

CHRONIC HEPATITIS C-INFECTED PATIENTS;

Assessment of relationship between serum alanine aminotranferase levels and liver histology.

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ABSTRACT... Background: In our region the sensitivity of serum alanine aminotranferase (ALT) levels in predicting the severity of hepatitis C virus (HCV) infection is unclear. **Objective:** To compare histologic scoring of liver pathology in patients with chronic HCV infection with normal or elevated serum ALT. **Study Design:** Prospective observational study. **Place & Duration of Study:** Liver clinic, Ghulam Mohammad Mahar Medical College Hospital, Sukkur, between January 2010 and December 2010. **Methods:** Liver biopsies were performed in patients with HCV infection and either normal (n=40) or elevated (n=76) serum ALT levels, and scored for activity and fibrosis using the modified histological activity index. **Results:** Patients with normal ALT and elevated ALT had similar demographic features. Median (range) histological activity grade was higher in patients with elevated ALT than in those with normal ALT (6 [1-15] vs. 5 [0-11], respectively; p=0.001), as was the fibrosis stage (2 [0-6] vs. 1 [0-6]; p=0.02). Two patients with normal ALT and 4 with elevated ALT had liver cirrhosis. **Conclusions:** Among patients with chronic HCV infection, liver lesions are milder in those with normal serum ALT levels than those with abnormal ALT levels. However, some patients with normal ALT too may have advanced liver disease.

Key words: HCV Infection, ALT, Liver Histology

Article Citation

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INTRODUCTION

HCV is a tremendous health problem not only in Pakistan but also worldwide. The world health organization estimates that approximately 3% of the world population have been infected with HCV thus far. There are about 170 million patients with HCV in the world, and three to four million individuals are diagnosed as new cases every year^{1,2}. An approximately 10 million are in Pakistan^{3,4}. Among patients with chronic infection, 5%-20% have been reported to develop cirrhosis over 20-25 years⁵. The efficacy of elevation of serum alanine aminotranferase (ALT) levels in prediction of severity of liver injury in patients with chronic hepatitis C is debated⁶. Up to 20% of patients with infection have persistently normal serum ALT levels. Since ALT levels in these patients may fluctuate, the label 'persistently normal ALT level' is a function of duration of follow up and frequency of ALT determinations⁷. Also, factors such as age, gender and body mass index may influence serum ALT levels in patients with chronic hepatitis C⁸. The histopathology in hepatitis C virus infection

encompasses the entire spectrum of liver damage ranging from acute fulminant hepatic failure to chronic hepatic failure to chronic hepatitis cirrhosis and hepatocellular carcinoma. There are two patterns of chronic hepatitis C, hepatitis C with elevated serum ALT and chronic hepatitis C with normal serum ALT^{9,10}.

To study this issue, we compared inflammatory activity and fibrosis on liver histology in patients with normal and elevated serum ALT levels.

METHODS

In this Prospective study, 116 patients with detectable serum anti-HCV (ELISA) and HCV RNA by PCR, but no history of antiviral (anti-HCV) therapy, were studied at Liver clinic at Ghulam Mohammad Mahar Medical College Hospital, Sukkur, between January 2010 and December 2010. None of the subjects had history of alcohol consumption, thalassemia major, other liver diseases, clinically identified cirrhosis, contraindication for liver biopsy, or positive results for anti-HAV IgM, anti-HBc, HBsAg or anti-HIV antibody.

During the study period six patients, who came with only one abnormal ALT value, were not included.

Of the 116 patients, 40 had normal serum ALT levels (<49 IU/L; our laboratory cut-off) on at least three consecutive determinations during the previous six months (persistently normal ALT group), whereas 76 had one abnormally high serum ALT determination at least once during the previous one month and on at least one other occasion during the last six months (elevated ALT group). Percutaneous liver biopsy was performed in all patients. Formalin-fixed specimens were assessed by one pathologist, who was unaware of the clinical and biochemical details. Histological activity (grade) was scored from zero to 18, and fibrosis (stage) from zero to six using the modified histological activity index⁵. The study protocol was approved by the Hospital Ethics Committee, and all patients provided written informed consent. Data were analyzed using SPSS (V 10.0.1) software, and student t test, chi-squared test, and Mann-whitney test as appropriate.

RESULTS

Patient characteristics and frequency of risk factors for HCV infection were similar in the two groups (Table).

The table shows distribution of histological activity grade and fibrosis stage in patients with normal and elevated ALT. Median (range) histological activity grade in patients with elevated ALT (6 [1-15]) was higher than that in patients with normal ALT (5 [0-11]; $p < 0.001$), as was the fibrosis score (2 [0-6] versus (1 [0-6]; $p < 0.02$) Among patients with elevated serum ALT, 4 (5.3%) had histological evidence of liver cirrhosis, and 12 (15.8%) had bridging fibrosis, as did two and one patients, respectively, with normal ALT.

DISCUSSION

Persistently normal ALT is usually defined as ALT levels in the normal range during a 6-to-12 months period^{11,12}. We defined persistently normal ALT as at least 3

Characteristics	ALT level	
	Normal (n=40)	Elevated (n=76)
Serum ALT level (IU/L)*	33 (10-45)	85 (50-985)
Age (y)	42 (18-67)	41 (19-64)
Gender (M:F)	35:5	63:13
Body mass index	23 (17.8-27.8)	22 (16.6-31.0)
Smoker	21 (53%)	40 (53%)
Risk factor		
Intravenous drugs abuse	9 (23%)	28 (37%)
Blood transfusion	5 (13%)	10 (13%)
Surgery	3 (8%)	4 (5%)
Prior dental surgery	8 (20%)	13 (17%)
Histological activity grade*		
0	2	-
1-3	12	11
4-6	17	28
7-9	8	23
10-12	1	12
13-15	-	2
16-18	-	-
Stage of liver fibrosis*		
0	5	5
1	16	21
2	9	19
3	6	9
4	1	6
5	1	12
6	2	4

Table-Characteristics of patients with HCV infection and normal or elevated ALT levels

Date are shown as median (range) or as number (%); * $p < 0.05$

consecutive serum levels below the upper limit of normal. Using this definition, we found that stage and grade of liver disease was lower among patients with persistently normal serum ALT. Nutt et al, found that mean (SD) HAI scores were 4 (2) among patients with normal serum ALT levels and 7 (3) among patients

with elevated levels¹². Corresponding figures were 2.96 (1.62) and 5.39 (2.81) in another case-control study¹³. Our findings are similar to those in previous studies, which found that patients with normal ALT values had milder liver damage than those with abnormal ALT values^{14,15,16}.

In our study, 5% of patients with normal ALT level had cirrhosis and 3% percent had bridging fibrosis. In the study by Nutt et al,¹² these figures were 11% and 9%, respectively. However, in another study of patients with normal serum ALT, none had cirrhosis and only 3.1% had bridging fibrosis. In another study, only 4% of patients with persistently normal ALT had chronic hepatitis and only 1% had cirrhosis¹⁵. Mathurin et al¹⁷ showed that in HCV RNA-positive patients with normal ALT values, the progression to fibrosis was slower than that in patients with elevated ALT. There is disagreement on whether HCV-infected persons with normal ALT values warrant treatment^{18,19}. In the study by Nutt et al, 46% of patients with normal serum ALT levels had histological activity index more than 5, compared to 86% of patients with elevated ALT levels. Our findings were similar to these in that normal serum ALT levels do not exclude histological findings that might constitute an indication for antiviral therapy.

Thus, regardless of the serum ALT level, the decision to initiate therapy should be based on the severity of liver disease on histology⁶.

In conclusion, though persistently normal ALT levels among patients with chronic hepatitis C are associated with milder histological activity and fibrosis, these do not exclude presence of advanced liver disease.

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