This screening study reveals an association between attending a Harrisburg, PA, area STD clinic and having an increased prevalence of hepatitis C antibody, but larger matched control studies will be needed to help clarify sexual transmission as a mode of transmission for the hepatitis C virus.

KEY WORDS
Incidence, non-A, non-B hepatitis, STD

Post-transfusion hepatitis is reported in 10–20% of patients receiving 3 or more units of blood. Many patients who contract hepatitis have no detectable antibody against type A or B hepatitis viruses and are classified as having non-A, non-B hepatitis. Ninety percent of post-transfusion hepa-

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titis has now been attributed to non-A, non-B hepatitis worldwide.[1,2] However, this type of transmission was recently estimated to account for as low as only 10–15% of patients with non-A, non-B hepatitis.[3] Recently, the isolation and cloning of a piece of DNA from non-A, non-B hepatitis virus and development of an assay for the antibody to hepatitis C virus (HCV) made possible the detection of many patients with a non-A, non-B hepatitis and the examination of transmission routes.[4,5] Recently, a 2nd-generation test for the detection of antibody vs. HCV was licensed.[6] This 2nd-generation test offers the advantage of increased sensitivity and specificity for the determination of HCV antibody.[5,6] Results have suggested that HCV is the major cause of transfusion-related non-A, non-B hepatitis,[7] especially in those cases that develop chronicity.[8] Additionally, HCV appears to be the major cause of a number of community-acquired non-A, non-B hepatitis for which no history of percutaneous exposure has been identified.[1,2,9]

Studies investigating the possible sources of infection for non-A, non-B hepatitis or HCV without a history of percutaneous exposure have been contradictory to date. Several small case reports have been published recognizing possible transmission due to perinatal and conjugal relationships that follow patterns similar to transmission of hepatitis B, human immunodeficiency virus (HIV), and human T-lymphotropic virus type I (HTLV 1).[10,11] In addition, other papers including studies relating HCV to patients with sexually transmitted diseases (STDs)[6,12] and to heterosexual activity with more than 1 partner have been published.[13] Contrary to these findings, other investigations have suggested only rare sexual transmission of HCV among homosexuals[3] and among sexual contacts of high-risk intravenous (IV)-drug abusers.[2]

To further delineate the possible method of spread for HCV, we studied the prevalence of hepatitis B infection and hepatitis C infection in an STD clinic population and correlated other known STDs as possible markers for patients at high risk for hepatitis B and hepatitis C.

SUBJECTS AND METHODS

Subjects

Women attending a Harrisburg area STD clinic were included in the study if they signed informed consent and completed a questionnaire assessing their risk factors (Table 1). Black, Caucasian, and Hispanic individuals were included in the study. The prevalence of hepatitis C in the central Pennsylvania blood donor population and the Harrisburg Hospital prenatal population was also evaluated.

TABLE 1. Demographic and clinical information collected on STD patients

Today's date: Age:		
1. Race (circle one): Black White Hispanic Asian Other		
2. Did you have a blood transfusion (received blood) between 1979 and May 1985?	Yes	No
3. Has there been any one year since 1980 during which you had more than 5 partners?	Yes	No
4. In the past 9 years, have you had sex with a person who was		
A. an IV drug abuser	Yes	No
B. a hemophiliac	Yes	No
C. a bisexual	Yes	No
D. a prostitute	Yes	No
5. Have you ever had sex with anyone who (to your knowledge) had AIDS or was infected with the AIDS virus?	Yes	No
6. Have you ever had any of the following STDs?		
Gonorrhea	Yes	No
Herpes	Yes	No
Chlamydia	Yes	No
Syphilis	Yes	No
Genital warts	Yes	No
Pelvic inflammatory disease	Yes	No
7. In the past 9 years, have you used IV drugs?	Yes	No
8. Have you ever had sex in exchange for money or drugs?	Yes	No

Laboratory Methods

Chlamydia trachomatis

Two direct antigen tests (enzyme immunoassay [EIA] methods, Chlamydiazyme, Abbott Laboratories, Abbott Park, IL, and a research membrane filtration technique, Seradyn, Inc., Indianapolis, IN) and culture were performed on the specimens collected from the patients for the diagnosis of infection with *C. trachomatis*. In addition, the culture transport fluid was analyzed by direct immunofluorescence (DFA) for the presence of *C. trachomatis* antigen as previously described.[14] A specimen was considered positive for *C. trachomatis* if the culture was positive or if 2 of the 3 direct antigen tests were positive. All chlamydial procedures were performed according to the manufacturers' specifications.

TABLE 2. Percentage of patients exhibiting multiple risk factors

Total number of risk factors	%
0	35
1	37
2	17
3	6
4	4
5	0
6	1
Total	100

Hepatitis B Testing

Auszyme, hepatitis BsAg (HBsAg), Corzyme, anti-hepatitis B core antigen (anti-HBc), and Ausab, anti-hepatitis Bs antigen (anti-HBs; Abbott Laboratories) were performed according to the manufacturer's specifications. Only those specimens that were repeatedly reactive were classified positive. For statistical analysis, those patients who exhibited 1 or all of the above markers without history of vaccination were considered to have evidence of hepatitis B infection at some time in the past.

Hepatitis C Testing

The presence of serum HCV (anti-HCV; Abbott Laboratories) antibody was measured according to the manufacturer's specifications. Both 1st- and 2nd-generation tests for the detection of antibody vs. HCV were used. Each reactive result was confirmed in duplicate and sent for confirmatory testing. The confirmatory test performed was the Chiron HCV recombinant immunoblot assay (RIBA; Chiron Corporation, Berkeley, CA).

Bacterial Culture and Syphilis Serology

Gonococcal cultures were performed on Martin Lewis agar medium in a 5% carbon dioxide atmosphere. Standard bacteriologic techniques were used to identify the isolates.[15] Syphilis serology utilized a standard Rapid Plasma Reagin (RPR) assay.[16]

Statistical Analysis

The goal of our analyses was to determine whether there was a significant association between the STDs, i.e., whether presence of 1 STD increased the chance of having another. Thus, every pair of STDs was tested for association using the Fisher-Irwin exact test (Table 2).[17] To determine whether the observed associations would hold up after controlling for STD risk status, we classified the women into high-risk and low-risk strata, then carried out a stratified analysis using the Cochran-Mantel-Haenszel (CMH) test.[18] We determined risk status by questionnaire and chart review (Table 3). Using these criteria, we called subjects "low risk" if they had no known behavioral or medical risk factors and classified those subjects with any risk factors as "high risk." Most computations were executed in the S-Plus language on a Sun SPARCstation 1 workstation.[19] Exact tests were computed with StatXact, version 2.0 (Cytel, Cambridge, MA).

TABLE 3. Total number of patients categorized by questionnaire and chart review for demographic data and risk characteristics

	%
Race	
Hispanic	4
Caucasian	49
Black	46
Asian	0
Other	1
Total	100
Age (years)	
13–20	45
21–30	37
31–40	14
41–50	3
51–54	1
Total	100
High-risk sexual practices	
Multiple sex partners	17
With IV-drug user	10
With hemophiliac	0
With bisexual	4
With prostitute	1
With someone having AIDS	1
For money or drugs	2
Previous medical conditions	
Blood transfusion	2
Gonorrhea	19
Syphilis	3
Herpes	3
Genital warts	19
Chlamydia	23
Pelvic inflammatory disease	6

RESULTS

Demographic information on patients seen at the Harrisburg area STD clinic is presented in Table 3. Subjects ranged in age from 13 to 54 years. The most frequent risk factors are presented as percentages in Table 3 and by prevalence in Table 2. The most prevalent risk factor was multiple sexual partners—26 (17%), followed by sex with an IV-drug

TABLE 4. Prevalence rates of 6 STDs with *P* values for tests of association[a]

Disease (prevalence)	*P* value from test of association				
	Hepatitis C	Chlamydia	Gonorrhea	Syphilis	HIV
Hepatitis B (16.0%)	0.052	0.701	0.557	0.327	ND
Hepatitis C (4.0%)		0.717	0.063	0.082	ND
Chlamydia (18.7%)			0.034	0.189	ND
Gonorrhea (7.4%)				0.151	ND
Syphilis (0.7%)					ND
HIV (0%)					

[a]*P* values are from 1-sided Fisher exact tests of the hypothesis of no association between the diseases against the alternative of positive association. ND indicates insufficient data to test the hypothesis. Sample sizes are 149 for gonorrhea, 148 for syphilis, 27 for HIV, and 150 for hepatitis B and C and chlamydia.

abuser—15 (10%). Thirty-five patients admitted to having had a chlamydial infection at some time in the past. There were 53 "low-risk" and 97 "high-risk" subjects as defined in the previous section. Prevalence rates of 6 STDs are presented in Table 4. When the 1-sided Fisher-Irwin test was performed, associations between chlamydia and gonorrhea ($P = 0.034$) and between hepatitis B and hepatitis C ($P = 0.052$) were found. After stratification using the CMH test, the chlamydia/gonorrhea test ($P = 0.052$) and the hepatitis B/hepatitis C test ($P = 0.086$) approach significant positive associations. These results support conclusions reached using the Fisher-Irwin test mentioned earlier. The only statistically significant association following stratification was found between hepatitis C and syphilis ($P = 0.044$). However, the association between these 2 diseases was negative.

Seven patients were found to be repeatedly reactive by the HCV EIA procedure. Six of the 7 (85.7%) reactive EIA specimens were found to be positive for antibody to HCV by the 2nd-generation HCV (EIA) procedure and by the RIBA. Of these 6 patients, 3 were also positive for hepatitis B core antibody. Of the subjects who were confirmed positive for HCV antibody, only 1 (16%) had no risk factor as defined earlier. Three or 50% of the HCV-positive subjects had multiple risk factors with the most common risk factors being previous blood transfusion (50%), IV-drug abuse (33%), and multiple sexual partners (33%). No statistically significant associations were found for HCV-positive subjects and their risk factors. Other STDs were detected in those patients positive for HCV; however, no statistically significant association was determined. The overall prevalence of hepatitis C in 3 populations (STD, prenatal, and blood donor) is presented in Table 5. They are significantly different by the exact test on the 3×2 table ($P = 0.0005$). Pairwise differences are significant for STD clinic vs. blood donor ($P = 0.0012$) and STD clinic vs. prenatal ($P = 0.04$). The blood donor and the prenatal groups are not significantly different.

TABLE 5. Comparison of hepatitis C antibody in 3 Harrisburg patient populations[a]

Population studied	Prevalence
STD clinic	6/150 (4%)
Blood donor	59/7,744 (0.76%)
Prenatal	0/100 (0%)

[a]All positive HCV antibody tests were confirmed by RIBA.

DISCUSSION

HCV has been shown to be the causative agent of the majority of cases of post-transfusion hepatitis,[1,20,21] especially high-risk transfusion patients such as hemophiliacs,[22–24] chronic renal patients, and those patients with recent cardiac surgery.[24] In addition, the agent has been found in U.S. veterans,[25] and implicated in maternal transmission,[11,26] sexual transmission,[12,13,27] and IV-drug abuse.[28,29] The purpose of the present study was to explore the relationships between STDs and current or prior HCV infection and thus identify known STDs as possible markers for HCV. To discriminate the prevalence of HCV in the high-risk groups from that in the normal population, we studied the prevalence of HCV in 2 low-risk patient populations in the Harrisburg area.

Positive associations between STDs were found in the 150 STD patients studied. As expected, pa-

tients positive for *C. trachomatis* were likely to be infected with *N. gonorrhoeae*. We also found hepatitis B virus (HBV) and HCV to be associated with one another. The presence of hepatitis B markers (anti-HBc, anti-HBe, HBeAg) has been related to the presence of HCV in blood donors and chronic HCV carriers.[30,31] However, significant debate continues on the reliability of surrogate markers in blood donor populations for predicting the presence of HCV.[32–34]

HBV and HCV seem to be transmitted concomitantly in the United States and most of Europe, while Japan and selected countries in Europe show little or no association between transmission of HBV and HCV. Differences in these associations could possibly be due to some unknown risk factors that are found in certain geographical locales and not in others. It has been suggested that several classes of HCV exist, with varying subtypes more prevalent in different countries. Geographical and/or genetic differences have yet to be explored as a method for interpreting transmission routes and prevalence rates. Studies have also suggested that heterosexual promiscuity and/or homosexual promiscuity with evidence of numerous prior STDs constitute significant risk factors for the transmission of both HBV and HCV.[12,13,27] Considerable debate over the role sexual practices have on the transmission of HCV can be found in the current literature.[3,9]

In the present study, antibody to HCV was detected in 4% of patients attending a Harrisburg area STD clinic, in 0.76% of volunteer blood donors from central Pennsylvania, and in none of the patients studied from Harrisburg Hospital's prenatal population. Hess et al.[9] found similar results with 4.7% and 0.51% positive anti-HCV results from STD and blood donor patients, respectively. Additional studies in the current literature have shown that the positive rates for HCV in blood donors range between 0.5 and 1.5%[1,21,34,35] Positive rates for sexual transmission of non-A, non-B hepatitis in heterosexual and homosexual populations have ranged between 4.7 and 50%.[9,12,13,27,35] Additional risk factors have included race, nationality, sex of the patient, multiple sexual partners, IV-drug abuse, previous or concurrent positive tests for HBV and HIV, and evidence of multiple STDs. Our data differ slightly from a recently published review by Lynch-Salamon and Combs.[35] The incidence reported in their review of the literature agrees with our data for blood donors and for those patients attending an STD clinic. However, the incidence of HCV positivity by risk groups in our study is lower than that previously reported.[35] This is undoubtedly due to the small number of HCV-positive patients found in the Harrisburg area STD clinic. The present study shows that attending a Harrisburg area STD clinic is associated with an increased prevalence of HCV compared with 2 other low-risk populations in the same geographical area. However, we were unable to identify any specific disease among the known STDs that correlated statistically with the presence of HCV for use as a marker for HCV infection. Additional larger studies involving matched controls would be helpful in order to help clarify the mode of transmission of HCV.

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