Prevalence of Hepatitis A, Hepatitis B, and HIV Among Hepatitis C–Seropositive State Hospital Patients: Results From Oregon State Hospital

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Background: Multiple studies have shown that individuals with severe mental illness are at increased risk for acquiring infection from human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV). Moreover, patients with chronic HCV infection are at risk for fulminant hepatitis from acquired infection with hepatitis A virus (HAV) or HBV, but there are limited data on the prevalence of HIV, HAV, and HBV in chronically hospitalized U.S. psychiatric patients without mental retardation who are HCV-seropositive. To address this issue, a comprehensive screening program was commenced at Oregon State Hospital (Salem, Ore.) beginning in 1999.

Method: The computerized records of all nongeriatric adult inpatients at Oregon State Hospital on April 23, 2001, were reviewed to assess physician compliance with screening and the prevalence of infection with HIV, HAV, HBV, and HCV.

Results: Among the 535 patient records reviewed, 94.8% of patients were screened for HCV, of whom 20.3% were seropositive. Among HCV-seropositive patients, only 1.9% were not screened for HAV and HBV, but 23.3% were not tested for HIV. In the HCV-seropositive group, 35.9% were HAV-positive, 49.5% HBV-positive, and 2.6% HIV-positive.

Conclusion: Chronic psychiatric inpatients have high HCV prevalence rates. Hepatitis C–seropositive individuals may be at risk for complications unless vaccinated for HAV and HBV.

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Patients with chronic severe mental illness have greater prevalence and severity of medical illness resulting in increased standardized mortality rates for many health conditions.[1,2] Both undertreatment of medical conditions and lifestyle behaviors contribute to the excess medical morbidity in patients with chronic mental illness, with the latter implicated as a primary explanation for the higher prevalence of sexually transmitted diseases seen in this population.[3,4] Among lifestyle-related factors, patients with chronic severe mental illness have high rates of homelessness, substance abuse or dependence (especially intravenous drug abuse), and high-risk sexual activity (e.g., absence of condom use, multiple partners, sexual activity while intoxicated), all of which increase the likelihood of contracting blood-borne pathogens such as human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV).[5–7]

A burgeoning literature on the subject of chronic mental illness and HIV developed in the 1990s documenting prevalence rates of HIV infection 15 to 50 times that of the general U.S. population (0.3%–0.4%), yet these studies focused primarily on urban settings in individuals with high rates of substance use and homelessness, a group not necessarily representative of the larger population of chronically mentally ill patients.[8–10] To address the fundamental lack of comprehensive data regarding prevalence of HIV, HBV, and especially HCV, the National Institute of Mental Health and Department of Veterans Affairs (NIMH/VA) sponsored a multicenter study of patients with chronic mental illness from diverse urban and rural backgrounds in Connecticut, Maryland, New Hampshire, and North Carolina.[7] This study revealed site-weighted prevalences of 3.1% for HIV (N = 931), 19.6% for HCV (estimated U.S. prevalence 1.8%), and 23.4% for HBV (estimated U.S. prevalence 4.9%) among the 751 individuals with blood suitable for HBV and HCV testing.[7] These data represented the first large U.S. surveillance study of HIV, HBV, and HCV in chronically mentally ill patients not drawn primarily from either urban or veteran populations and was driven in large measure by the need to accurately assess the prevalence of HCV in this cohort.

Chronic infection with hepatitis C has become a recognized public health issue over the past decade due to the development of reliable testing for the virus and subse-

quent recognition that fully 80% of infected individuals fail to clear the virus after acute infection.[11] An estimated 1.8% of the U.S. population is HCV-seropositive, with 20% of these individuals progressing on to cirrhosis over the ensuing 10 to 30 years. Moreover, among those with cirrhosis, there is an annual 1% to 4% risk of hepatocellular carcinoma.[12] Several studies emerged from the international literature examining HCV prevalence among the chronically mentally ill,[13–17] but the U.S. literature was largely confined to examination of chronically institutionalized developmentally disabled patients[18–21] or veteran populations[22] until the 2001 publication by Rosenberg and colleagues[7] of the NIMH/VA multicenter results.

While the NIMH/VA study made a significant contribution to the literature on medical comorbidity from blood-borne diseases and severe mental illness, none of the U.S. published studies to date have examined populations from the western states, nor state hospital patients without a primary diagnosis of mental retardation, and none have documented the prevalence of hepatitis A virus (HAV) seropositivity in HCV-positive patients with severe mental illness. Hepatitis A is typically a self-limiting viral illness, mostly transmitted via water-borne contamination, with fatality rates in young, healthy adults well under 1%.[23] The general U.S. prevalence of HAV exposure is 33%, and evidence of HAV serum antibodies increases with age, a finding that may explain why exposure prevalence among white chronic HCV patients is slightly lower (27%), as they typically represent a younger demographic.[24]

The issue of HAV serology in HCV-exposed individuals has rapidly become a subject of public health concern following the publication in 1998 of data from a 7-year Italian study of 432 patients with HCV.[25] In this comprehensive prospective study, all patients underwent liver biopsy to assess histologic evidence for cirrhosis, and serial HAV antibodies were obtained every 4 months. Of the 17 HCV patients who were coinfected with HAV during the period of observation, there were 7 cases of fulminant hepatitis and 6 deaths (35%), a fatality rate 10 times that seen in studies of HAV infection among large population groups.[26] Notably, none of the deaths occurred in HCV patients with cirrhosis. The Italian results echoed the findings of a retrospective study examining Centers for Disease Control (CDC) data acquired from 1989 through 1992 which demonstrated that death from HAV was significantly more prevalent in those with chronic liver disease (27.5%) compared to those without (3.4%).[27] Other studies of acute HAV infection in patients with chronic liver disease have also raised the issue of increased morbidity and mortality from HAV, a viral infection with typically very low mortality in healthy adults.[26,28–34] A similar concern also exists for HCV patients who acquire HBV infection, with substantial data documenting increased acute and long-term risks of coinfection. In particular, the incidence of hepatocellular carcinoma is more than doubled in patients seropositive for HBV and HCV compared with those with chronic HCV alone.[35]

On the basis of these studies, and recommendations issued by the CDC, National Institutes of Health, and Veterans Health Administration that patients with chronic liver disease, particularly from HCV, be vaccinated for both HAV and HBV,[23,35] a voluntary monitoring program began at Oregon State Hospital (Salem, Ore.) in 1999 to screen all patients for HAV, HBV, HCV, and HIV. Identifying chronic HCV patients who are HAV-negative for vaccination is a particular priority at Oregon State Hospital, as the state of Oregon ranks third in the nation in HAV cases, with a rate of 40 per 100,000 population, 4 times the national average and 8 to 20 times the prevalence seen in most of the eastern United States.[23]

METHOD

Patients

The computerized records of all nongeriatric adult patients hospitalized at Oregon State Hospital on April 23, 2001, (N = 535) were reviewed to elucidate evidence of testing for hepatitis A, hepatitis B, hepatitis C, and HIV and the results of such testing when performed. The computerized laboratory database is complete through 1997. For patients admitted prior to that date for whom no computer record of hepatitis or HIV testing was found (N = 13), the paper chart was reviewed for evidence of testing and results were included in the analysis. One HCV-seropositive patient had been immunized for hepatitis A and B and was excluded from the analysis. All specimens were venous blood samples processed by Quest Laboratories, Inc., which employed enzyme immunoassay kits for hepatitis screening manufactured by Abbott Laboratories (Abbott Park, Ill.). These screening kits measure total HAV antibodies, HBV core antibody, and HCV. The HCV assay is a second-generation test with listed specificity of 99.83%. At that time, routine confirmatory recombinant immunoblot assay was not performed on all seropositive HCV patients. HIV testing was also performed by Quest Laboratories, Inc., using enzyme-linked immunosorbentassay for HIV-1/HIV-2 antibodies (Abbott Laboratories, Abbott Park, Ill.), with positive results confirmed subsequently by Western blot analysis.

The following demographic variables were collected on each patient: age, gender, ethnicity, primary diagnosis (coded as either psychosis related [i.e., schizophrenia, schizoaffective disorder, delusional disorder, or psychosis not otherwise specified] or other specific diagnosis), diagnosis of a substance use disorder, legal status (forensic or civil), and most recently recorded serum transaminases (alanine aminotransferase [ALT], aspartate aminotrans-

Table 1. Screening Results for HCV Antibody at Oregon State Hospital[a]

Demographic Variable	HCV-Positive (N = 103)	HCV-Negative (N = 404)	p Value
Age, mean, y	40.6	43.2	NS
Gender (male)	76.7	74.3	NS
Primary psychotic diagnosis	74.8	78.2	NS
Ethnicity (white, non-Hispanic)	85.4	83.2	NS
Legal status (forensic)	75.7	73.8	NS
Any listed substance diagnosis	72.8	30.7	< .001
HAV antibody–positive	35.9 (N = 101 tested)	34.6 (N = 394 tested)	NS
HBV core antibody–positive	49.5 (N = 101 tested)	18.3 (N = 394 tested)	< .001
HIV-positive	2.6 (N = 79 tested)	2.7 (N = 338 tested)	NS

[a]Values shown as percentages unless otherwise noted.
Abbreviations: HAV = hepatitis A virus, HBV = hepatitis B virus, HCV = hepatitis C virus, HIV = human immunodeficiency virus.

ferase [AST]) at the time of serologic diagnosis. No liver function results were obtained more than 3 months from the time of hepatitis serology.

Data Analysis

The Student t test for independent samples and chi-square analysis were used to examine the demographic differences between HCV-positive and HCV-negative patients. These tests were 2-tailed. One-way analysis of variance was employed to examine difference in serum transaminase levels between groups according to HAV and HBV serologic status among the HCV-positive patients. Post hoc comparisons between individual groups on the basis of HAV and HBV serologic status were performed and were assessed with Bonferroni correction to control for the number of individual comparisons between the 4 groups (HAV–/HBV–; HAV+/HBV–; HAV–/HBV+; HAV+/HBV+). All statistical analysis was performed using SPSS version 9.0 (SPSS, Inc., Chicago, Ill.).

RESULTS

Among the 535 nongeriatric adult patients at Oregon State Hospital on April 23, 2001, 507 (94.8%) had serologic results for HCV, of whom 103 (20.3%) were HCV seropositive. Overall 34.8% of all tested patients were seropositive for HAV, with little difference in prevalence between HCV-positive and -seronegative groups, while 24.7% of all patients were HBV core antibody–positive, with a significant difference in prevalence on the basis of HCV status. The HCV-seropositive patients did not significantly differ from HCV-negative patients on the basis of age, gender, ethnic distribution, legal status (forensic vs. civil commitment), frequency of any psychotic disorder as a primary diagnosis, or prevalence of HAV or HIV exposure; however, there were significant differences in frequency of substance use disorders and HBV exposure (Table 1). A separate comparison on the basis of race revealed no significant differences between the white, non-Hispanic population and other ethnicities in the frequency of HCV seropositivity; moreover, among those with HCV, there were no significant differences between the 2 racially defined groups in frequency of HAV, HBV, or HIV exposure; age; sex distribution; or frequency of any psychotic disorder as a primary diagnosis or legal status.

Although 94.8% of patients had serology obtained for HCV, only 77.9% were screened for HIV. There was no significant difference in the seroprevalence rates for HIV between HCV-positive patients (2.6%, N = 79 screened) and HCV-negative patients (2.7%, N = 338 screened). Among the 317 patients in this analysis admitted to Oregon State Hospital prior to 1999, 41.6% were screened for HCV and 38.5% for HIV during the interval before 1999.

One fourth (25.2%) of the HCV-positive patients did not have a psychotic disorder listed as the primary diagnostic category. The most common nonpsychotic diagnoses included bipolar disorder (6.8%), depressive disorder (4.8%), substance-induced mood disorder (2.9%), posttraumatic stress disorder (2.9%), and cognitive disorder/dementia (1.9%). There was a trend for forensic patients to be less likely than the civilly committed patients to have psychosis as their primary diagnosis, but this did not reach statistical significance ($\chi^2 = 3.068$, $p = .080$).

Examination of the serum transaminase levels obtained at time of HCV confirmation revealed that 59% of these confirmed HCV-seropositive patients had abnormal AST levels, and 32% had abnormal ALT levels. When serum transaminase levels in HCV-seropositive patients were examined between cohorts grouped on the basis of HAV and HBV serology, there were no significant differences in either mean AST or mean ALT between the groups (Table 2). Moreover, none of the post hoc comparisons between groups employing Bonferroni correction were statistically significant.

DISCUSSION

Presented here are the first U.S. data from a systematic screening program for all hepatitis viruses and HIV in a

Table 2. Serum Transaminase Levels by Serologic Status in Hepatitis C–Seropositive Patients at Oregon State Hospital

Transaminase	HAV-Negative, HBV-Negative (N = 36)	HAV-Positive, HBV-Negative (N = 14)	HBV-Positive, HAV-Negative (N = 28)	HAV-Positive, HBV-Positive (N = 22)	Statistics
ALT[a]					p = .535
Mean, U/L	141	108	52	65	(F = 0.733, df = 3)
Median, U/L	41	51.5	40	56	
Range, U/L	7–2502	8–560	7–285	13–178	
% Elevated	56	57	54	73	
AST[b]					p = .443
Mean, U/L	86	63	35	49	(F = 0.903, df = 3)
Median, U/L	32.5	30	31	37.5	
Range, U/L	10–1206	11–212	12–109	15–215	
% Elevated	28	43	25	41	

[a]Reference range, 10–40 U/L.
[b]Reference range, 10–40 U/L.
Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, HAV = hepatitis A virus, HBV = hepatitis B virus.

group of chronic psychiatric inpatients. Nearly 95% of patients were completely screened for HAV, HBV, and HCV, although screening for HIV occurred at a lower frequency than for hepatitis viruses, with only 80% of patients tested for hepatitis also being tested for HIV. Testing for HIV requires a consent not necessary for hepatitis testing, a process complicated by the difficulty in obtaining informed consent from severely mentally ill individuals. This fact alone may explain the lower rates of HIV screening, although this represents an area worthy of further inquiry.

The seroprevalence findings here corroborate those from the NIMH/VA study[7] with regard to the high prevalence of HCV, HIV, and HBV among persons with chronic mental illness. The Oregon State Hospital HCV prevalence of 20.3% is nearly identical to the site weighted prevalence of 19.6% reported by Rosenberg and colleagues[7] for the NIMH/VA multicenter study, and the HIV seropositivity rate (2.6%) among these chronic inpatients is also very close to that reported by Rosenberg and colleagues (site weighted prevalence 3.1%). Interestingly, the state hospital HCV-seropositive subgroup did not have a significantly higher prevalence of HIV, while 13 (10.7%) of 122 of the NIMH/VA HCV-positive patients were coinfected with HIV. Hepatitis B exposure was very common among the HCV-seropositive state hospital patients (49.5%), again nearly identical to the 54.1% coprevalence of HCV and HBV exposure reported by Rosenberg and colleagues, and the overall prevalence of any substance diagnosis was 39.3% in the state hospital patients, quite similar to the 42% figure noted in the NIMH/VA study.

The most important result of this study is the reporting of HAV seroprevalence data among chronically mentally ill inpatients infected with HCV. The finding of high fatality rates among noncirrhotic Italian patients with chronic HCV subsequently infected with HAV[25] raised the concern about protection of patients with HCV and other chronic liver disease from HAV or HBV superinfection. Various retrospective studies have not always corroborated the findings of the Italian trial, including those from Switzerland, Finland, and France, yet data from the 1988 Shanghai HAV epidemic involving 310,746 cases related to ingestion of raw clams found over 5-fold higher fatality rates among those with chronic liver disease from HBV infection.[26–34] Another study of Thai patients with chronic liver disease related to HBV or HCV found that acute HAV infection may be quite severe, even fatal, in patients with underlying chronic HBV or HCV infection, especially among the elderly.[30] The primary author of the prospective Italian study states that the particularly high fatality rates in his trial may be an unusual finding, and postulates certain human leukocyte antigen (HLA) haplotypes found among 4 of the fatalities as a possible associated risk factor,[34] yet the combined results of both prospective trials and other retrospective studies have increased awareness of the need to vaccinate patients for HAV and HBV who manifest evidence of chronic liver disease from HCV or other etiologies.

While roughly 80% of HCV-infected individuals maintain chronic viremia, confirmation that HCV patients do indeed have chronic liver disease is important. Although a large fraction of HCV-positive patients recorded abnormal AST or ALT levels at the time of HCV testing, use of transaminases as the sole means for determining chronic liver disease is not sufficient. Laboratory markers of liver injury and deficient synthetic function (e.g., elevated serum bilirubin, low serum albumin, increased prothrombin time) combined with clinical findings (e.g., spider angiomata, ascites, caput medusa) should be utilized, along with liver biopsy if possible for histologic confirmation of cirrhosis. Both the CDC and the Department of Veterans Affairs have issued recommendations that recommend hepatitis A and hepatitis B vaccination for HCV-seropositive persons not previously exposed to HAV or HBV.[36,37] Once the decision to vaccinate has been made, it has been convincingly demonstrated that among patients with chronic HCV infection, one can achieve high

seroconversion rates (94.3%) after a full course of HAV vaccination, with even higher seroconversion rates noted after vaccination for HBV.[38,39]

The limitations of these preliminary data include the absence of confirmatory HCV testing reported systematically on all initial seropositive patients and an absence of biopsy results or other data documenting the extent of liver disease in the HCV-positive group. (Chronic HCV is defined by the presence of fluctuating or persistently elevated serum ALT for 6 months or more accompanied by demonstrable circulating HCV viral RNA.) There is also lack of transmission data or other demographic variables related to risk of contracting HIV or other blood-borne pathogens, and no assessment of substance abuse patterns as noted in the NIMH/VA comprehensive survey study.[7] The sample under scrutiny here is clearly a sample of convenience and may not necessarily be representative of all U.S. state hospital patients, although it is significant that these results essentially replicate findings of the NIMH/VA multisite study from the eastern United States.

Nonetheless, there are many unique aspects to the data presented here. These data represent the first data of this type from the western United States; the first comprehensive examination of HIV, HBV, and HCV seroprevalence in a chronic U.S. state hospital population; and the only extant data on hepatitis A seropositivity in mentally ill individuals exposed to HCV. Despite the limitations noted above, the preliminary data accrued at Oregon State Hospital confirm and underscore the conclusions from multiple other studies which report that individuals with chronic severe mental illness are at increased risk for sexually transmitted diseases, particularly HIV, and HCV, of which 15% to 20% of cases may be acquired through sexual contact.[36] As the comprehensive care of patients with severe mental illness focuses more on the treatment of chronic medical conditions in what is typically a medically underserved population, assessment of HAV serology status and the need for vaccination should be considered during the routine screening for HIV and hepatitis B and C viruses.

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