Hepatitis C Experience at a Community Teaching Hospital

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Background. The purpose of this study was to review the initial serologic testing experience for hepatitis C (HCV) and physician response at a community teaching hospital.

Methods. A retrospective chart review was performed for the 59 (5%) HCV-positive patients of 1244 patients who were tested by means of a new enzyme immunosorbent assay (EIA) for HCV antibodies between October 28, 1990, and October 27, 1991.

Results. Physicians identified HCV risk factors, including intravenous drug use (n=14, 25%) and having received blood products (n=15, 27%). One half of the patients were not queried about the known risk factors for HCV. The most common reason for ordering an HCV assay was elevated liver enzymes. None of the patients underwent supplementary HCV testing (ie, polymerase chain reaction or recombinant immunoblot assay). In 23 (40%) of the HCV-positive patients, no action was taken by the physician, and 15 (27%) were lost to follow-up. The remaining 18 patients (33%) had further follow-up with laboratory or treatment.

Conclusions. These results indicate the need for increased physician awareness of risk factors for HCV and improved documentation of these factors in taking patient history. In addition, primary care physicians need to be educated about new laboratory tests and how to interpret test results and when to order supplemental testing.

Key words. Hepatitis C; substance abuse, intravenous; liver; enzymes. (*J Fam Pract 1994; 39:257-261*)

The causative agent of parenterally acquired non-A, non-B hepatitis was identified in 1989 as a single-stranded ribonucleic virus,[1] later called the hepatitis C virus (HCV). The hepatitis C virus was identified by means of an unprecedented approach to virology: cloning the suspected agent and then developing immunoassays to detect antibodies to the protein products of these clones.[2] This discovery was unique in that this was the first virus cloned by molecular biologic techniques after its nucleotide sequence was identified. Serologic tests that detect HCV antibodies by an enzyme immunosorbent assay (EIA) subsequently became available for clinical investigation and confirmed that HCV is the major cause of posttransfusion non-A, non-B hepatitis worldwide.[3] In May 1990, first-generation EIA testing kits became available commercially. This assay uses a single nonstructural antigen to detect serum antibodies that are present in approximately 70% of patients with acute non-A, non-B hepatitis. It subsequently has become incorporated into the hepatitis panel in many clinical laboratories.

Since the inception of this assay, several problems have been noted. There is a potentially long window of nonreactivity occurring between the initial HCV infection and seroconversion. Although in most cases (90%) conversion takes place within 3 to 6 months, it can take as long as 6 to 12 months. False-positive results are seen with autoimmune hepatitis and in many random blood donors. With such uncertainty, there is clearly a need for more sensitive and specific testing.

Since the completion of this study, a second-generation EIA test has been licensed for clinical use. With two additional HCV antigens used, this latter assay has proved more sensitive in detecting the presence of antibodies. However, even with this improvement, false-

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positive and false-negative tests still occur with notable frequency and require further supplementary or confirmatory tests, such as the recombinant immunoblot assay (RIBA-2) and polymerase chain reaction. The RIBA-2 test incorporates four recombinant HCV antigens onto nitrocellulose strips. Although not licensed as a confirmatory test, it is helpful as corroborative evidence of infection or lack of infection in low-risk patients. The purpose of this retrospective study was to evaluate the first year of HCV testing experience at a community teaching hospital to determine physicians' reasons for ordering the HCV test and their response to positive results.

Methods

A first-generation EIA was employed for the hepatitis C testing (Abbott Laboratories, North Chicago, Ill) at a 588-bed community-based teaching hospital. To reduce the likelihood of false positives, the study included only patients whose EIA absorbance levels were repeatedly >1.5 Other studies have shown that a high EIA ratio correlates with a positive result on the RIBA-2.[4] A chart abstraction instrument was used to review complete hospital and clinic patient records in the following areas: demographics (age, race, sex, and marital status); risk factors for HCV infection, such as intravenous drug use or a history of receiving blood products, as well as potential risk factors, such as alcohol abuse or dependence,[5] multiple sexual partners, or a history of sexually transmitted diseases (STDs).[6]

The instrument also included an examination of pertinent laboratory data: liver enzymes, chemistry panel, serologic markers for hepatitis A and B, and serologic evidence for STDs (ie, positive results on the rapid plasma reagin and VDRL tests, or cultures of or antigen detection for *Chlamydia trachomatis* and *Neisseria gonorrhoeae*). Liver enzymes were examined as a marker for disease severity. The liver function tests included were performed within 1 month before or after the date of the HCV assay. Because of the retrospective nature of this study, liver function tests were obtained in a variety of ways: by a liver profile, as part of a chemistry-12 panel, or by individual assays.

The physicians' reasons for ordering HCV serology and their response to positive test results were also included in the abstraction instrument assessment. Potentially ambiguous items were deleted after discussion and further analysis. Data were analyzed with Epi Info version 5 statistical program (Centers for Disease Control). Data were compared using a *t* test for continuous data and chi-square for discrete data, with a level of significance set at $P=.05$.

Results

Of the 1244 patients who were tested at a single hospital-based laboratory during the first year of testing, 103 were initially positive according to the EIA method cut-off, but only 59 (5% of the total) were positive by our criteria (EIA absorbance level repeatedly >1.5). Of these 59 patients, 93% had complete hospital and clinic patient records available for review. The HCV test was ordered as part of a hepatitis panel for 89% of the patients. The remaining 11% underwent hepatitis C testing only. None had supplementary testing, such as a RIBA-2 or polymerase chain reaction assay, neither of which was widely available during the study period.

EIA absorbance was ≥2.0 in most patients (91%). Of the 55 patients whose charts were examined, 69% were men; 42% were black and 58% were white. The mean age was 44 years, with a range of 15 to 84. Documentation of known risk factors for HCV included a history of intravenous drug use in 25% and a history of having received blood products before HCV testing in 27%. Forty percent of the patients had no documentation of being asked about drug use, and 47% had no documentation of inquiry about blood transfusions. Forty percent had chart documentation of a diagnosis of alcohol abuse or dependence. All but 9% of the patients were asked about alcohol use. Sexual history was not documented in 65% of the patients.

Overall in the study group, 80% of the patients had one or more abnormal liver function tests: aspartate aminotransferase (AST, previously SGOT), alanine aminotransferase (ALT, previously SGPT), gamma-glutamylaminotransferase (GGT), or alkaline phosphatase. The means for these tests were all above the normal range: AST mean=99.7 U/L ±100.0 (normal, 10 to 42 U/L); ALT mean=79.3 U/L ±66.6 (normal, 10 to 60 IU/L); GGT mean=270.8 U/L ±426.6 (normal, 7 to 64 U/L); alkaline phosphatase mean=116.1 U/L ±79.7 (normal, 25 to 90 U/L).

Similarly, the values for total protein, albumin, and globulin were reviewed. The mean was within the normal range for total protein and albumin (total protein mean=6.7 g/dL ±1.1 [normal, 6.0 to 8.0 g/dL]; albumin mean=3.4 g/dL ±0.8 [normal, 3.0 to 4.8 g/dL]), but was above the normal range for globulin (mean=3.3 g/dL ±0.8 [normal, 2.5 to 3.0 g/dL]). The mean values for the bilirubin tests were above the normal range (total bilirubin mean=1.4 mg/dL ±1.20 [normal, 0.2 to 1.0 mg/dL]; direct bilirubin mean=0.4 mg/dL ±0.48 [normal, 0.0 to 0.2 mg/dL]; indirect bilirubin mean=0.9 mg/dL ±0.65 [normal, 0.0 to 0.8 mg/dL]). None of the patients had serologic evidence of prior hepatitis A infection. Of the patients in the study group, 35% demonstrated serologic evidence of past or current hepatitis B

Table. Reasons Cited by Physicians for Ordering the Hepatitis Panel or Hepatitis C Virus (HCV) Test for Patients Who Were Identified As HCV-Positive Based on Repeatd EIA Absorbance Levels of >1.5 (n=55)

Reason Cited	Patients No. (%)
Elevated liver enzymes	22 (40)
Abnormalities on physical examination	21 (38)
Risk factors for viral hepatitis	20 (36)
History of viral hepatitis	7 (13)
Positive for HIV	5 (9)
Screening for blood donation	4 (7)
Occupational exposure	2 (3)

EIA denotes enzyme immunosorbent assay; HIV, human immunodeficiency virus.

infection. Of those who did not have sole HCV testing, 4% were positive for hepatitis B surface antigen (HBsAg), whereas 39% were positive for hepatitis B core antibody (HBcAb), and 22% were positive for hepatitis B surface antibody (HBsAb). Of the 55 patients, dual infection with human immunodeficiency virus (HIV-1) was found in 5 (9%). The reasons documented for ordering the hepatitis panel or HCV assay are listed in the Table.

Physician response was variable. Thirty-three percent of the patients had appropriate follow-up or treatment, arbitrarily defined in this study as ordering follow-up liver-function tests, consulting a subspecialist in consideration of a liver biopsy for persistently elevated ALT, or ordering supplementary testing. However, 27% of the patients were lost to follow-up, and in 40%, no documented action was taken. This lack of documented action was evident in both hospital and clinic records. None of the HIV-positive patients in the study group were lost to follow-up.

Of the six patients who had liver biopsies, three had micronodular cirrhosis. Of these, one also had hepatocellular carcinoma, and another also had chronic active hepatitis and died during the study period. Another patient had chronic persistent hepatitis, and a fifth showed fatty degeneration. The sixth patient showed acute hepatitis suggestive of chronicity. Two of the liver-biopsy patients received alfa-interferon treatment. Biopsy showed that one of these patients had chronic active hepatitis along with micronodular cirrhosis, and the other had acute hepatitis suggestive of chronicity.

Because of the similarities in risk factors for HCV and HIV, a comparison was made between the patients who were HIV-positive with those who were HIV-negative to see if there were any significant differences in the levels of the liver function test as a marker for severity of disease. The only liver enzyme test that was found to be significantly different in the HIV-positive group as compared with the HIV-negative group was GGT, which was significantly higher in the HIV-positive group ($P=.02$). The levels of total protein, albumin, and globulin also were compared. Total protein and globulin levels were significantly higher in the HIV-positive group: total protein and globulin ($P=.002$ and $P=.007$, respectively).

Since the study was performed at a teaching hospital, it was of particular interest to observe the difference between staff physicians and private physicians in documenting risk factors for HIV. Thirty of the 55 (54.5%) HCV-positive patients were followed by staff physicians and 25 (45.5%) were followed by private physicians. These two groups were compared in the following areas: diligence in documenting whether there was a history of intravenous drug use or receiving blood products, or a diagnosis of alcohol abuse or dependence. There were no statistically significant differences found between the two groups of physicians in any of the three areas. Similarly, in terms of follow-up and treatment, a comparison of the staff and private physician responses to positive HCV results revealed no significant differences.

Discussion

Chronic liver disease is the ninth leading cause of death in the United States and results in years of lost productivity. Chronic hepatitis is now known to be a common problem among patients with hepatitis C infection. A prospective study of community-acquired hepatitis C found that among patients who were positive for anti-HCV, 62% developed chronic hepatitis within 9 to 48 months.[7] The incidence of posttransfusion-associated hepatitis has decreased over the last decade as a result of blood donor screening. HCV now accounts for only about 4% of cases of transfusion-related hepatitis. The specific risk of posttransfusion hepatitis C is roughly three cases per 10,000 units of blood.[8] However, non-A, non-B hepatitis associated with parenteral drug use doubled in the 7 years from 1981 to 1988.[9] Even in the absence of other known or suspected risk factors for viral hepatitis, there is an increased prevalence of HCV antibodies in alcoholic patients with severe liver disease. The impaired liver function in patients with these antibodies suggests that hepatitis C virus is involved in liver damage in patients with chronic alcoholism.[10]

A significant number of HCV cases are community acquired, with sexual contact being a suspected factor. Although it can occur, sexual transmission of HCV is much less frequent than that of HIV-1 and hepatitis B. More recently, repeated sexual exposure over time (eg, heterosexual transmission between spouses) has been identified as a more important risk factor than a single exposure.[11] However, concurrent parenteral exposure, especially with intravenous drug use, is thought to be a

probable coexisting factor in many of these cases.[12] Nevertheless, in many instances of community-acquired HCV infection, there are no recognizable risk factors. The mode of acquisition does not appear to alter either the clinical features of acute viral hepatitis or the probability of chronic disease.

Among patients in this study, the most likely reason an HCV assay was performed was the presence of elevated liver enzymes. It is noteworthy that in 40% of the cases, no documented action was taken. However, because the HCV assay was ordered as part of the full hepatitis panel in 89% of the study group, it is likely that many physicians were unaware that the hepatitis C assay was already included in the panel, and therefore were neither seeking this information nor prepared to interpret the results and take appropriate action. Thus, it is likely that the technology of HCV antibody detection preceded physician education regarding this insidious infection.

A study at the James A. Haley Veterans Hospital in Tampa, Florida,[13] implemented a feedback program that included both systematic reporting of objective data and individual and group education efforts related to the appropriate use of laboratory tests. The program noted a consistent reduction in the number of tests that fell outside the predetermined guidelines during the period of implementation. Another study[14] revealed that when monthly feedback of clinical laboratory test use and revenue expenditure was provided to physicians, they modified their request behavior, resulting in cost reduction without any adverse changes in patient care. The study suggested that providing feedback of laboratory data to clinicians achieved a sustained change in physician test-ordering behavior. Both studies included direct feedback to the physicians in a way that was acceptable and meaningful in educating them. The results of our study support the theory that at the time the first-generation EIA became commercially available, the majority of community and staff physicians were ill prepared to accurately interpret the HCV test results, to determine when supplementary testing was indicated, or to follow and treat patients with repeatedly high positive EIA levels.

It is important to know when a screening HCV assay will provide useful information so that appropriate counseling and follow-up care can be provided if the test result is positive. If the test is initially negative in a high-risk patient, the assay should be repeated at 3 and 6 months because there is often a long window of seronegativity between the initial HCV infection and seroconversion. It is important to remember that most patients with a positive HCV test are asymptomatic. Therefore, it is usually a positive screening test for HCV antibodies that precipitates a patient's visit to a physician. Commonly, patients will have had a hepatitis panel performed to evaluate abnormal liver function tests (as was true in this study), or they will have been screened when donating blood. There is a high degree of false positivity when testing random blood donors. Unselected blood donors and healthy subjects have a seroprevalence rate of 0.5% to 2.2% worldwide. With this in mind, the likelihood of a true positive test result should be based on the patient's risk factors. The persons most likely to be truly infected are blood donors implicated in the transmission of HCV, donors with elevated ALT levels, and those with identifiable risk factors for hepatitis C. These are the patients in whom repeatedly reactive EIA results are most likely to have supplemental test results that corroborate the initial assay. The converse is also true. For donors not implicated in the transmission of HCV, donors with normal ALT values, and persons with no known risk factors for hepatitis C, an initial positive test will likely be judged false positive by the supplemental tests.

In evaluating patient risk factors, the results of this study emphasize the importance of taking a thorough history. Although no significant difference in risk-factor documentation was found between the physician subgroups, the clear lack of adequate written evidence of verbal screening in both groups highlights the need to emphasize careful history-taking with regard to the primary risk factors for HCV: use of intravenous drugs, receiving blood products, and potential factors such as sexually transmitted disease and ethanol use. A positive history will strengthen the true-positive rate (specificity) of the screening test. Since no identifiable risk factors can be found in approximately 40% of hepatitis C cases, however, a negative history does not preclude further evaluation. The first- or second-generation positive EIA should be followed by a supplementary test, such as the RIBA-2 assay or liver function test. Based on current information, if these are both negative or normal, no further action is necessary. If the supplementary test is indeterminate or positive and liver function tests are elevated (ALT greater than two times normal), the patient should be followed periodically with repeat liver function tests every 8 weeks for at least 6 months. These patients should be informed that there is at least a 50% likelihood of developing chronic liver disease, including cirrhosis, and hepatocellular carcinoma. A normal ALT value on follow-up could indicate either HCV carrier state or recovery. A repeat ALT should be obtained every 6 months to confirm this finding. If the ALT remains persistently elevated, a liver biopsy should be considered. Patients whose biopsies show histologic evidence of severe liver disease, including chronic active hepatitis, bridging necrosis, or active cirrhosis, are candidates for medical therapy.

Current treatment options are limited. Glucocorticoids and acyclovir have proved ineffective. Alfa-inter-

feron has been shown to normalize ALT levels and produce temporary histologic improvement in some patients. In 1989, a large, multicenter, randomized, placebo-controlled trial with alfa-interferon revealed that 46% of patients receiving 3 million units subcutaneously three times a week for 6 months attained normal or near-normal ALT levels and had histologic improvement on repeat liver biopsies.[15] Relapse occurred, however, in approximately one half of the patients within 6 months after conclusion of the therapy. Patients whose serum ALT levels do not significantly improve after 16 weeks of therapy are unlikely to benefit from further therapy. If relapse occurs, as verified by elevated ALT levels, a repeat 6-month trial is a reasonable consideration. In addition to the high relapse rate, there are other disadvantages to interferon therapy, even if further studies show that higher doses with or without longer treatment periods are more efficacious. It has numerous side effects, the most common being flulike symptoms, which can be partially ameliorated by premedicating with acetaminophen or ibuprofen. Expense is another discouraging factor, with therapy costing approximately $2100 per course of treatment. Alfa-interferon has also been noted to exacerbate autoimmune hepatitis.[16] Therefore, because false-positive results on initial HCV assay testing have been reported in patients with autoimmune hepatitis,[17] it is particularly important to verify that the initial hepatitis C serologic findings represent true positives.

There has been less progress in the area of prophylaxis against hepatitis C. A review of a trial of immune globulin in American military personnel stationed in Korea suggests that pre-exposure immunization with immune globulin is effective in preventing hepatitis C.[18] Until more studies verify this, it is reasonable to give 0.06 mL/kg of pooled γ-globulin when the risk of infection is significant (eg, after needle stick or sexual contact with an infected person).

Based on the results of this study, the recommendations made to the community physicians include the need to improve risk-factor documentation for hepatitis C virus as well as follow-up of positive test results. When any new laboratory test becomes available to the general physician population, physicians need to be educated about how to interpret the test results. The laboratory at our institution inadvertently added the hepatitis C assay to the standard hepatitis panel without providing sufficient instruction to physicians. As a result of this study, our laboratory was directed to qualify the limitations of the HCV screening test and to suggest supplementary testing for positive screening results. This directive ensures that physicians are informed of the addition of a new test and educated regarding its use.

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