

THE CORRELATION BETWEEN THE SERIC LEVEL OF THE TRANSAMINASES AND THE DEGREE OF HEPATIC FIBROSIS IN THE CHRONIC VIRAL HEPATITIS

C. DAINA¹

University of Oradea

Cuvinte cheie: hepatita cronică virală, fibroza hepatică, puncție biopsie hepatică, ALAT, ASAT

Rezumat: Reacția fibrogenică este consecința mecanismelor imunologice desfășurate în prezența virusului care are influență asupra fibrogenezei. Scopul studiului a fost de a observa dacă există o legătură între modificările histologice și valorile crescute ale ALAT și ASAT. În acest studiu toți pacienții au avut un anumit grad de fibroză, fapt explicat prin simptomatologia subiectivă ușoară a bolii și lipsa unor teste fiabile pentru descoperirea fibrozei în afară de biopsia hepatică. Raportul ASAT/ALAT a fost <1 la toate cazurile. Conform rezultatelor obținute indicele de activitate histologică este în corelație cu gradul de fibroză, valorile serice ASAT și ALAT sunt semnificative în raport cu gradul de fibroză, ele putând fi recomandate în urmărirea tratamentului de regresie a fibrozei sub tratament.

Keywords: chronic viral hepatitis, liver fibrosis, percutaneous liver biopsy, ALT, AST

Abstract: Fibrogenic reaction is a consequence of the immunological mechanisms that have developed in the presence of the virus influencing fibrogenesis. The aim of this study is to observe whether there is any correlation between the histological change and high ALT and AST values. All patients included in our study presented some degree of fibrosis, a fact that may be explained by the easy subjective symptomatology of the disease and the lack of reliable tests, except liver biopsy, for the detection of the fibrosis. The AST / ALT report has been <1 in all cases. According to the results we have obtained, the histological activity index may be correlated with the degree of fibrosis, and the AST and ALT serum values are significant in relation to the degree of fibrosis; therefore they may be used for the purpose of monitoring the treatment of fibrosis regression during therapy.

INTRODUCTION

Hepatic viral infections are one of the major causes for the development of the liver fibrosis. It is still uncertain why human beings are not able to eliminate the infection with B and C hepatitis viruses (1). Once in the body, 40-50% of the hepatic viruses latently evolve towards a chronic form; in a relatively long period, of 20 to 30 years, 20% of these viruses evolve to cirrhosis. 1-4% of the patients with cirrhosis will present hepatocellular carcinoma.

Fibrosis is a dynamic process, which depends on the transcriptional gene and the extra-cellular matrix that synthesizes the proteoglycans and organizes them into a three-dimensional structure. Experimental models (2) contributed to defining the mechanisms whereby hepatic fibrosis is induced. Fibrogenic reaction is a consequence of immunological mechanisms that have developed in the presence of the virus influencing fibrogenesis.

THE AIM OF THE STUDY

The purpose of this study is to investigate the correlation between the histological activity index (HAI) and the degree of fibrosis to the serum levels of alanin-aminotransferase (ALAT) and aspartatamino-transferase (ASAT), in patients with chronic hepatitis of B and C viral etiology, taking as reference standards the histological results obtained from the material collected by liver biopsy.

MATERIAL AND METHOD

This study is based on the observation of 140 patients

with chronic viral hepatitis (type B, C and B + C) at whom percutaneous liver biopsy (PLB) was performed in Oradea County Hospital, between March 2009 - March 2010.

The criterion for inclusion in the study was the absence of antiviral therapy in patients with chronic hepatitis.

The distribution of cases by sex, age and etiology is shown in Table I:

The histological diagnosis was based on the material obtained by liver biopsy. Tissue samples were placed in 10% formaldehyde solution. The processing was performed in paraffin blocks of which 5μ slices were cut and colored in standard hematoxylin and eosin staining, Masson Trichrome staining and the reticulin method. The histopathological changes observed were the parenchymal lesions of the liver, as well as the size and composition of the port space, the changes in Kupffer cells, biliary canalicula and others.

The liver lesions were categorized and scored using the Metavir and the Knodell scores (3,4). Such forms of evaluation are essential for diagnosing, treatment choice, prognosis estimation, and the clinical observation of these pathologies.

The serum levels of ALT and AST were obtained by kinetic method using a Hitachi 902 Cobas-Mira device type (normal values: AST <38 U/L in men and <32 U/L in women, ALT <41 U/L in men and <31 U/L in women).

For the statistical interpretation of the data, the SPSS, version 17, was used for calculating the averages of parameters, the standard deviations, the median, the coefficient of variations, the variation range (min-max) and the quartila variation (5).

¹Corresponding Author: C. Daina, 82/A Tetchea street, Bihor, România; e-mail: luci_daina@yahoo.co.uk; tel +40-0 755740950
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Table I. The distribution of subjects in relation to etiology, sex and age groups

ETIOLOGY																	
HCV						HBV						HBV+HCV					
<40 years old		40-60 years old		>60 years old		<40 years old		40-60 years old		>60 years old		<40 years old		40-60 years old		>60 years old	
M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
12	18	35	45	2	2	5	7	5	3	1	0	2	0	1	1	1	0
Total: 114 cases						Total: 21 cases						Total: 3 cases					
PERCENT																	
24.5	27.7	71.4	69.2	4.1	3.1	45.5	70	45.5	30	9.1	0	50	0	25	100	25	0

The Student Test was used to compare the average values with the normal distribution.

RESULTS

Laboratory results were compared with the results obtained after performing liver biopsy, which constituted the reference standard for the diagnosing of liver fibrosis.

The mean values of serum transaminases (ALT, AST) (see Table II) were significantly increased statistically ($p < 0.001$), as compared to normal values in both chronic hepatitis B (HBV) and in chronic hepatitis C (HCV). The highest values of AST and ALT, as compared to the normal ones, were recorded in HBV, with a mean value of 84.62 U/L, respectively 99.24 U/L.

Table no. 2. Mean values of transaminases in chronic viral hepatitis, in relation to etiology and sex

Sex	Etiology	ALT	AST	
Masculine	HVC	Mean	94.43	82.29
		N	49	49
		Std. Deviation	18.753	18.677
	HVB	Mean	94.45	79.45
		N	11	11
		Std. Deviation	9.310	16.121
	HVC+HVB	Mean	92.25	74.00
		N	4	4
		Std. Deviation	13.817	14.213
Feminine	HVC	Mean	90.75	77.85
		N	65	65
		Std. Deviation	21.091	15.733
	HVB	Mean	104.50	90.30
		N	10	10
		Std. Deviation	20.845	22.774
	HVC+HVB	Mean	102.00	67.00
		N	1	1
		Std. Deviation	.	.

Mean transaminase values are higher in males as compared to those in females, though the differences are not statistically significant ($p > 0.05$) for both ALT and for AST).

Depending on the value of the necrotic inflammatory index, the hepatitis activity was considered minimally active (METAVIR score A1F1-A1F2), moderately active (METAVIR score A2 or 3F2 or 3) and severely active (METAVIR score A3F3 or 4) (Table III)

AST Values

- were higher in the first category, the one with minimum active hepatitis (A1F2);
- were increased in patients with A1F2 METAVIR score (78.25 ± 17.06)
- were higher in moderately active hepatitis, in those with A3F3 (88) activity – having no statistical significance for the present study, as there is only one case.

Table no. 3. The necrotic-inflammatory index and the serum transaminase level

Activity	Score	AST	ALT	
Minimally Active	A0F1	Mean	68.00	74.00
		N	2	2
		Std. Deviation	.000	1.414
	A1F0	Mean	71.83	87.00
		N	12	12
		Std. Deviation	11.769	17.220
	A1F1	Mean	70.55	86.65
		N	20	20
		Std. Deviation	10.570	16.516
	A1F2	Mean	78.25	94.80
		N	20	20
		Std. Deviation	17.060	22.336
Moderately Active	A2F1	Mean	67.00	77.60
		N	5	5
		Std. Deviation	3.317	14.153
	A2F2	Mean	84.96	94.53
		N	51	51
		Std. Deviation	18.702	18.196
	A2F3	Mean	87.20	100.92
		N	25	25
		Std. Deviation	19.205	21.629
	A3F3	Mean	88.00	116.00
		N	1	1
		Std. Deviation	.	.
A3F4	Mean	87.00	115.00	
	N	1	1	
	Std. Deviation	.	.	
Severely Active	A2F3	Mean	70.50	99.50
		N	2	2
		Std. Deviation	3.536	4.950
	A3F3	Mean	94.00	98.00
		N	1	1
		Std. Deviation	.	.

ALT values:

- the highest values were recorded in the first category (minimum active hepatitis A1F2) (78.25 ± 17.06);
- in terms of age groups, a higher value was obtained at the age group of people over 60 years old, in those with hepatitis C (117 ± 31.003), as compared to other etiological categories.

AST and ALT values were consistently higher in patients with viral hepatitis C, as compared to the other categories, presenting an average value of 79.25 ± 17.125 AST and of 92.33 ± 20.116 ALT.

The majority of patients included in the study presented moderately activity, the histological activity index (HAI) ranging between 9 and 12 points, while at the 55 patients with minimally activity, 2-7 points were obtained. The Spearman correlation coefficient was of 0.79 ($p < 0.01$) for patients with chronic hepatitis C, indicating a correlation between the HAI score and the fibrosis stage.

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Table no. 4. Serum transaminase values by etiology types

Etiology/ Transaminase		No. of cases	Minimum	Maximum	Mean	Std. Deviation
HCV	ALT	114	46	149	92.33	20.116
	AST		60	131	79.75	17.125
HBV	ALT	21	76	141	99.24	16.288
	AST		63	135	84.62	19.853
HCV+HBV	ALT	5	72	103	94.20	12.736
	AST		61	94	72.60	12.700

DISCUSSIONS

Several studies (6,7,8,9,10) have discussed the values of serum markers (ALT, AST) in chronic viral hepatitis, especially in the cases of infection with the C virus; however, the fluctuations in the serum transaminase levels and their connection to inflammatory activity and the degree of the fibrosis is still uncertain. Among the cases of hepatitis that have been studied so far, the ones caused by virus C raise special problems, as 20% of the cases evolve to cirrhosis and 1-4% of them develop liver-cell carcinoma each year.

The control of infection, of fibrosis progression and the therapeutic trials for the remission of fibrosis have been actively investigated lately. Recent years research on the factors that initiate and influence the development of the extra-cellular matrix towards fibrosis show that these processes may be reversible (11,12,13,14).

Our aim has been to observe whether there is a correlation between histological changes and high ALT and AST values. All patients included in our study presented some degree of the fibrosis, a fact easily explained by the easy subjective symptomatology of the disease and lack of the reliable tests for the detection of the fibrosis, except liver biopsy. Although there are systems to detect serum parameters indicating liver fibrosis, these are not reliable enough and therefore are not used extensively (15), biopsy remaining the main method for detecting liver fibrosis. Performing percutaneous liver biopsy in patients with normal levels of serum transaminases is still under study (16,17,18). Our results indicate a significant correlation between the degree of fibrosis and the serum values of ALT and AST. The AST / ALT report is <1 in all cases, being consistent with the results of some authors (19) and inconsistent with the results of others (20). Some authors consider that increased ALT levels might be correlated with a high degree of fibrosis progression, while the normal values of this parameter are not frequently associated with it (17,21).

CONCLUSIONS

According to the results we have obtained, the histological activity index may be correlated with the degree of the fibrosis, and the AST and ALT serum values are significant in relation to the degree of the fibrosis; therefore they may be used for the purpose of monitoring the treatment of the fibrosis regression during therapy.

REFERENCES

- Eng FJ, Friedman SL. Fibrogenesis I. New insights into hepatic stellate cell activation: The simple become complex. *Am J Physiol Gastrointest Liver Physiol* 2000; 279: G7–G11.
- Rojkind M, Greenweel P. Pathophysiology of liver Fibrosis. In Arias MI et al (ed), *The Liver Biology and Pathobiology* 4th ed. Lippincot Williams & Wilkins, 2001: 721–738.
- Knodell RG, Ishak KG, Black WC, et al. Formulation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis. *Hepatology*. 1981;1:431–435.
- Batts KP, Ludwig J. Chronic hepatitis an update on terminology and reporting. *Am J Surg Pathol*. 1995; 19:1409–1417.
- Achimas-Cadariu A. Metodologia cercetării științifice medicale, Ed. Medicală Universitară „Iuliu Hațieganu”, Cluj Napoca, 1999.
- Ghany MG, Kleiner DE, Alter H et al. Progression of fibrosis in chronic hepatitis C. *Gastroenterology* 2003; 124: 97–104.
- Haber MM, West AB, Haber AD et al. Relationship of aminotransferases to histological status in chronic hepatitis C. *Am J Gastroenterol* 1995; 90: 1250–1257.
- Battaler R, North KE, Brenner DA. Genetic polymorphism and the progression of liver fibrosis: A critical appraisal hepatology 2003; 37: 493–503.
- Mayers RP, Patel K, Pianko S et al. The rate of fibrosis progression is an independent predictor of the response to antiviral therapy in chronic hepatitis C. *J Viral Hepat* 2003; 10:16.
- Zarski JP, Mc Hutchinson JP et al. Rate of natural progression in patients with chronic hepatitis C. *J Hepatol* 2003; 38: 307–314.
- Giannini E, Rizzo Dbotta F et al. Validity and clinical utility of the aspartate aminotransferase-alanin aminotransferase ratio in assessing disease severity and prognosis in patients with hepatitis C virus-related chronic liver disease. *Arch Intern Med* 2003; 163: 218–224.
- Rosenberg W, Burt A, Becka M et al. Automated assays of serum markers of liver fibrosis predict histologic hepatic fibrosis. *Hepatology* 2000; 32: 183A.
- Imbert-Bismut F, Ratzu V, Pieroni L et al. Biochemical markers of liver fibrosis in patients with hepatic C virus infection: a prospective study. *Lancet* 2001; 357: 1069–1075.
- Cristensen C, Bruden D, Livingston S et al. Diagnostic accuracy of a fibrosis serum panel (FIBROSpect II) compared with Knodell and Ishak liver biopsy scores in chronic hepatitis C patients. *J Viral Hepat* 2006; 13: 652–658.
- Forns X, Ampurdanes S, Llovet JM et al. Identification of chronic hepatitis C patients without hepatic fibrosis by a simple predictive model. *Hepatology* 2002; 36, 4: 986–992.
- Bedossa P, Dargere D, Paradis V. Sampling Variability of liver fibrosis in chronic hepatitis C. *Hepatology* 2003; 38: 1449–1457.
- Renou C, Pol S, Halfon P et al. Controversis about histological features of chronic HCV patients with persistantly normal alanine transaminase levels: What can we do about the present definition? *Gastroenterology* 2002; 123: 1748–9.
- Young Sok Lee, Seung Kew Yoon, Eun Sun Chung, Si Hyun Bae, Jong Young Choi, Joon Yeol Han, Kyu Won Chung, Hee Sik Sun, Boo Sung Kim, Byung Ki Kim. The relationship of Histologic Activity to Serum ALT, HCV genotype and HCV RNA titers in Chronic Hepatitis C. *J Korean Med Sci* 2001; 16: 585-91.
- Reedy DW, Loo AT, Levine RA. AST/ALT ratio ≥ 1 is not diagnostic of cirrhosis in patients with chronic hepatitis C. *Dig Dis Sci* 1998; 43: 2156–9.
- Imperiale TF, Said AT, Cummings OW et al. Need for validation of clinical decision aids: Use of the AST/ALT ratio in predicting cirrhosis in chronic hepatitis C. *Am J Gastroenterol* 2000; 95: 2328–32.
- Becon BR. Chronic hepatitis C and normal ALT: Consideration for treatment. *Am J Gastroenterol* 2004; 99: 1706-1707.