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Assessment of Liver Histology in Chronic Alcoholics with and Without Hepatitis C Virus Infection

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Patients with alcoholic liver disease have a high prevalence of hepatitis C virus (HCV) infection. The histological appearances of the liver in patients with alcoholic liver disease and HCV infection are well described. However, liver histology in individuals with dual pathology, both chronic alcohol abuse and HCV infection, is less well understood. The purpose of the present study was to examine this issue and to determine if there is any correlation between specific histological features and the serum biochemical abnormalities seen in these patients. Eighty-six chronic alcoholics, 65 with HCV infection and 21 uninfected subjects, were included in the study. All patients had history of heavy alcohol abuse (consuming 80 g or more of ethanol a day for at least 10 years). The following data were collected on each patient: demographic information (age, gender, race), the amount and duration of alcohol intake, biochemical results, and liver biopsy abnormalities including the histological activity index (HAI) score. HCV-infected alcoholics were younger ($P = 0.05$) and were more often African American than Caucasian ($P < 0.01$). Alcohol consumption was significantly greater in uninfected alcoholics compared to those with HCV infection ($P < 0.05$). Liver histology in subjects with HCV infection showed higher HAI scores for intralobular necrosis ($P = 0.008$) and periportal inflammation ($P = 0.004$). Features of "chronic hepatitis" and focal lymphoid aggregates were more frequent in HCV-infected alcoholics ($P = 0.001$ for each). By contrast, cirrhosis was present in a higher proportion of uninfected alcoholics compared to those with HCV infection ($P = 0.05$). Histological findings of hepatic fibrosis and total HAI score showed a significant correlation with serum albumin and platelet count in HCV-infected alcoholics. Chronic alcoholics with HCV infection have specific histological appearances that can usually help distinguish these patients from uninfected alcoholics. Correlation analysis indicates that of the various laboratory tests, serum albumin and platelet counts are the best predictors of the severity of liver damage at histology. In chronic alcoholics, the development of cirrhosis is related more to the amount of alcohol consumed than to the presence of HCV infection.

KEY WORDS: hepatitis C; alcohol abuse; liver histology.

The overall prevalence of hepatitis C virus (HCV) in the general population in the United States is 1.8% (1). In certain subsets of the population, the prevalence of HCV infection is very high. Worldwide, the

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highest infection rate is seen in intravenous drug abusers, reaching nearly 80% in the United States (2, 3). Other groups at increased risk of acquiring HCV infection are patients on renal dialysis (4), subjects requiring multiple blood transfusions such as thalassemics and hemophiliacs (5), and solid-organ transplant recipients (6). Recently, chronic alcohol abuse has been identified as another risk factor for HCV infection; the infection rate in this group varies from 15% to as high as 50% (7–12).

The influence of combined HCV infection and alcohol abuse on the severity of liver disease is the subject of some controversy. Several workers have observed more severe liver disease in alcoholics with HCV infection compared to those without HCV infection (9, 10, 13–17), while others have found no difference between the two groups (7, 18–20). Some studies have noted an earlier onset of liver disease in HCV-infected alcoholics compared to uninfected alcoholics, but the final outcome was found not to be different (7, 19, 21). It has been suggested that high alcohol intake may have a direct impact on hepatitis C virus kinetics. Enhanced HCV replication has been reported in alcoholics (22–24), with a decrease in serum HCV-RNA levels after abstinence (24). However, other studies have found no difference in viral levels between alcoholics who were actively drinking at the time of analysis and complete abstainers (25).

In view of the close association between chronic alcohol abuse and HCV infection, it is of interest to determine the influence of dual pathology on the severity of histological abnormalities in the liver and to compare the results with alcoholics without HCV infection. The present study was carried out to examine this issue and to assess the presence of any correlation between specific histological abnormalities, the amount of alcohol consumed and serum biochemical tests.

MATERIALS AND METHODS

All chronic alcoholics presenting to the Alcohol Rehabilitation Unit or the Gastroenterology Clinic at the Veterans Affairs Medical Center in Houston, Texas, were eligible for inclusion into the study. The essential criteria for inclusion were: (1) history of heavy alcohol abuse, defined as the consumption of ≥80 g of ethanol per day for a minimum of 10 years, and (2) availability of liver biopsy, obtained as part of the patients diagnostic work-up. The presence of HCV infection was determined by the second generation recombinant immunoblot assay (RIBA-2 test). Patients with liver disease due to causes other than alcohol and HCV infection, including those with hepatitis B and HIV infections were excluded from the study. A detailed assessment was made of the amount of alcohol intake (grams per day) and the duration of consumption. Data were recorded with respect to the following laboratory tests: serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), AST/ALT ratio, albumin, prothrombin time, and total bilirubin.

Table 1. Demographic Findings in Alcoholics with and Without HCV Infection

Parameter	*Alcoholics*		P*
	With HCV (65)	*Without HCV (21)*	
Age (yr)	45 ± 7.5	48.7 ± 10.2	0.05
Gender	All men	All men	
Alcohol			
Amount (g/day)	195 ± 148.5	304.4 ± 211.2	NS
Duration (yr)	24.7 ± 6.8	25.1 ± 7.7	NS
Race [N(%)]			
Caucasians	26 (40)	16 (76.1)	0.01
African American	33 (50.7)	4 (19)	
Latin Americans	6 (9.2)	1 (4.7)	NS

*NS = not significant.

Liver Histology. All liver biopsy specimens were formalin-fixed, paraffin-embedded, sectioned, and stained with hematoxylin and eosin. Biopsy specimens were also stained with Mason's trichome, reticulin, and periodic acid-Schiff (PAS) stains. The specimens were analyzed blindly by two experienced histopathologists who were unaware of the patient's clinical data including risk factors, clinical presentation, biochemical data, and serological results. The liver biopsy specimens were graded using the Knodell's histological activity index (HAI) score. According to this scheme, the higher the HAI score, the worse the histological damage (26). A descriptive assessment of the histological abnormalities was also made, and the frequency of findings such as fatty infiltration, chronic hepatitis, lymphoid aggregates, fibrosis, and cirrhosis was noted.

Statistical Analysis. Numerical values were expressed as mean ± standard deviation (SD). Comparisons between groups were performed using the Student's *t* test, chi-square test (χ^2) and the Mann-Whitney rank-sum test. Correlation between values was analyzed by the Pearson's product moment correlation.

RESULTS

A total of 86 chronic alcoholics were included in the study. These consisted of 65 patients with a positive RIBA-2 anti-HCV antibody test (group I) and 21 patients with a negative anti-HCV test (group II). The demographic data, including total alcohol consumption, of the two study groups is shown in Table 1. HCV-infected alcoholics were younger than the uninfected subjects ($P < 0.05$). The mean daily alcohol consumption was significantly higher in patients without HCV infection compared to infected alcoholics.

TABLE 2. RESULTS OF BLOOD TESTS IN ALCOHOLICS WITH AND WITHOUT HCV INFECTION*

Parameter	Alcoholics: With HCV (65)	Alcoholics: Without HCV (21)	P
Bilirubin (mg/100 ml)	1.29 ± 2.19	1.41 ± 1.14	NS
Albumin (g/100 ml)	3.94 ± 0.58	3.6 ± 0.79	0.03
AST (units/ml)	88.8 ± 87.8	81.7 ± 68.8	NS
ALT (units/ml)	103 ± 80.5	49.4 ± 32.4	0.001
AST/ALT ratio	0.89 ± 0.34	1.71 ± 0.68	0.0001
Prothrombin time (sec)	12.1 ± 0.71	12.6 ± 1.23	NS
Anti-HBs-positive [*N* (%)]	20 (30.7)	4 (19)	NS
Platelets (mm^3)	201.9 ± 74.7	191.8 ± 87.8	NS

*AST = aspartate aminotransferase, ALT = alanine aminotransferase, Anti-HBs = antibodies to hepatitis B surface antigen, NS = not significant.

In the two study groups, there were 42 (49%) Caucasians, 37 (43%) African Americans, and 7 (8%) Latin Americans. The HCV infection rate was significantly higher in the African American compared to Caucasian subjects ($\chi^2 = 7.7$; 89% vs 62%; $P < 0.01$). There were too few Latin Americans in the study for meaningful statistical analysis.

Liver Biochemical Tests. The results of blood tests are shown in Table 2. The serum ALT values were significantly higher in alcoholics with HCV infection compared to uninfected subjects ($P = 0.001$). The AST/ALT ratio was significantly lower in infected alcoholics compared to subjects without HCV infection ($P = 0.0001$). Other laboratory tests were essentially similar between the two groups except for serum albumin, which was lower in the HCV-negative alcoholics ($P = 0.03$).

Liver Histology. The findings at liver histology are shown in Tables 3 and 4. There was no difference between the two groups with respect to the frequency of fatty infiltration. Alcoholics with HCV infection showed features of "chronic hepatitis" significantly more frequently compared to uninfected alcoholics. The presence of chronic hepatitis with piecemeal necrosis was noted in 20 of 65 (31%) HCV-infected alcoholics compared to none of the HCV-negative subjects ($P = 0.01$). Focal collections of lymphocytes (lymphoid follicles) in the portal tracts or in the hepatic lobules were noted in most HCV infected alcoholics (83%) compared to only 28.5% in uninfected alcoholics ($P = 0.001$). The presence of hepatic fibrosis was not different between the two groups, but features of cirrhosis were seen more frequently in uninfected alcoholics vs infected subjects ($P = 0.05$).

TABLE 3. HISTOLOGICAL ABNORMALITIES IN ALCOHOLICS WITH AND WITHOUT HCV INFECTION*

Parameter	Alcoholics [N (%)]: With HCV (65)	Alcoholics [N (%)]: Without HCV (21)	P
Fatty change [*N* (%)]	39 (60)	12 (57.1)	NS
Chronic hepatitis	37 (56.9)	3 (14.2)	0.001
CPH	17 (26.1)	3 (14.2)	NS
CAH	20 (30.7)	0	0.01
Lymphoid aggregates	54 (83)	6 (28.5)	0.001
Fibrosis	7 (10.7)	1 (4.7)	NS
Cirrhosis	14 (21.5)	10 (47.6)	0.05

*CPH, chronic persistent hepatitis; CAH, chronic persistent hepatitis; NS, not significant.

TABLE 4. HISTOLOGICAL ACTIVITY INDEX HAI SCORES IN ALCOHOLICS WITH AND WITHOUT HCV INFECTION

Parameter	Alcoholics: With HCV (65)	Alcoholics: Without HCV (21)	P*
Periportal necrosis	0.09 ± 0.42	0	NS
Intralobular necrosis	0.52 ± 0.73	0.04 ± 0.21	0.008
Periportal inflammation	1.75 ± 1.13	1.0 ± 1.45	0.004
Fibrosis	1.34 ± 1.73	2.14 ± 2.0	NS
Total HAI score	3.71 ± 2.61	3.19 ± 2.77	NS

*NS = not significant.

The results of histological activity index scores are shown in Table 4. The total HAI score was not significantly different between the two groups. However, scores for intralobular necrosis ($P = 0.008$) and periportal inflammation ($P = 0.004$) were significantly higher in alcoholics with HCV infection compared to uninfected subjects. Other parameters such as periportal necrosis and fibrosis did not differ between the two groups.

Correlation Analysis. There was no correlation between the amount of daily alcohol consumption and any of the HAI component scores or liver tests in either of the two study groups. The results of correlation analysis between serum biochemical tests and liver histology in HCV-infected alcoholics are shown in Table 5. There was a positive correlation between serum ALT values and the total HAI score ($P = 0.04$) as well as between serum bilirubin and the severity of periportal necrosis ($P = 0.01$). The serum albumin and platelet counts showed a strong negative correlation with both the severity of hepatic fibrosis and the total HAI score. In alcoholics without HCV infection, a significant negative correlation was observed between serum albumin and portal inflammation ($r = -0.43$; $P = 0.04$) and the total HAI score ($r = -0.5$; $P = 0.02$).

TABLE 5. COEFFICIENT CORRELATION (*r* VALUE) BETWEEN LIVER HISTOLOGICAL ABNORMALITIES AND VARIOUS CLINICAL AND LABORATORY PARAMETERS IN HCV-INFECTED ALCOHOLIC SUBJECTS*

	Periport nec r (P)	*Intralob nec* r (P)	*Periport inf* r (P)	*Fibrosis* r (P)	*Total HAI score* r (P)
ALT	NS	NS	NS	NS	0.25 (0.04)
AST/ALT ratio	NS	NS	−0.31 (0.009)	0.38 (0.001)	NS
Albumin	NS	NS	NS	−0.47 (0.0005)	−0.31 (0.01)
Bilirubin	0.3 (0.01)	NS	NS	NS	NS
Platelet	NS	NS	NS	−0.3 (0.01)	−0.25 (0.04)

*Only statistically significant *r* values are shown. Periport nec = periportal necrosis, Intralob nec = intralobular necrosis, Periport inf = periportal inflammation, HAI = histological activity index. The presence of a minus sign before a value denotes negative correlation. NS = not significant.

DISCUSSION

The histological abnormalities of the liver in patients with alcoholic liver disease or hepatitis C virus infection have been well described. However, liver histology in patients with dual pathology (alcoholic liver disease and HCV infection) is less clearly understood. In a previous study, Nakano et al assessed liver biopsy abnormalities in 17 alcoholics with anti-HCV antibodies (27). However, an important drawback in this study was that the authors did not record the amount and duration of alcohol consumption, or whether the patients were actively drinking at the time of the liver biopsy. Similarly, Uchimura et al, in their study on 46 alcoholics with HCV infection, do not mention whether their subjects were abstinent or drinking when the liver biopsy was obtained (28). This information is important because alcohol-related histological abnormalities may improve rapidly after abstinence. In the present study, we included only those patients who were heavy abusers of alcohol and were continuing to drink at the time of the liver biopsy. The mean alcohol consumption in our patients was >195 g/day, which is appreciably higher than the usual definition of heavy alcohol use (≥80 g/day).

The liver biopsy specimens were examined by two pathologists who were unaware of the clinical diagnosis of the patients. Several interesting differences were observed between alcoholics with (group I) and without HCV infection (group II). The total HAI score was low in both groups (3.7 for group 1 and 2.4 for group II), indicating the relatively mild nature of tissue necrosis in these patients. The scores for periportal inflammation were significantly higher in HCV-positive alcoholics compared to uninfected subjects (1.75 vs 1.0; $P = 0.0001$). The comparative lack of diffuse lymphocytic infiltration in alcoholic patients with HCV infection may reflect a suppressive effect of ethanol on the lymphocytic immune response. These findings are in agreement with the observations of Nakano et al, who also noted reduced lymphocytic infiltration of the portal tracts in HCV-positive alcoholics compared to nonalcoholic subjects with HCV infection (27).

The Knodell HAI scoring system has been criticized for combining disease activity (necroinflammatory processes) with the stage of illness (fibrosis and cirrhosis), and for lumping piecemeal necrosis and bridging necrosis in the same category (29, 30). To overcome this deficiency, we also analyzed our results according to the conventional method of assessing liver pathology. Several histological findings helped to differentiate alcoholics with HCV infection from uninfected subjects. The most useful feature was the presence of dense lymphoid aggregates in the portal tracts and hepatic lobules. Unlike diffuse lymphocytic infiltration, lymphoid aggregates were a prominent abnormality, seen in 83% of HCV-infected alcoholics compared to 28.5% in uninfected subjects ($P = 0.001$). The findings of chronic hepatitis were seen in 57% patients with HCV infection compared to 14% in uninfected alcoholics ($P = 0.001$). Sparse but definite acidophilic bodies (evidence of intralobular necrosis) in the hepatic parenchyma were present in 35% HCV-positive alcoholics compared to 0% in the uninfected group. It is interesting to note that cirrhosis was seen significantly more often in uninfected alcoholics than in those with HCV infection (47.6% vs 21.5%; $P < 0.05$). This is perhaps related to the higher alcohol consumption in the uninfected group.

In routine clinical practice, most patients with chronic liver disease are diagnosed by the presence of persistently elevated serum aminotransferase levels. In hepatitis C virus infection, the serum ALT is usually higher than AST and AST/ALT ratio is <1. By contrast, in alcoholic liver disease, the reverse is generally the case, with AST being higher than ALT, and the AST/ALT ratio is usually >2.0. In the present study, the aminotransferase values in patients with

dual pathology were midway between these two extremes. The serum ALT values were higher in alcoholics with HCV infection compared to uninfected subjects, while the AST/ALT ratio was significantly higher in the uninfected alcoholics (Table 2). Thus, the presence of HCV infection in an alcoholic subject can be inferred on the basis of routine liver tests; uninfected alcoholics generally have an AST/ALT ratio of >1.0 while in HCV positive subjects the ratio is <1.0.

There was no correlation between the serum aminotransferase values and any of the individual components of the HAI score. However, the total HAI score showed a significant correlation with serum ALT values in HCV-infected alcoholics (Table 5). Similarly, in these subjects there was a strong negative correlation between serum albumin and platelet counts and the severity of hepatic fibrosis and the total HAI score. Uninfected alcoholics also showed a significant correlation between serum albumin and periportal inflammation and the total HAI score. These findings indicate that of the various biochemical tests, serum albumin and platelet counts most closely reflect the severity of the histological damage.

In conclusion, the present study shows that the biochemical and histological abnormalities in alcoholics with and without HCV infection are fairly distinctive, and it should generally be possible to differentiate one condition from the other. The presence of lymphoid aggregates, periportal inflammation, and chronic hepatitis suggests HCV infection, whereas findings of a modest elevation of serum ALT and a high AST/ALT ratio favors the diagnosis of pure alcoholic liver disease. Our results indicate that in chronic alcoholics, the development of cirrhosis is related more to the amount of alcohol consumed than the presence of HCV infection.

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