Incidence of Hepatitis C in Patients with Chronic Elevations of Aminotransferases

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Background: **We undertook a study to determine the incidence of hepatitis C in patients with persistent elevations of aminotransferases, either alanine aminotransferase (ALT) or aspartate aminotransferase (AST).**

Methods: **We conducted a retrospective review of medical records at the Family Practice Center from 1992 to 1993. Patients in whom aminotransferase levels were elevated 1.5 times normal for at least 6 months were eligible for the study. Sixty patients met our eligibility criteria. Patients were tested for hepatitis B and C and other possible causes of elevated aminotransferase levels.**

Results: **Of these 60 patients, 35 (58 percent) tested positive for hepatitis C virus by first-generation enzyme-linked immunosorbent assay (ELISA-I); 30 had positive results confirmed by second-generation recombinant immunoblot assay (RIBA-II). The other 5 patients were lost to follow-up, and their status was not confirmed. Of the 30 patients with a positive RIBA-II, 14 had liver biopsies showing chronic persistent hepatitis or chronic active hepatitis, both consistent with hepatitis C infection. Of the 60 patients, 2 (3 percent) had hepatitis B. None had active hepatitis B coexisting with hepatitis C.**

Conclusions: **Our data show a much greater incidence of hepatitis C (50 percent) in our patients with chronic elevations of aminotransferase levels compared with data reported from previous studies.**

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The virus hepatitis C was cloned by Choo and associates in 1989.[1] It is a lipid-encapsulated, single-stranded ribonucleic acid (RNA) virus with properties similar to those of flavivirus, a subcategory of togaviruses. About 150,000 new cases of hepatitis C are diagnosed each year in the United States.[2] Approximately 50 to 70 percent become chronic,[3] and 20 to 50 percent of these progress to cirrhosis within 10 years of onset.[4] Some cirrhosis patients succumb to end-stage liver disease and hepatocellular carcinoma.

Infected individuals usually report a history of blood transfusion, sharing needles among drug users, accidental needlestick of health care workers, or hemodialysis.[5] Transmission through familial,[6-8] sexual,[9,10] or mother-to-infant exposure[11,12] is uncommon. Body secretions (saliva, semen, urine, stool, tears) tested by polymerase chain reaction reveal positive results in some patients[13,14] and negative in others.[15,16] About 50 percent of seropositive individuals have no definite, identifiable cause.[17]

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Methods

We reviewed charts of 167 patients with abnormal aminotransferase levels who were seen at the Family Practice Center of the Jamaica Hospital between 1 January 1992 and 31 December 1993. Liver function tests had previously been performed as part of an evaluation for existing medical problems or identifiable risk factors for hepatitis. Patients were asymptomatic for liver disease.

At the hospital laboratory, normal values for aspartate aminotransferase (AST) are 0 to 31 U/L, and for alanine aminotransferase (ALT) are 7 to 56 U/L. Patients who had elevated aminotransferase levels persisting for 6 months or longer and who were tested for viral markers (hepatitis B and C) were accepted into the study. Testing for hepatitis B included hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), hepatitis B surface antibody (HBsAb), hepatitis B virus deoxyribonucleic acid (HBV DNA), and

Table 1. Workup of Patients with Hepatitis C to Rule Out Other Causes of Chronic Hepatitis (n = 30).

Test	Patients with Workup (No.)	Normal Results No. (%)	Abnormal Results No. (%)
Abdominal sonogram	29	19 (66)	10 (34)
Antimitochondrial antibody	27	25 (93)	2 (7) (1:20)
Antinuclear antibody	27	15 (56)	12 (44) (1:20-1:640)
α_1-Antitrypsin	27	25 (93)	2 (7) 231 and 235 (normal value 93-224)
Ceruloplasmin	30	29 (97)	1 (3) (high)
Hepatitis B surface antigen (HBsAg)	30	30 (100) (negative)	0 (0)
Iron studies	28	26 (93)	2 (7) (transferrin saturation > 50%)
Smooth-muscle antibody	25	23 (92)	2 (8) (1:20)
VDRL/rapid plasma reantigen	24	19 (79)	5 (21)

hepatitis B e antigen (HBeAg). Testing for hepatitis C included first-generation enzyme-linked immunosorbent assay (ELISA-I) and second-generation recombinant immunoblot assay (RIBA-II).

Elevations greater than 1.5 times the maximum normal were arbitrarily chosen as our cutoff point. An increase in either ALT or AST was sufficient for inclusion in the study.

Charts were reviewed for patient demographics, alcohol consumption, illicit (intravenous) drug use, blood transfusions, medications, past and current medical problems, sexual history, and workups for other causes of liver disease. Because certain medications can cause reactions that mimic autoimmune hepatitis, hepatotoxic drug intake history was investigated in all patients. Workups for other causes of liver disease included complete blood count and chemistry panel; antinuclear antibody, antimitochondrial antibody, and smooth-muscle antibody titers; ceruloplasmin level and α_1-antitrypsin level measurements; imaging studies; tests for syphilis (VDRL); and liver biopsy.

Results

Of the 167 charts showing abnormal levels of aminotransferases, 60 satisfied our criteria. There were 32 (53 percent) female and 28 (47 percent) male patients: 30 (50 percent) were African-American, 24 (40 percent) were Hispanic, 4 (7 percent) were white, and 2 (3 percent) were other. Ages ranged from 10 to 77 years, with a mean of 43.6 years.

Overall, AST levels ranged from 20 to 280 U/L, with a mean of 88.4 ± 24.9 U/L. ALT levels ranged from 20 to 375 U/L, with a mean of 104.7 ± 28.4 U/L.

Of the 60 patients, 35 (58 percent) tested positive for hepatitis C by ELISA-I, 30 of which were confirmed by RIBA-II. The other 5 patients were lost to follow-up, and their status could not be confirmed (1 died of acquired immunodeficiency syndrome [AIDS]-related disease). Liver biopsies were performed on 14 of the 30 hepatitis C patients whose positive results were confirmed by RIBA-II. The results of these biopsies revealed chronic active hepatitis in 10 patients, chronic persistent hepatitis in 1, chronic hepatitis (activity not specified) in 1, cirrhosis in 1, and fibrous tissue in 1. Concomitant or other causes of chronic hepatitis were ruled out with the following tests: antinuclear antibody titers; ceruloplasmin levels; serum iron, serum ferritin, and total iron binding capacity; α_1-antitrypsin levels; and abdominal sonograms (Table 1).

The following risk factors for chronic hepatitis were found in 55 patients: alcohol consumption, medications, intravenous drug use, blood transfusions, and history of liver disease (Table 2). Sexual history, though a risk factor, was not included because of inconsistencies in chart documentation.

Table 2. Risk Factors for Chronic Hepatitis C Found in Patients with Hepatitis C and with Nonhepatitis C

Risk Factors	Hepatitis C (n = 30) No. (%)	Nonhepatitis C (n = 25) No. (%)	Chi-square Analysis*
Alcohol consumption	11 (37)	2 (8)	4.71, $P < 0.05$
Blood transfusion	10 (33)	2 (8)	3.753, NS
Hepatitis B core antibodies (HBcAb)	20 (67)	7 (28)	6.68, $P < 0.05$
Intravenous drug use	11 (37)	2 (8)	4.71, $P < 0.05$

*One-tailed, Yates correction.

The most regularly available laboratory markers for alcoholic hepatitis were mean corpuscular volume greater than 95 μm^3 and an AST-ALT ratio greater than 2:1. Only 3 patients in the hepatitis C group had a mean corpuscular volume greater than 95 μm^3; only 1 of these admitted alcohol consumption of 80 g for several years. In the nonhepatitis C group, 2 had a mean corpuscular volume greater than 95 μm^3, neither of whom admitted drinking alcohol. No one in either group had an AST-ALT ratio greater than 2:1.

In the hepatitis C group, 11 of the 30 patients (37 percent) had a history of intravenous drug use, compared with 2 of the 25 patients (8 percent) in the nonhepatitis C group. A history of blood transfusion was obtained in 10 (33 percent) hepatitis C patients and in 2 (8 percent) patients without hepatitis C. Of the hepatitis C patients, 11 (37 percent) had a history of alcohol consumption, compared with 2 (8 percent) in the nonhepatitis C group. Twenty (67 percent) hepatitis C patients were positive for core antibody to hepatitis B (HBcAb), compared with 7 (28 percent) in the nonhepatitis C group. No patient was on hemodialysis, and there was no health care worker in the group, nor was there any history of liver disease among the patients. Family history was noncontributory. Chi-square analysis with Yates correction was used to determine whether there were differences in risk factors between hepatitis C and nonhepatitis C patients; intravenous drug use, alcohol consumption, and previous hepatitis B exposure were found to be significantly different.

In the hepatitis C group, all 30 patients tested negative for HBsAg; 20 were positive for HBcAb, of whom 9 were also positive for HBsAb. The remaining 11 were tested for HBcAb immunoglobulin M (IgM), and all results were negative.

Of the 30 patients with hepatitis C, 29 had abdominal sonograms, 10 of which had the following abnormal findings: 3 patients had cholelithiasis, 1 had cholelithiasis with pancreatic fatty replacement, 1 had cholelithiasis with either fatty liver or neoplastic infiltration, 3 had splenomegaly, 1 had hepatomegaly, and 1 had increased liver echogenicity with possible fatty infiltration or cirrhosis (Table 3).

In the nonhepatitis C group, 2 patients tested positive for HBsAg and HBcAb, but negative for HBsAb; all test results persisted for 2 years. HBV DNA and HBeAg were negative in both patients, and all other causes of liver disease were ruled out. HBcAb was positive in 5 patients in the nonhepatitis C group. Two of them were also positive for HBsAb, while the remaining 3 tested negative for HBcAb IgM.

In the nonhepatitis C group, antinuclear antibody titers were positive in 5 patients (20 percent), with a range from 1:40 to 1:640. Smooth-muscle antibody titers were abnormal in 2 patients, with ratios of 1:20 in both cases. Ceruloplasmin levels were low in 1 (170 mg/L, normal value 230–530 mg/L). Iron studies were abnormal in 1 (transferrin saturation greater than 50 percent). All patients had normal levels of α_1-antitrypsin. VDRL was nonreactive in all patients, and antimitochondrial antibodies were not detected in any patient. Abdominal sonograms showed abnormalities in 12 of 25 cases (48 percent): 7 had fatty liver, 2 had cholelithiasis, 1 had choledocolithiasis, 1 had cholelithiasis with multiple liver densities, and 1 had nodular contour borderline liver with ascites and cholelithiasis (Table 3).

Discussion

In earlier studies of patients with chronic elevation of aminotransferases,[18,19] researchers did not test for hepatitis C virus. In 1991 Katkov and

Table 3. Comparison of Findings from Abdominal Sonograms of Hepatitis C (n = 29) and Nonhepatitis C (n = 25) Patients.

Results	Hepatitis C No.	Nonhepatitis C No.
Choledocolithisiasis	0	1
Cholelithiasis	3	2
Cholelithiasis with pancreatic fatty replacement	1	0
Cholelithiasis with fatty liver and/or neoplastic infiltration	1	1
Fatty liver	0	7
Hepatomegaly	1	0
Increased liver echogenicity with possible fatty infiltration or cirrhosis	1	0
Normal	19	13
Nodular liver with ascites and cholelithiasis	0	1
Splenomegaly	3	0

associates[20] tested the preserved sera of such patients, finding that 17 percent were positive for hepatitis C.

Our data suggest that hepatitis C plays a much greater role in persistent elevation of aminotransferase levels than studies have reported. Our finding of a 50 percent rate of infection was not surprising, however, since intravenous drug use, blood transfusions, alcohol consumption, and surrogate markers (HBcAb) were all higher in this group.

Screening in patients with hepatitis C showed that 67 percent had had exposure to the B form, as shown by the presence of HBcAb. The HBsAg and HBcAb IgM were negative, excluding hepatitis B as the cause of elevated aminotransferase levels. As shown in Table 2, previous exposure to hepatitis B is a significant risk factor for acquiring hepatitis C ($P < 0.05$).

It should be noted that 11 patients with hepatitis C admitted some degree of alcohol ingestion on a regular basis. Statistical analysis by chi-square showed that this consumption was a significant risk factor for hepatitis C ($P < 0.05$). It could be argued that the lifestyles of alcohol abusers predispose them to viral hepatitis. Only 1 patient admitted consuming more than 80 g for several years. This patient had a mean corpuscular volume of 95.6 μm^3, and a mean AST-ALT ratio of 1.5. Because of the considerable amount of alcohol consumed, alcoholic hepatitis coexisting with hepatitis C was a distinct possibility in this patient, but no liver biopsy was done to confirm it.

Blood transfusion, although a well-known risk factor for hepatitis C, was not a statistically significant factor in this study. This conservative assessment could be due to underestimation of blood transfusions in our population, especially for those who had had major surgery in the past.

Persons with chronic autoimmune hepatitis usually have high antinuclear antibody titers (mean 1:500), positive smooth-muscle antibody titers (mean 1:160), ALT levels greater than 200 U/L, and increased total bilirubin (greater than 1.2 U/L).[21] Of our patients, 2 had positive smooth-muscle antibody titers (1:40), 1 of them also having a positive antinuclear antibody titer (1:640). No risk factors for hepatitis C were present in this case. It might have been a false positive for hepatitis C, representing a true autoimmune hepatitis. Low titers of smooth-muscle antibody, 1:40 or less, and low antinuclear antibody titers, 1:160 or less, are not infrequent in chronic hepatitis C.

Tests for ceruloplasmin, α_1-antitrypsin, and antimitochondrial antibodies did not show abnormalities sufficient to establish any diagnosis other than hepatitis C. Although 2 patients had high transferrin saturations (53 and 80 percent), no further investigation to rule out hemochromatosis was pursued.

Although polymerase chain reaction is the reference standard for confirming hepatitis C, we did not have this information available in the charts reviewed. We supported our data using RIBA-II, which has a fair level of sensitivity (90.4 percent) and specificity (95 percent) for confirmation of hepatitis C.[22]

Conclusions

The results of our study make it appear appropriate to do screening tests for hepatitis C in patients whose elevated AST and ALT levels have been repeated and confirmed, as well as in patients with normal aminotransferase levels but with risk factors for hepatitis C.

Several therapeutic agents are currently being studied for treatment of hepatitis C, interferon alfa-2b having particularly emerged as an agent of proven efficacy. It is given at a dose of 3,000,000 U subcutaneously 3 times weekly for 6 months. Between 40 and 50 percent of patients respond to

interferon initially, but one half of these patients relapse within 6 months after therapy ends. In patients with end-stage liver disease secondary to hepatitis C, liver transplantation is an option. Although reinfection of the graft is usual, there is no rapid onset of chronicity.

Hepatitis C has become a public hazard that can no longer be ignored. Health care providers have a responsibility to promote public awareness, education, and instruction in the recognition of this disease as they now do with AIDS and hepatitis B.

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