Clinical Biochemical and Histological Profile of Chronic Hepatitis C Patients with Normal Serum Aminotransferases

Thesis

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ABSTRACT

Hepatitis C virus (HCV) is a major public health problem and is considered the most common etiology of chronic liver disease in Egypt. Chronic hepatitis C virus (HCV) patients with persistently normal transaminases represent a subgroup of patients with mild, slowly progressive disease, natural history, and optimal management of these patients needs to be investigated in Egypt.

Aim of work: to assess the severity of hepatic fibrosis and response to therapy in a cohort of Egyptian HCV patients with normal transaminases

Patients and methods: Retrospective demographics, laboratory, histological features and treatment outcome of patients included in the national program for the control of viral hepatitis in Egypt since 2008-2012 were collected. Combined pegylated IFN/ribavirin therapy was given for patients with fibrosis stage ≥ F1 and elevated transaminases while those with normal transaminase; therapy was initiated only in patients with fibrosis stage ≥ F2.

Results: Normal ALT and AST were detected in 1308/4277 (30.6%) and 1662/4277 (38.9%) patients, respectively, while both enzymes were normal in 943 patients (22%). Multivariate regression analysis showed that lower AFP and higher platelets count (compared with elevated transaminases group) were significantly correlated with normal transaminases ($P<0.01$), however, HCV-RNA levels did not show such significance. The number of patients with HAI score ≥ A1 was significantly lower in normal than elevated transaminases (36.5% vs 40.9%, respectively, $P < 0.01$) and patients with fibrosis ≥ F2 was significantly lower in normal than elevated transam-inases (36.4%) and (43%), respectively ($P < 0.01$). There was no significant correlation between baseline transaminases levels and response to treatment. Conclusion: Normal transaminases are frequently encountered in chronic HCV Egyptian patients (22%). They show low AFP level, mild degree of activity and stage of fibrosis with no correlation with response to therapy

Key words: Chronic HCV- ALT-AST-AFP

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Last, but certainly not least, I owe to the patients included in this study may God alleviate their sufferings and may all our efforts be just for their own benefit.

List of Abbreviations

AASLD	:	American Association for the Study of Liver Diseases.
AFP	:	Alpha feto protein
ALT	:	Alanine aminotransaminase.
ALP	:	Alkaline phosphatase.
ANA	:	Anti nuclear antibody.
AST	:	Aspartate aminotransaminase.
BMI	:	Body mass index.
CHC	:	Chronic hepatitis C.
DDB	:	Dimethyl-4,4_-dimethoxy-5,6,5_,6-dimethylenedioxybiphenyl- 2,2_ dicarboxylate.
DM	:	Diabetes milletus.
EASL	:	European Association for the Study of the Liver.
ECG	:	Electrocardiography.
cEVR	:	Complete early virological response.
ETR	:	End of treatment response.
EVR	:	Early virological response.
GGT	:	Gamma glutamyl transpeptidase.
GTP	:	Guanosine triphosphate.
HCC	:	Hepatocellular carcinoma.
HBV	:	Hepatitis B virus.
HBS antigen	:	Hepatitis B surface antigen
HCV	:	Hepatitis C virus.
HIV	:	Human immnuno deficiency virus.
IMPDH	:	Inosine 5'-monophosphate dehydrogenase.
INF	:	Interferon
INR	:	International normalized ratio.
LDH	:	Lactate dehydrogenase.
m RNA	:	Messenger ribonucleic acid
NALT	:	Normal serum ALT.
NIH	:	National institute of health.
PCR	:	Polymerase chain reaction.

pEVR	:	Partial early virological response.
PEG-IFN	:	Pegaylated interferon
PNALT	:	Persistent normal ALT.
PT	:	Prothrombin time.
ULN	:	Upper limit of normal.
RBV	:	Ribavirin.
RVR	:	Rapid virological response.
RCT	:	Randomized controlled trials.
SEM	:	Standard error of mean.
SGOT	:	Glutamic oxaloacetic transaminase.
SGPT	:	Glutamic pyruvic transaminases.
RIBA	:	Recombinant immunoblot assay
RNA	:	Ribonucleic acid.
RVR	:	Rapid virological response.
SVR	:	Sustained virological response.
TSH	:	Thyroid stimulating hormone.
WHO	:	World Health Organization.

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INTRODUCTION

The observation that hepatitis C virus (HCV) infection could exist in persons with normal serum alanine aminotransferase (ALT) concentrations was first made in otherwise apparently healthy blood donors who tested anti – HCV positive. ***(Rossini et al.,1995).***

Approximately 65 percent of anti HCV and (RIBA) positive individuals with normal serum ALT are viremic ***(Prieto et al., 1995).*** The reminder have either low level viremia (below detectable levels) or resolved infection.

Although the serum ALT concentration is within the normal range in these patients at the time of diagnosis, these value may occasionally fluctuate out of the normal range. however it is unusual for the value to exceed 1.5 times the upper limits of normal ***(Rossini et al., 1995).***

HCV infection with a normal ALT is defined by the presence of anti-HCV. antibodies, either a positive RIBA or detectable HCV-RNA and serum ALT concentration that is persistently within the normal range.

Persistance of a normal ALT should be documented on at least three occasions over a six month period. Using this definition approximately 25- 40 percent of patients with chronic HCV infection have persistently normal serum ALT ***(Marcellin et el., 1997 & Inglesby et al.,1999).***

One major problem when developing guidelines for management of patients with normal ALT levels is how to ascertain the "optimal"

upper limit of normal value that must be established for each individual laboratory also ALT value differs by ages race, gender and body mass ***(Dufour DR et al., 2000).***

The reason why serum ALT concentration are normal in some patients and elevated in others, is not well understood. However several intriguing associations have been noted.

The serum HCV-RNA concentration does not correlate with the serum ALT ***(Martinot et al., 1994)***

In one report, anti-HCV positive blood donors with normal ALT concentrations were older and more often women than those with abnormal levels ***(Shakil et al.,1995).***

In another study, HCV infected patients with a normal serum ALT were much more likely to be HLA-DR13 positive than those with an elevated ALT ***(Kuzushita et al.,1996).***

The available literature suggest that patients with persistent normal ALT (PNAL) are characterized by higher prevalence of female sex . No major difference in the prevalence of any HCV genotype is agreed to exist worldwide ***(Calvaruso and Craxi, 2009).***

PNAL with chronic HCV have been classified as a "healthy" or "asymptomtic" ***(Alberti et al.,1992& Puotietal et al., 1997)*** not thought to progress and thus excluded from antiviral treatment.

It is now accepted that those patients have some degree of histological liver damage ***(Rumi et al.,2005 & Dienstag, 2006)*** although usually mild ***(Mathurin et al., 1998 & Persico et al., 2000)***, however, the

association of normal ALT with more severe chronic hepatitis or cirrhosis has been reported ***(Cividini et al., 2001; Hui et al., 2003; Ghany et al , 2003 & Okanone et al , 2005) .***

There is disagreement about whether HCV infected persons with normal ALT value should undergo a liver biopsy ***(Shiffman et al., 2006)***.

Three large randomized trials have shown that patient with PNAL have significantly lower inflammation and fibrosis scores on liver biopsy than patients with elevated ALT ***(Shiffmann et al., 2006).***

Although the spectrum of liver fibrosis tends to be more severe in patient with elevated ALT than in those with normal ALT, between 14 and 24% of persons with persistently normal values have more than portal fibrosis on liver biopsy. These persons may have progressive liver disease over time despite persistent of normal ALT value ***(Huick et al., 2003).***

A standardized approach to the management of chronic HCV carriers with normal ALT is important since up to 60 % of HCV infected first time blood donors and of injection drug users have normal enzymes values ***(Pratid et al., 2002)***.

The decision to initiate antiviral therapy in HCV infected patients with persistently normal ALT values is controversial ***(Deuffic et al., 2009).***

Some experts believe that liver disease progression is uncommon in most of these persons, thus the adverse events associated with current standard of care (SOC) treatments would outweight the probability of

benefit of therapy. The few early studies of interferon monotherapy in (PNAL) patients suggest no significant beneficial effects. Subsequently the response rate of PNAL to non pegylated interferon plus ribavirin was found to be comparable to that of patient with abnormal values , and early reports of ALT flares resulting from interferon monotherapy were not been confirmed ***(Zeuzem et al., 2004).***

The national institutes of health (NIH) consensus conferences recommendation state indicate that viraemic patients with normal ALT should not be considered to be healthy carriers and that numerous factors must be considered in recommending treatment including favourable genotype, presence of hepatic fibrosis, patient motivation, symptoms, severity of comorbid illness and the patients age ***(NIH, 2002).***

The recommendation of American Association for the Study of Liver Diseases (AASLD) practice guidelines suggest that regardless of the serum aminotransferase levels, the decision to initiate therapy with interferon and ribavirin should be individualized based on the severity of liver disease (***Strader et al., 2004).***

AIM OF WORK

The aim of the study is to assess the reflection of Serum aminotransferases on the clinical, biochemical and histological features of Egyptians patients of chronic hepatitis C.

Asses the severity of hepatic fibrosis and response to therapy in a cohort of Egyptian HCV patients with normal transaminases.

We therefore investigated the correlation between normal transaminases (AST and/or ALT) and liver fibrosis and response to combined antiviral therapy.

CHAPTER 1

1.1 Serum Transaminases

Transaminase is an enzyme which catalyses the transfer of an amino (NH2) group from one amino-acid to a keto-acid, thus producing another amino acid and another keto-acid, there are two transaminases of importance, glutamic oxaloacetic transaminase (SGOT) and glutamic pyruvic transaminases (SGPT) ***(Agress, 1959)***.

Both enzymes require pyridoxal- 5'-phosphate (vitamin B6) in order to carry out this reaction, although the effect of pyridoxal-5'-phosphate deficiency is greater on ALT activity than on that of AST ***(Dufour et al., 2000).***

The amounts of enzymes which are normally present in serum are small compared to those locked up inside the cells. Hence, when a cell dies and the integrity of the basement membrane is lost, the contained transaminases enter the circulation, causing a rise in specific transaminase activity; the transaminase is not liberated all at once, and may take some time to appear in the blood after necrosis commences ***(Agress, 1959).***

The liver contains 400 U ALT/g proteins (mainly cytoplasmic) and 500U AST/g proteins (>80% contained in mitochondria and endoplasmic reticulum), Damage to one gram of liver tissue (or the membranes of 171 million hepatocytes) results in a significant increase in the serum ALT activity ***(Pratt & Kalpan 2000).***

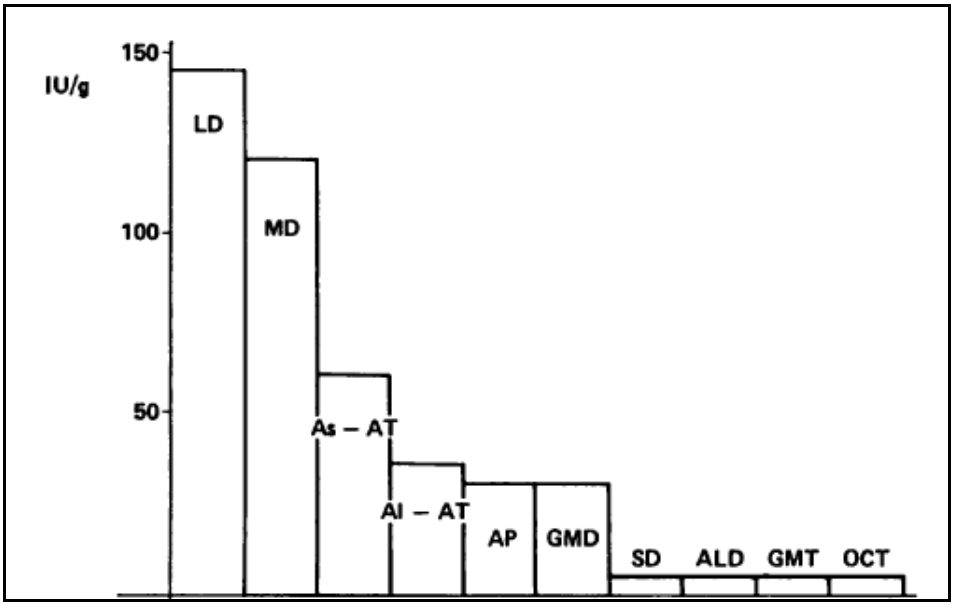

Figure (1): Concentration of important enzymes in liver, expressed in international units per gram fresh liver tissue.

LD = lactate dehydrogenase, MD = malate dehydrogenase, As-AT = aspartate aminotransferase, Al-AT = alanine aminiotransferase, AP = alkaline phosphatase, GMD = glutamate dehydrogenase, SD = sorbitol dehydrogenase, ALD = ketose-phosphate aldolase, GMT = D-glutamyltransferase and OCT = ornithine carbamoyltransferase. (*Wieme and Demeulenaere (1970))*

Aminotransferase clearance is carried out within the liver by sinusoidal cells ***(Kamimoto, 1995)***. The half-life in the circulation is about 47 hours for ALT, about 17 hours for total AST and, on average, 87 hours for mitochondrial AST ***(Dufour et al., 2000)***.

Aspartate aminotransferase (AST):

AST is found in the liver, cardiac muscle skeletal muscle, kidneys, brain, pancreas, lungs, leucocytes, and red cells; it is less sensitive and specific for the liver ***(Pratt & Kaplan, 2000).*** Serum AST may be 15 % higher in African American males ***(Dufor, 1998).***