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Original Research Article

Clinical and histological spectrum of hepatitis C disease associated with persistently normal alanine aminotransferase levels

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ABSTRACT

Background: Around 20% of patients with chronic hepatitis C infection (HCV) have persistently normal alanine aminotransferase (PNALT) levels. These patients are considered to have mild degree of histological hepatic damage. This study was conducted to compare the histological degree of necro-inflammation and stage of fibrosis among HCV patients with PNALT and patients with persistently or intermittently elevated serum ALT (PIEALT) levels..
Methods: This study includes 154 untreated patients with serological and histological diagnosis of chronic HCV infection. A total of 70 patients with PNALT (group A) and 84 patients with PIEALT (group B) were identified and treated with 6 months interferon therapy. Histological grade of necro-inflammatory activity and the stage of fibrosis was evaluated by Ishak scoring system. HCV-RNA quantification was done by real-time polymerase chain reaction (PCR). Further univariate and multivariate analysis was done to evaluate correlation between patients characteristics and significant hepatic fibrosis..
Results: Out of one hundred and fifty four patients, mean ALT was 30.59 ± 5.59 U/L in group A as compare to 68.65 ± 23.17 U/L in group B ($p = 0.001$). Patients with PNALT were younger ($p = 0.005$) with milder grade of necrosis ($p = 0.037$), lower serum HCV viral load ($p = 0.044$) and significant achievement of sustained virological response ($p = 0.012$) as compare to patients with abnormal ALT. Different variable were also analysed by univariate and mutivaraite analysis among patients with significant and insignificant fibrosis. High serum HCV-RNA level was found to be the independent variable predictive of advanced fibrosis among HCV infected patients (OR = 0.89; 95% CI = 1.65-1.94; $p < 0.001$) with r2 = 80%.
Conclusions: Our study suggests that normal serum ALT does not mean healthy liver. So, histological evaluation is still an essential tool to assess liver damage precisely.

Keywords: HCV-RNA, Liver biopsy, PNALT, PIEALT, SVR

INTRODUCTION

Infection with hepatitis C virus has become the leading cause of chronic liver disease worldwide, which ultimately leads to cirrhosis in 25-30% of patients and end-stage liver disease in 5-10% of cirrhotic patients [1]. Attempts are making to diagnose severity of disease progression in HCV infected patients by using blood tests

and other indices with reasonable specificity and sensitivity [2]. Early detection of fibrosis is also important to lessen cirrhosis-related deaths [3].

The degree of liver inflammation and stage of fibrosis are the key histological predictors of cirrhosis. In HCV infection, gold standard criteria to predict the severity of hepatic disease is liver biopsy [4]. Liver biopsy is helpful in decision making about natural history of disease to reach a diagnosis and make beneficial therapeutic decisions, but with recognized limitations. Since it is a costly and invasive procedure, so challenging to be accepted by several patients. Secondly, liver biopsy can sometimes cause life threatening complications. Another important limitation of biopsy procedure is sampling variability [5, 6]. Non-invasive measures to assess hepatic disease include biochemical parameters (ALT, AST), quantitative viral load and serum markers of fibrosis. During hepatic injury, alanine transaminase (ALT) is an enzyme which is released from hepatocytes. Although serum ALT commonly fluctuate but in few cases of HCV infection, persistently normal level of ALT (PNALT) can also be appreciated [7].

According to literature, PNALT is defined as measurement of serum ALT levels ≤ 35 U/L on three different occasions separated by at least one month. Several controversies exist regarding epidemiological, virological and histological characteristics in HCV infected patients with PNALT.

Significant correlation and differences between different levels of serum ALT and histological grade and stage has been observed in several studies.[4,8] Some studies have been mentioning that PNALT is considered to be associated with milder disease in term of hepatic necro-inflammation and fibrosis.[3] Similarly, increase in serum transaminase levels are considered as pathological and according to the duration of necro-inflammatory process of liver [9]. Other studies regarding serum ALT levels and its correlation to histological activity index (HAI) score have shown conflicting results.[10,11] The majority of patients with PNALT also showed moderate to severe histological evidence of hepatic fibrosis, cirrhosis and eventually hepatocellular carcinoma.[12,13]

The aim of this study was to evaluate the relationship of PNALT with degree of histopathological damage and achievement of sustained virological response (SVR) in comparison with HCV infected patients of elevated ALT group.

METHODS

Setting and subjects

This prospective study was carried out at department of biochemistry and molecular biology, Islamabad medical and dental college in collaboration with General Hospital, Pakistan. The study was approved by Institutional Ethics committee and by FDA-1996 & Declaration of Helsinki [14]. By using research protocol, 154 out of 560 HCV-infected patients met the study criteria. Written informed consent was taken from each patient participating in this study. ALT activity was inferred retrospectively from their biochemical check-ups record supplied by the patients or their general practitioners. Serum ALT level less than or equal to 35 U/L in males and 19 U/L in females was taken as normal value. Patients were categorized as *persistently normal ALT* (PNALT) if they had at least three consecutive ALT levels ≤ 35 U/L in males and ≤ 19 U/L in females, 2 months apart over a period of 6-month. PIEALT was defined as patients with *persistently or intermittently elevated ALT*, if they had at least 3 consecutive ALT levels > 35 U/L in males and 20-40 U/L in females, 2 months apart over a period of 6-month [7].

Inclusion and exclusion criteria

Patients were considered eligible for this study if they were: 1) 18 years of age or older at the time of diagnosis; 2) sero-positive for antibodies to anti-HCV detected by means of third generation enzyme immunoassay (ELISA) along with detectable serum HCV-RNA levels; 3) having persistently normal serum ALT (PNALT) or persistently/intermittently elevated ALT (PIEALT).

None of the patients was dropped from the study secondary to elevated serum ALT levels or side effects related to antiviral therapy. None of the patients had history of any other liver disease including hepatitis B virus, autoimmune hepatitis, clinically diagnosed cirrhosis or contraindication for liver biopsy.

Virological assays

At the time of enrolment in this study, all patients underwent biochemical analysis, quantitative viral assay and percutaneous ultra-sound guided liver biopsy. Antibodies for anti-HCV were detected by Fourth Generation ELISA method and real-time reverse transcription-polymerase chain reaction (RT-PCR) was performed for quantification of serum HCV-RNA by Cobas® Amplicor HCV monitor v2.0 (Roche Molecular systems, Pleasanton, CA, USA).

Liver biopsy and histology

For histological assessment, percutaneous liver biopsy using 18-20 gauge Trucut needle was performed on all patients. Histological evaluation was done on hematoxylin and eosin stained, formalin-fixed and paraffin embedded sections of liver biopsies. The modified histological stage of hepatic fibrosis and grade of hepatic necro-inflammation, were calculated by using Ishak's modified hepatic histological activity index (HAI).[15] They were evaluated by single pathologist who was unaware of patients' biochemical data. For statistical analysis, the necro-inflammatory grade and fibrosis stage

were categorized as minimal to mild (grade 0-9; stage 0-3) and moderate to marked (grade 10-18; stage 4-6).[15]

All subjects were treated with interferon-alpha (6 MU) subcutaneously thrice a week and oral ribavirin 800–1200 mg daily for duration of six month. Sustained virologic response (SVR) was assessed by HCV RNA negative by branched DNA (bDNA) 24 weeks after discontinuation of treatment.

Statistical analysis

Data were checked, entered and analyzed by using SPSS (Statistical Package for the Social Sciences) version 20. Data was expressed as mean ± SD for quantitative variables, number along with their corresponding percentages for qualitative ones. Student's t test was applied for continuous variables while Fisher's exact tests for dichotomous variables. Two-tailed *p*-value of less than 0.05 was considered significant. Multiple logistic regression analysis was subsequently applied (for variables significant at univariate analyses) to evaluate the variables independently predictive of advanced fibrosis among HCV infected patients.

RESULTS

Demographic characteristics and biochemical, virological and histological data of the patients with persistently normal and elevated serum ALT levels are given in Table 1, including age, gender, serum ALT levels, serum HCV-RNA, grade and stage of liver biopsies. A total of 154 HCV infected patients, 79 (51.2%) males and 75 (48.7%) females were selected. The normal ALT group has 70 (45.45%) patients with persistently serum ALT level less than 35 U/L (PNALT) and group B comprises of 84 (54.54%) patients with persistently or intermittently serum ALT level more than 35 U/L (PIEALT). Patients with normal ALT were younger than those with raised ALT levels (35.36±5.33 vs. 37.92±5.51; p= 0.005). No significant difference was observed concerning gender of the patients between the two groups.

Table 1: Demographic and clinical characteristics of patients.

Characteristics	Group A (PNALT)†	Group B (PIEALT)‡	P value
Patients, n (%)	70 (45.45%)	84 (54.54%)	
Age (years)	35.36±5.33 (25-47)	37.92±5.51 (29-50)	**0.005***
ALT, U/L	30.59 ± 5.59	68.65 ± 23.17	**0.001***
< 0.5 × ULN‖	32 (45.7%)		
0.5 to 1 × ULN	38 (54.3%)	-	
1-2 x ULN	-	48 (57.1%)	
> 2 x ULN	-	36 (42.8%)	
Gender, n (%)			
Male	31 (44.3%)	48 (57.1%)	0.323**
Female	39 (55.7%)	36 (42.9%)	
Ishak modified grade of necro-inflammation			
Minimal to Mild	55 (78.6%)	49 (58.3%)	**0.037****
Moderate to Marked	15 (21.4%)	35 (41.6%)	
Ishak modified stage of liver fibrosis			
Minimal to Mild	44 (62.8%)	45 (53.5%)	0.159**
Moderate to Marked	26 (37.1%)	39 (46.4%)	
HCV-RNA titer, n (%)			
< 4 x 10^5 IU/ml	49 (70.0%)	42 (50.0%)	**0.044****
> 4 x 10^5 IU/ml	21 (30.0%)	42 (50.0%)	
SVR§, n (%)			
Responders	58 (82.8%)	32 (38.1%)	**0.012****
Non-responders	12 (17.1%)	08 (9.5%)	

Note: All data expressed as mean ± SD or number (%); *Two-tailed t-tests. ** Fisher's Exact Test. †: persistently normal alanine aminotransferase level, ‡: persistently or intermittently elevated alanine aminotransferase levels, ‖: Upper limit of normal serum ALT value, §: sustained virological response.

A comparison of histological findings between two groups was also carried out. Minimal to mild scores for portal inflammation with no evidence of necrosis was observed in 78.6% of patients in normal ALT group and 58.3% in elevated ALT group, which was statistically significant (p=0.037). Regarding stage of fibrosis, milder

alterations were observed in group A patients with PNALT. Forty four (62.8%) patients had minimal to mild histological features and 26 (37.1%) had moderate to marked histological fibrosis despite of having normal serum ALT but the difference between group A and group B was not significant (p=0.159). Concerning HCV-RNA level, 49 (70.0%) patients in group A showed significantly lower viral load (<4 x10^5 IU/ml) as compare to 42 (50.0%) patients in group B (p=0.044). A statistically significant difference was found with respect to serum ALT levels (30.59±5.59 vs. 68.65±23.17; p = 0.001) and achievement of sustained virological response between the two groups (82.8% vs. 38.1%, p = 0.012).

Univariate analysis was also applied among study population with significant fibrosis and insignificant fibrosis in Table 2. Eighty nine (57.79%) patients were identified as having minimal to mild stage of hepatic fibrosis and sixty five (42.20%) patients with moderate to marked hepatic fibrosis. There was no significant differences between two groups for serum ALT levels. The mean age of patients with advanced fibrosis was significantly higher than that of those without advanced fibrosis (37.97±5.90 vs. 35.80±5.12; p = 0.016). Patients with advanced fibrosis were mainly males (66.2% vs. 40.4%; p = 0.001) with higher titer of HCV-RNA (92.3% vs. 3.4%; p<0.001), moderate to marked necro-inflammatory grade (84.6% vs. 10.1%; p<0.001), and resistant to interferon plus ribavirin therapy (78.5% vs. 14.6%; p<0.001) as compare to patients without advanced fibrosis.

Significant variables associated with advanced fibrosis were further analyzed by multivariate logistic regression (Table 3). Serum HCV-RNA titer › 4 x 105 IU/ml [odds ratio (OR), 0.89; 95% confidence interval (CI), 1.65-1.94; p < 0.001] was independently associated with advanced fibrosis in HCV infected patients with r2 = 80%.

Table 2: Characteristics of patients with insignificant fibrosis versus significant fibrosis.

Characteristics	Insignificant fibrosis n (%)	Significant fibrosis n (%)	P value
Patients, n (%)	89 (57.79%)	65 (42.20%)	
Age (years)	35.80±5.12	37.97±5.90	**0.016**
ALT, U/L	48.99±27.86	54.58±22.55	0.185
Gender, n (%)			**0.001**
Male	36 (40.4%)	43 (66.2%)	
Female	53 (59.6%)	22 (33.8%)	
HCV‡‡-RNA titer, n (%)			**< 0.001**
< 4 x 10^5 IU/ml	86 (96.6%)	05 (7.7%)	
> 4 x 10^5 IU/ml	03 (3.4%)	60 (92.3%)	
Ishak modified grade of necro-inflammation			**0.001**
Minimal to Mild	80 (89.9%)	10 (15.3%)	
Moderate to Marked	09 (10.1%)	55 (84.6%)	
SVR§, n (%)			**< 0.001**
Responders	76 (85.4%)	14 (21.5%)	
Non-responders	13 (14.6%)	51 (78.5%)	

All data expressed as mean ± SD or number (%). *Two-tailed t-tests. ** Fisher's Exact Test; ‡‡: Hepatitis C virus, §: Sustained virological response.

Table 3: Parameters predictive of advanced fibrosis among HCV infected patients.

Variables	Regression Coefficient	Odds Ratio	95% CI¶	P value
High HCV-RNA‡‡	1.79	0.89	1.65-1.94	< 0.001*

95% Confidence Interval, *: Highly significant p value, ‡‡: Hepatitis C virus; r^2 = 0.80%.

DISCUSSION

Many studies regarding relationship of hepatic damage with HCV-RNA titer and serum ALT level in HCV patients have been carried out. Serum ALT has long been used as a parameter to assess therapy response and whether to start an antiviral therapy in HCV infected patients.[10,16]

According to the usual algorithm for the management of HCV infected patients, antiviral therapy is usually not considered for patients with persistently normal ALT level as such patients have significantly lower hepatic

cells proliferation and apoptosis rates as compare to patients with elevated serum ALT.[17]

Long term follow-up of HCV patients with PNALT showed fluctuation in serum ALT levels which may temporarily decrease to normal value for several months. Similarly, patients with persistently normal serum ALT show varying degrees of hepatic damage.[18]

In the present study, we choose HCV infected patients with normal (group A) and elevated serum ALT levels (group B). The levels of ALT were observed for duration of twelve months before therapy. Serum ALT levels were significantly higher among patients with PIELAT in comparison with PNALTs (68.65±23.17 vs. 30.59±5.59; p=0.001). Most of the patients with PNALT were of younger age (35.36±5.33 vs. 37.92±5.51; p = 0.005) with low serum HCV-RNA level (70.0% vs. 50.0%; p = 0.044) as compare to the patients with PIEALT. Previous studies agreed with our findings, whereas other studies found no correlation between serum ALT level and HCV-RNA titer.[4,19,20] There was also a significant difference in terms of patient's response to interferon plus ribavirin therapy between two groups (82.8% vs. 38.1%; p = 0.012). Other clinical studies also showed that most patients with persistently normal serum ALT responded better to interferon therapy than as compare to patients with elevated serum ALT levels. No correlation was found between the level of serum ALT and gender of the patients.

In agreement with previous studies, our histological data show that 78.6% of patients with PNALT have minimal to mild histological grades of necro-inflammatory alterations.[21,22] On the other hand, more severe necro-inflammation was predominant among 41.6% patients with PIEALT (p = 0.037). However, no significant difference was noted in the histological activity of liver fibrosis among patients with PNALT or PIEALT (p = 0.159). In our study, 62.8% of patients with PNALT showed minimal to mild staging of fibrosis as compare to 53.5% patients with elevated serum ALT. These findings clearly indicate that serum ALT level is not a predictor of hepatic damage or correlate with severity of hepatic histological stage of fibrosis in HCV infected patients. The phenomena of having persistently normal ALT in HCV infected patients along with high stage of hepatic fibrosis and necrosis is still unclear. It is suggested that the HCV infected patients with persistent normal ALT levels shows less activated cellular immune response favoring the histological profile progression.[23] Calabrese and colleagues demonstrated that patients with normal ALT presented with the progressive nature of hepatic inflammation and loss of hepatocytes by apoptosis.[24]

Similarly, patients with persistently normal serum ALT may present with progressive hepatic fibrosis, cirrhosis, extra-hepatic manifestations and hepatocellular carcinoma.[21] So, liver biopsy should be considered in all patients as HCV infected patients with PNALT showed some degree of histological liver damage and are even at risk of developing hepatocellular carcinoma.[7] Some researchers suggested that liver biopsy is essential to stage the hepatic fibrosis accurately and to select the patients for therapy initiation, so it should be offered to all cases with PNALT.[25] In agreement with our results, *R. Zapata et al* described that 20-30% of patients with PNALT showed significant disease progression towards cirrhosis if left untreated.[26] Studies also showed poor correlation between serum ALT and degree of hepatic damage along with significant hepatic histological abnormalities in patients with persistent normal serum ALT levels.[13,27] Puoti C, et al studied HCV infected patients with PNALT, 17% to 34% of patients had normal to minimal liver histology, 44% of them had mild hepatitis and 4% to 1% had developed cirrhosis.[28] So, male gender, advanced age, severe fibrotic stage and ALT flare are the factors responsible for disease progression. Careful evaluation of such patient is mandatory to assess the disease progression and need for antiviral therapy.

Contrary to our results, *M. Hassan and Mustapha* suggested that the lower level of serum ALT in HCV mono-infected patients is an indication towards good prognosis of the disease.[22] It was also suggested that such patients should be only routinely monitored without any treatment as disease progression is either slow or absent.[18]

Although patients with PNALT shows benign liver histology and may be elevated with advancement of hepatic damage but this is a weak relationship which cannot predict the severity of hepatic injury in chronic HCV infected patients and probably of no clinical use.[19,29] In reality serum ALT can be helpful in detecting patients non-responsive to anti-viral therapy rather defining patients with no hepatic damage. The 2002 NIH Consensus Development Conference statement on the management of HCV patients discussed the matter of re-evaluation of treatment option for patients with PNALT and mild disease. It was recommended that liver biopsy should be indicated for taking therapy decisions.[30] Combination therapy of interferon and ribavirin is indicated for HCV infected patients with PNALT which is as effective as it is in patients with PIEALT. So ALT level alone cannot be taken as a parameter to make a decision whether to treat or not to treat a HCV infected patient as other factors such as patient's age, gender, HCV-RNA loads, staging of histological fibrosis, patient motivation and the presence or absence of symptoms should also be considered.[31] Serum ALT level can be used to assess the response during and after treatment, but cannot reflect the histological liver change accurately. So, liver biopsy remains a gold standard tool to assess the severity of hepatic damage in HCV infected patients as it can help to distinguish true healthy carriers from those with chronic hepatitis.

Whether liver biopsy should be performed in HCV infected patients with PNALT is controversial. We further extended our research with finding of correlation between patients with significant or insignificant fibrosis to different parameters by univariate and multivariate analysis. Most patients with insignificant fibrosis were females (59.6% vs. 33.8%; p = 0.001) and of younger age (35.80±5.12 vs. 37.97±5.90; p=0.016), which is consistent with earlier findings.[12]

There was a significant difference in terms of serum HCV-RNA titer (96.6% vs. 7.7%; p<0.001), HAI grade of hepatic fibrosis (89.9% vs. 15.3%; p = 0.001) and successful sustained virological response to therapy (85.4% vs. 21.5%; p<0.001) between the two groups. Patients without advanced fibrosis showed lower serum HCV-RNA level, minimal to mild grade of inflammation and responded well to interferon therapy irrespective of any significant change in serum ALT level as compare to patients with advanced fibrosis. Furthermore, multivariate analysis was done to analyse the independent variable predictive of advanced fibrosis in HCV infected patients. The results showed that only high level of HCV-RNA was significantly associated with the presence of advanced fibrosis in HCV infected patients (OR = 0.89; 95% CI = 1.65-1.94; p < 0.001) with r^2 = 0.80%. Such variable is an indicator to start interferon plus ribavirin therapy in HCV patients whether their serum ALT level is persistently normal or elevated. Previous studies also have found that high titer of HCV-RNA is significantly associated with progression of liver fibrosis.[32] Results indicate that clinicians may consider monitoring of aminotransferases levels in HCV infected patients but liver biopsy is still a key factor to assess the severity of liver disease and decision to initiate an antiviral therapy.[18]

In the light of these findings, more revision is required regarding definitions and recommendations to HCV infected patients with persistently normal serum ALT and especially for populations living in HCV hyper-endemic areas. Our study has few limitations. First, biochemical markers other than serum ALT were not considered. Secondly, a relatively small sample size was selected which might not be a true representative of patients with PNALT. Further studies are required with higher sample size to assess true distribution of significant histological disease among chronic hepatitis C infected patients.

CONCLUSION

Serum ALT level is a general biochemical marker to evaluate patients with chronic hepatitis C. Our data suggest that serum ALT levels are comparable between patients with persistently normal and elevated serum ALT but the decision to treat HCV infected patients with persistently normal ALT levels should be made on an individual basis. The recommended factor indicating histological severity of liver disease is high HCV-RNA titer.

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