Original Article

Liver Histology in Hepatitis C Virus positive patients with Normal and Elevated Alanine Amino Transferase levels

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Abstract

Objective: To compare liver histology in HCV RNA positive patients with normal and elevated Alanine Aminotransferase Level (AST).

Methods: This Cohort (prospective) study was conducted at Civil Hospital Karachi from Jan 2007 to July 2007. Forty patients with positive HCV RNA were included. Their liver function tests were followed for three months. Those having normal ALT on three occasions were taken as controls and those having elevated ALT were taken as cases. Liver biopsy was performed, Specimens were reviewed by single pathologist. Scheuer's scoring for grading of inflammation and staging of fibrosis of chronic hepatitis was used.

Results: Out of Forty patients having positive HCV RNA, 14 (35%) were male and 26 (65%) were female. Mean ALT in control group was 27.3 ± 6.1u/l, mean ALT in cases was 91.7 ± 39.95u/l. Mean age in controls was 34.2 ± 10.75 years and in cases was 33.6 ± 9.40 years. On histopathology, the mean grade of inflammation in controls was 1.40 ± 0.681 while in cases was 1.20 ± 0.834, which was not statistically significantly different in the two groups (p= 0.411). Similarly mean staging of fibrosis in controls was 1.20 ± 0.768 and in cases was 1.35 ± 1.348 which was also not statistically different in the two groups (p=0.668). Stage 3 and 4 fibrosis was seen only in raised ALT group and not in the controls.

Conclusion: Patients with persistently normal ALT and elevated ALT, although had similar grading of inflammation but the fibrosis score was more in elevated ALT group. None of the patients with normal ALT had normal histology, so decision for antiviral treatment should be individualized in this group also (JPMA 59:832; 2009).

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] The prevalence rate is high among middle aged persons and patients receiving haemodialysis or who received blood transfusion before the advent of HCV diagnostic tools.[5]

Elevated serum ALT (eALT) has traditionally been a criterion in selecting patients for liver biopsy and treatment in chronic hepatitis C. However, in recent years, it has become apparent that a small number of hepatitis C patients may be cirrhotic despite normal ALT. ALT levels commonly fluctuate. Normal ALT at a point in time may not accurately reflect the course of the hepatitis.

The efficacy of elevation of serum ALT levels in prediction of severity of liver injury in patients with chronic hepatitis C is debated.[6,7] Upto 20% of patients with chronic 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 determination.[6-8] Persistently normal ALT is usually defined as ALT levels in the normal range during 6-12 month period.[9] Dor -Muhammadi etal defined persistently normal ALT as at least three consecutive serum levels below the upper limit of normal.[10] As the efficacy of serum ALT levels in predicting the severity of Hepatitis C virus infection is unclear so we aim to compare histological scoring of liver pathology in patients with chronic HCV infection with normal or elevated serum ALT.

Patients and Methods

This was a prospective study. Forty patients with recent positive test for HCV RNA were included. Viral load and Genotyping were not done. Patients with concomitant HBV, HDV infection, history of taking alcohol and hepatotoxic drugs were excluded from the study. Their liver function tests were followed at intervals of four weeks for three months. The follow up period was reduced from six months in standard definition of persistently normal ALT, to three months as we intended to treat patients with three successive normal ALT, which according to guidelines should be individualized based on severity of liver disease by liver biopsy, the potential side effects, the likelihood of response and the presence of comorbids.[7] Those having normal ALT on three occasions were taken as controls and those having

elevated ALT on three occasions were taken as cases. After taking informed consent for liver biopsy, their Haemoglobin, Prothombin time, Partial Thromboplastin time were checked as a prerequisite for liver biopsy. Liver biopsy was performed by 16 G Lumbar puncture needle. Specimens were fixed in 10% Formalin and reviewed by a single pathologist. Scheuer's scoring for grading of inflammation and staging of fibrosis of chronic hepatitis was used. According to which grading of inflammation and staging of fibrosis is scored from 0 to 4 according to severity.[11] Data was interpreted via SPSS version 15. Students T test was used to compare cases and controls. Chi square test was applied to compare categorical data.

Results

Out of forty patients having positive HCV RNA, 14 (35%) were male and 26 (65%) were female. Mean age in controls was 34.2 ± 10.75 years and in cases was 33.6 ± 9.40 years. Out of 20 controls, 5 (25%) were male and 15 (75%) were female whereas in 20 cases, 9 (45%) were male and 11 (55%) were female. Mean ALT in control group was 27.3 ± 6.1 u/l, mean ALT in cases was 91.7 ± 39.95u/l. On histopathology, the mean grade of inflammation in controls was 1.40 ± 0.681 and in cases was 1.20 ± 0.834, which was not significantly different (p= 0.411). Although grade 1 inflammation was seen in 12 (60%) of raised ALT group and grade 1 and 2 inflammation in 8 (40%) and 10 (50%) respectively in normal ALT group (Table-1). Similarly mean staging of fibrosis in controls was 1.20 ± 0.768 and in cases was 1.35 ± 1.348 which was also not different in the two groups (p=0.668). Stage 0 fibrosis in 7 (35%), stage 3 and 4 fibrosis in 4 (20%) of patients with raised ALT group. In the normal ALT group stage 0 fibrosis in 4 (20%), stage 1 and 2 in 16 (80%), and none had stage 3 and 4 fibrosis (Table-2). Fatty change was seen in three patients (15%) in either group which was similar in both groups, out of which two patients had mild to moderate fatty change with Grade 0 inflammation and Stage 0 fibrosis in both elevated and normal ALT group.

Table-1: Grading of inflammation according to Scheuer's classification in normal and raised ALT groups.

Serum ALT	None or minimal inflammation Grade 0	Portal inflammation inflammation Grade 1	Mild piecemeal necrosis Grade 2	Moderate piecemeal necrosis Grade 3	Severe piecemeal necrosis Grade 4	P value
Increased	3 (15%)	12 (60%)	3 (15%)	2 (10%)	0(0%)	0.411
Normal	2 (10%)	8 (40%)	10 (50%)	0 (0%)	0(0%)	

Table-2: Staging of fibrosis according to Scheuer's classification in normal and raised ALT groups.

ALT group	None Grade 0	Enlarged fibrotic tract Grade 1	Periportal or porta portal septa Grade 2	Fibrosis with archeicture distorted Grade 3	Cirrhosis Grade 4	P value
Increased	7 (35%)	5(25%)	4(20%)	2(10%)	2(10%)	0.668
Normal	4 (20%)	8 (40%)	8 (40%)	0 (0%)	0 (0%)	

Discussion

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.[12] Histologic assessment of liver biopsy specimens remains the 'gold standard' for quantifying fibrosis and is the only way to determine the amount of fibrosis in a liver biopsy.[13] It is unclear whether degree of serum ALT elevation or quantitative Hepatitis C virus RNA can predict level of histological damage. According to Mc Cormick SE[14] although there is a correlation between serum ALT and degree of hepatic injury based on HAI score, this relationship is weak and probably of no clinical use. There is no significant correlation between HCV RNA and serum ALT or HCV RNA and degree of hepatic injury in individual patients. Hepatic histological evaluation continues to be required for clinical assessment of patients with chronic Hepatitis C.[14]

The natural history of HCV infection in patients with normal liver biochemistry remains poorly characterized. So we performed liver biopsies in patients with persistent normal and raised ALT levels to see the histological difference. None of the patients with normal ALT levels had a normal histology, as two patients (10%), who had Grade 0 inflammation and Stage 0 fibrosis had mild to moderate fatty change on histology. Grading of Inflammation and staging of fibrosis was done according to Scheuer's scoring. Grading of inflammation and staging of fibrosis was not significantly different between the cases and controls (p=0.411). Although none of the patients in normal ALT group had grade 3 and 4 fibrosis, which was seen in raised ALT group. Nutt et al[9] found more fibrosis score in raised ALT group than normal ALT

group. Similarly Dor Mohammadi et al[10] also found that the patients with normal ALT values had milder liver damage than those with abnormal ALT values. None of our patients in normal ALT group had cirrhotic findings i.e. beyond stage 2 fibrosis (Table-2). Whereas Dor Mohammadi et al[10] found that 5% of patients with normal ALT levels had cirrhosis and 3% had bridging fibrosis. Also in the study by Nutt et al[9] these figures were 11% and 9% respectively. However, in another study of patients with normal ALT, none had cirrhosis and only 3.1% had bridging fibrosis.[15] In HCV RNA positive patients with normal ALT values, the progression of fibrosis was slower than that in patients with elevated ALT.[16] Steatosis was not significantly different in the two groups in our study, whereas 32.7% patients had steatosis on liver biopsy in one study.[17] Zahid Latif et al showed 65.7% had steatosis of various grades and reported steatosis as quite common in patients of HCV infection as a contributing factor in the development of fibrosis in chronic hepatitis C.[18]

There is a debate whether HCV infected persons with normal ALT warrant treatment.[19,20] As the previous studies, our study also shows that normal serum ALT levels do not exclude histological findings that might constitute an indication for antiviral therapy. Sustained response rates for patients with normal ALT levels were same as those of patients with elevated ALT levels and degree of elevation of ALT level did not correlate with overall response rates to antiviral therapy for Hepatitis C. The safety of treatment of patients with normal ALT levels, which was a concern with Interferon monotherapy has not been a problem with combination therapy of Interferon and Ribavarin. The presence of normal ALT levels has been used as a marker of mild and non-progressive liver disease. It should be stressed that the use of ALT levels to assess severity of liver disease is not always reliable. Furthermore patients with mild disease may have other indications for therapy including presence of symptoms, extrahepatic manifestations, serious comorbids or major concerns regarding infectivity. Patients autonomy dictates that the desires of patients be weighed in any decision for or against treatment.[21] Thus regardless of serum ALT level, patients with normal ALT should also receive antiviral therapy, which can be decided on patients will, age, duration of infectivity, viral genotype and HCV RNA levels.

Conclusion

Patients with persistently normal ALT and those with elevated ALT although had similar grading of inflammation but the fibrosis score was more in elevated ALT group. None of the patients with normal ALT had normal histology, so decision for antiviral treatment should be individualized in this group also. In addition as the degree of fibrosis is less in normal ALT group these patients will have more advantage of anti viral therapy.

Acknowledgement

We would like to thank Dr. Naila Zahir, Histopathologist at Karachi Medical & Dental College for being kind enough to report the histopathology slides.

References

1. V Lo Re, Kostman JR.Management of chronic Hepatitis C. Postgrad Med J 2005; 81: 376-82.
2. Ray K W. Global epidemiology and burden of Hepatitis C. Microbes Infect 2004; 4: 1219-25.
3. Higuchi M, Tanaka E, Kiyosawa K. Epidemiology and clinical aspects on Hepatitis C. Jpn J Infect Dis 2002; 55: 69-77.
4. Hamid S, Umer M, Alam A, Siddiqui A, Quraishi H, Butt J. PSG consensus statement on management of Hepatitis C virus infection. J Pak Med Assoc 2004; 54: 146-50.
5. Nadeem SR, Khalid AJ. Epidemiology of Hepatitis C infection in Pakistan. J Microbiol Immunol and Infect 2008; 41: 4-8.
6. Pradat P, Alberti A, Poynard T, Esteban JI, Weiland O, Marcellin P, et al. Predictive value of ALT levels for histologic findings in chronic Hepatitis C: A European collobrative study. Hepatology 2002; 36: 973-7.
7. Strader DB, Wright T, Thomas DL, Seef LB. Diagnosis, management and treatment of Hepatitis C. Hepatology 2004; 39: 1147-71.
8. Prati D, Taioli E, Zanella A, Della Torre E, Butelli S, Del VE, et al. Updated defination of healthy ranges for serum ALT levels. Ann Intern Med 2002; 137: 1-10.
9. Nutt AK, Hassan HA, Lindsey J, Lamps LW, Raufman JP. Liver biopsy in the evaluation of patients with chronic hepatitis C who repeatedly have normal or near normal Serum Alanine Aminotransferace. Am J Med 2000; 109: 62-4.
10. Taraneh DM, Naseer ED, Muhammad B, Ali AH, Babak H, Ali RS et al. Relationship between serum ALT levels and liver histology in chronic hepatitis c infected patients. Indian J Gastro 2005; 24: 49-51.
11. Scheuer PJ. Classification of chronic hepatitis c a need for reassessment. J Hepatol 1991; 13: 372-74.
12. Sood A, Vandana M, Neena S, Harpreet K, Malhotra V, Awasthi G. Chronic hepatitis C in Northern India. The pathological and clinical spectrum. JAPI 2004; 52: 380-4.
13. Afdhal NH, Nunes D. Evaluation of liver fibrosis: a concise review. Am J Gastro 2004; 99: 1160-74.
14. Mc Cormick SE. Evaluation of liver histology, ALT elevation and HCV RNA titer in patients with chronic hepatitis C. Am J Gastro 1996; 91: 1516-22.
15. Pasquale G, Sagnelli E, Coppola N, Scarano F, Scolastico C, Balliona PF. Is liver biopsy necessary for hepatitis C virus carrier with persistently normal aminotransferase levels? Eur J Gastroenterol Hepatol 2003; 15: 831-3.
16. Mathurin P, Moussali J, Cadranel JF, Thibault V, Charlotte F, Dumouchel P, et al. Slow progression rate of fibrosis in hepatitis C virus patients with persistently normal ALT activity. Hepatology 1998; 27: 868-72.
17. Sadik M, Akber M, Hanif G, Noman K. Liver biopsy in patients infected with chronic hepatitis c and persistently normal serum ALT levels. J Liaquat Uni Med Health Sci 2008; 7: 87-92.
18. Zahid L, Hammamatul BK, Umer M, Shoaib S, Haider B, Syed IF, et al. Liver steatosis and fibrosis in chronic hepatitis C: a study of 76 cases. J Rawal Med Coll 2003; 7: 18-20.
19. Gholson CF, Morgan K, Catinis G, Faurot D, Taylor B, Gonzalez E, et al. Chronic hepatitis c with normal aminotransferase levels: a clinical histologic study. Am J Gastrol 1997; 92: 1788-92.
20. Martinot PM, Boyer N, Cazals HD, Pham BN. Prospective study on hepatitis C virus positive patients with persistently normal serum ALT. J Pediatr Gastroentrol Nutr 2002; 34: 52-8.
21. Bruce RB. Treatment of patients with hepatitis C and normal serum Aminotransferase levels. Hepatology 2002; 36: S179-84.