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SERUM TRANSAMINASE LEVELS AND FIBROSE STAGE IN ZERO BIOPSY OF THE LIVER IN CHRONIC HEPATITIS C

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Summary. *An infection by hepatitis virus C causes damage and inflammation in the liver, which is responsible for the development of liver fibrosis. Natural history of fibrosis in chronic hepatitis is gained to the inflammation in and around portal tracts, as an immunological event whose influence to fibro-genesis is not clarified. A marked characteristic of chronic hepatitis C (HHC) is mild symptomatology with frequent discrepancy of biochemical parameters and morphological findings, thus escaping the diagnosis in the early phases of disease. The aim of the investigation was to determine the correlation of serum transaminase levels to morphological changes and state of fibrosis in zero biopsy of the liver i.e. at the time of making the diagnosis of "chronic hepatitis C". The analyses were done in 23 patients with HHC, mean age 32.78 years, who underwent blind aspiration liver biopsies. Despite histological parameters, we analysed routes of the infection and serum levels of aspartat transaminase (AST) and alanin aminotransferase (ALT). The results showed that 50% of patients had only slightly elevated AST levels, while ALT was above normal ranges in all tested patients. HAI have demonstrated marked variations among individuals. Only five patients were without fibrosis. They had normal AST serum levels statistically significantly lower than in patients with fibrosis ($p<0.05$). The values of ALT were the highest in the cases with advanced fibrosis. The results showed statistically significant relation of ALT levels to the stage of fibrosis in HHC group of patients ($p<0.01$). In conclusion, AST and ALT serum levels are in significant mutual dependence ratio to a degree of fibroses, so they are recommended for taking care of the disease and degree of fibrosis.*

Key words: *Hepatitis C, ALT, AST, fibrosis*

Introduction

An infection by a hepatitis C virus (HCV) causes damage and inflammation in the liver, which is responsible for the development of liver fibrosis. It is still not clear why humans can not eliminate HCV infection (1). The progression of the infection toward a chronic form is found in 40-50% of the infected, 20% of who develop cirrhosis during relatively long period of twenty to thirty years. The incidence of hepatocellular carcinoma is 1-4% per year among the infected with cirrhosis.

The fibrosis is a dynamic process that depends on gene transcription and extra-cellular matrix proteins and a proteoglican synthesis and its organization in a three-dimensional meshwork. The mechanisms of liver fibrogenesis are definitively introduced thanks to the investigation in experimental models (2). In cases of chronic Hepatitis C (HHC) a fibro-genesis is joined to inflammatory reactions in and around portal tracts. The reaction is the consequence of immunological events in viral presence, and its influence on fibro-genesis is not clarified. A few marked characteristics of viral C infection determine a chronic form of the disease: subjective symptoms of the disease are absent in a great number of infected persons, so that advanced morphological changes are found during a routine, control analysis of blood. On the other hand, serious morphological changes can be followed by relatively normal biochemical parameters of the liver function. The facts about the individual differences among the infected in the developing cirrhosis are of great importance, what make some of them rest stable for 5 to 10 years from the beginning of the infection (3). In large prospective studies we find that those patients can be divided according to the stage of fibrosis into the groups of fast, intermediary and slow fibroses, developing the fibrosis in a few decades (4). The investigation of individual differences in fibrosis point to the influence of age, male gender, and alcohol consumption. On the contrary, the serum levels of HCV RNA and viral genotype do not influence the progression to a fibrosis in HHC (5, 6). The role of HFE gene is controversial, but it was recently shown that obesity has a negative influence on the degree and the progression of fibrosis (7).The investigations in the experiment and in human material have shown that reversion of fibrosis is possible (8).

The gold standard in evaluating fibrosis is the liver biopsy analysis. The scoring system enables a semi

quantitative determination of fibrosis and is the basic tool for the investigation of natural course of HHC in clinical investigations and therapy (9).

There are no specific tests in predicting the liver fibrosis in individual cases. Serum aminotransferase levels characteristically fluctuate in chronic Hepatitis C and their relationship to a particular grade (i.e. inflammatory activity) and stage (i.e. degree of fibrosis) were widely investigated (9, 10, 11). High levels of alanin aminotransferase are joined to higher risk of fibrosis progression, while worsening of the fibrosis in permanently normal serum ALT levels is not usual (12, 13).

The modalities of disturbances of biochemical parameters of liver function with fibrosis and their interdependence are of critical importance in everyday clinical work.

The Aim

The aim is to investigate the correlation of stage of fibrosis to histological index of activity (HAI) in HHC to the levels of alanin aminotransferase (ALT) and aspartat aminotransferase (AST) in zero biopsy of the liver.

Material and Methods

We used the material from 23 patients with HHC, who were treated in the Clinic for Infectious Diseases in Nis during the period 2001- 2003. By the Elisa test of second generation, all patients were proven to be infected by Hepatitis C virus (HCV). The selection of patients was made according to HBsAg and HBcAg negativity as well as by the absence of antiviral treatment.

The level of necro-inflammatory activity and fibrosis were determined in a zero biopsy (it is custom to follow progression of the illness by consecutive biopsies, so we treat the biopsy which takes a part in making diagnosis as "zero"). Despite histological parameters, we analyzed routes of the infection, the duration of the infection, and the serum levels of AST and ALT.

All patients underwent blind aspiration biopsy of the liver. The tissue samples were fixed in 10% formalin solution and were routinely prepared for a light microscopy analysis. Tissue samples were cut into 5μ slices and were stained by hematoxilin and eosin, trichrom Mallory and reticulin methods.

The serum levels of ALT and AST were determined by the standard biochemical methods.

The degree of histological activity and fibrosis is determined by using modified Knodall's scoring system, in which the fibrosis was given degrees from 0-6, where fibrosis 6 would be cirrhoses.

To make sure those scientific hypotheses are correct, we have used a statistical method of quantitative analysis. We have used these statistical parameters: arithmetical mean (X), standard deviation (SD), coefficient of variation (Cv), median (Me), inter quartile difference (25.-75. percentile), structure index (%), and variation interval (min-max).

According to the kind of statistical marks (numerical or attributive), the kind of distribution (normal-irregular, unknown), as well as the number of the groups compared and their sizes, we have used these statistical tests:

– The Student's test - for comparison of continuous numerical marks mean values with normal distribution.

– The Mann-Whitney U test – for the comparison of continuous numerical marks with irregular distribution, as well as discontinuous numerical marks.

– The Spirman's coefficient of rang correlation (r_s) – for fortification of mutual dependence between the values of different marks and

– The Fisher's test of exact probability of zero hypotheses – for comparison of certain marks frequency.

The analyses have been done on a computer, by using standard programs for statistical data.

The results of statistical analyses are shown in tables.

Results

In the group of 23 patients, 18 were males and 5 females. The youngest patient was 20 year old and the oldest had 51 years. The average age in the group was 32.78 years. The relation of number of patients toward gender and age is demonstrated on Table 1.

Table 1. The relation of gender and age in tested group of patients

Age	Male		Female		Total	
	Number	%	Number	%	Number	%
15-24	4	22.22	–	–	4	17.39
25-34	11	61.11	1	20.00	12	52.17
35-44	1	5.56	2	40.00	3	13.04
45-54	2	11.11	2	40.00	4	17.39
Total	18	100.00	5	100.00	23	100.00
X± SD	30.50± 8.01		41.00 ± 9.82		32.78 ± 9.31	

In 47.89% of cases, the source of infection was intravenous drug abuse of whom, 11 were male and one female patient.

Pathohistological analysis demonstrated spectrum of morphological changes known as being characteristic for HHC: edema of portal tracts with lymphatic aggregates, interface hepatitis, unicellular or necrosis of small groups of hepatocytes surrounded by lymphocytes, confluent necrosis, degenerative changes in parenchymal cells (fig. 1, 2, 3, 4). Different morphological expressions of the infection were the base for determination of HAI and categorization of the patients in respect to fibrosis and HAI score. The sum of the results is shown in Table 2.

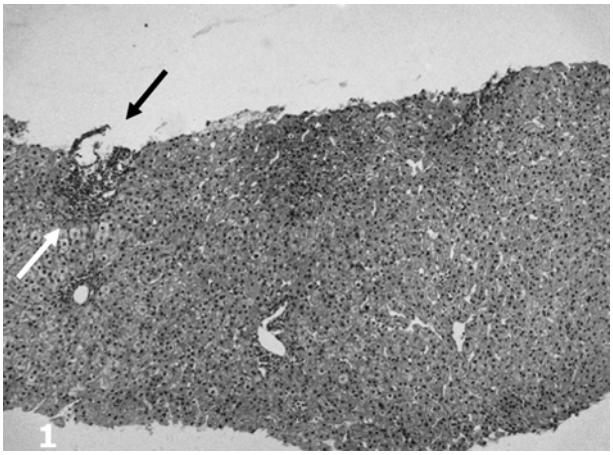

Fig. 1. Edema of the portal tract (arrows) HHC with HAI 6 (HE x 40)

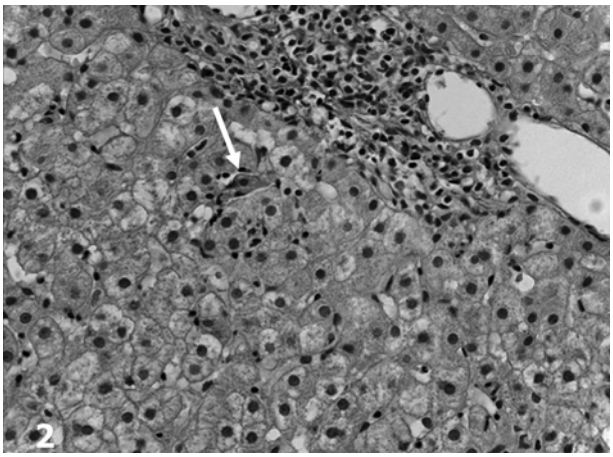

Fig. 2. Acidophile necrosis of hepatocyte (arrow); absence of interphase hepatitis (HE x 100)

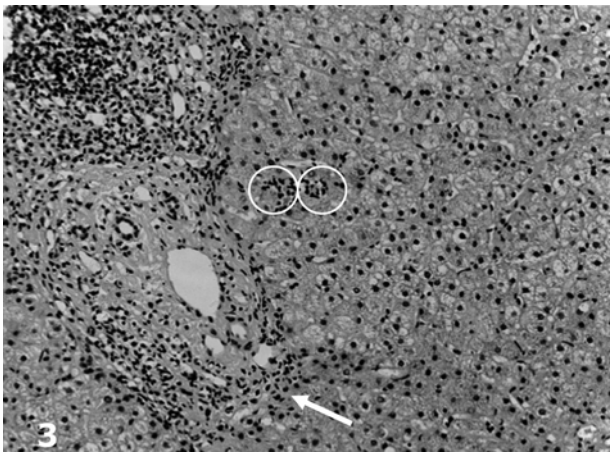

Fig. 3. Lobullar activity designated 1 (circles); interphase hepatitis (arrow) (HE x 100)

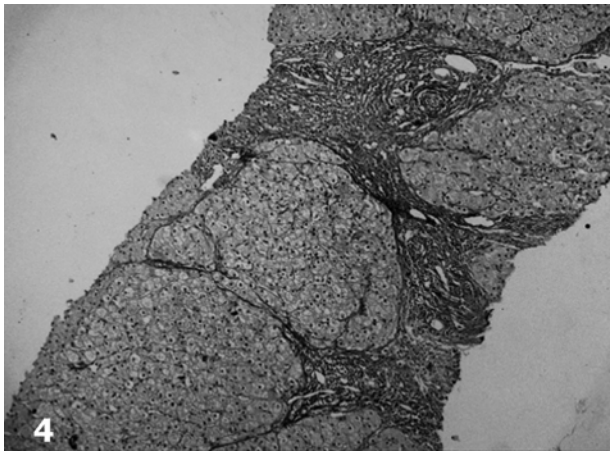

Fig. 4. Cirrhosis in the course of HHC (HE x 40)

Table 2. Distribution of patientes by gender, age and biochemical parameters

Gender	Age	ALT	AST	HAI	Fibrosis
Male	32	41.1	34.2	3	0
Male	50	46.8	29.7	5	1
Male	49	48.5	32.6	4	0
Male	26	49.6	36.4	3	0
Male	27	51.8	42.2	4	0
Male	28	61	42.8	4	2
Male	32	62.9	25	5	1
Female	40	71.8	42.6	5	1
Male	27	97.3	56.6	5	1
Female	25	103.1	62.2	7	2
Male	28	103.2	55.7	6	1
Male	32	106.5	56.1	4	1
Female	51	108.9	62.8	7	2
Male	34	110	56	3	1
Female	43	116.5	63.1	5	1
Male	31	121	49.5	5	2
Female	46	127	50.1	12	3
Male	23	131.1	51.3	5	2
Male	23	133.5	76.3	13	6
Male	28	166.9	50.6	12	6
Male	24	175.5	76.5	6	3
Male	20	205.6	99.5	11	6
Male	35	765	392.5	8	2

a) The values of AST

The values of AST ranged from 25.0 to 392.5 U/l. The mean value was 67.14U/l and standard deviation 72.91U/l. The coefficient of variation is very high 108.6% and is the consequence of individual high levels of AST. The same aspects give the values of median 51.3U/l and inter quartile difference 42.4-62.5U/l. This parameter demonstrates than in 50% of patients the values of AST were only slightly raised.

b) The values of ALT

All patients have shown elevated levels of ALT above normal (40.0U/l).They ranged from 41.1U/l to

even 765U/l. Median, standard deviation of 145.11U/l and coefficient of variation of 111.08% all point to the high levels of ALT in HHC in tested group of patients. A median 106.5% and inter quartile difference of 61.95 to 125.05U/l showed that the levels of ALT were high in tested group even if we disregard individual extreme differences (Table 3).

Table 3. The levels of AST and ALT

Statistical parameter	AST	ALT
Min-max	25.00 – 392.50	41.10 – 765.00
X ± SD	67.14±72.91	130.64 ± 145.11
Cv%	108.60	111.08
Me	51.3	106.50
Inter quartile difference	42.40 – 62.50	61.95 – 129.05

c) Fibrosis stage in zero liver biopsy

There was no fibrosis in the livers of 4 patients (17.39%). They were designated F0. The most frequent finding in the tested group was a slight fibrosis, F1 in 34.78% of cases. The percentage is then lowering to a higher level of fibrosis. Cirrhosis was found in 3 cases (13.04%) Table 4.

Table 4. Distribution of patients with HHC according to fibrose stage

Fibrose stage	F0	F1	F2	F3	F4	F6 - cirrhosis
Number	4	8	5	2	1	3
%	17.39	34.78	21.74	8.70	4.35	13.04

d) HAI values

In the group of patients without fibrosis the values for HAI in "null biopsy" ranged from 3 to 8. The majority of patients had a mild histological activity. Patients with the advanced fibrosis demonstrated HAI ranging from 4 to 12, while the cirrhotic patients had HAI scores above 9. The mean values of HAI scores had shown elevating levels in concordance with a fibrose aggravation and are statistically significantly higher then those with fibrosis F0, F1 and F2 ($p<0.05$).

The HAI indexes in the group of patients without fibrosis were lower than in all other groups ($p<0.05$).

Spirman's coefficient of rang correlation rs=0.80 ($p<0.001$) showed extremly high interconnection of fibrose stage and HAI score. Fibrosis stage is specially connected to confluent necrosis (rs=0.75; $p<0.05$) and interface hepatitis (rs=0.65; $p<0.001$).

e) The values of AST in different fibrosis stages

Five of our patients who had normal values of AST had no fibrosis, and were designated F0, but one who was F1.

The statisticaly important differences according to the values of AST and fibrose stage, were found among patients without fibrosis, F0 and the group of patients with fibrosis F2 ($p<0.05$). Aritmentical mean for AST values is the highest in those with mild fibrosis (X= 173.03 U/l), but the variability of individual values was the highest (Cv=110.11%) so that median for this group and the group with cirrhosis were almost equal (76.5:76.3 U/l).

Patients without fibrosis have mean values of AST in normal range and those were significantly lower than in patients with F2,F3,F4 and cirrhosis ($p<0.05$).

There were no statistical differences among other groups of patients.

Spirman's coefficient of rang correlation rs=0,64 point to an important relation between fibrosis stage and AST values in patients with HHC.

f) The values of ALT in relation to fibrosis

All of the patients had elevated serum ALT levels. The highest values were for the patients with advanced fibrosis (X=335.8 , Me=175.5) as a consequence of very high individual values.The mean values of ALT in patients without fibrosis are significantly lower then in all other groups ($p<0.05$) but are still above normal. In F1 group, ALT values are significantly lower than in group with advanced fibrosis and cirrhosis ($p<0.05$).

There is statisticaly significant relation among ALT values and fibrosis stage in tested group of patients with HHC ($p<0.01$).

Discussion

The risk and natural history of fibrosis associated with HCV have been greatly clarified as a result of several large clinical studies incorporating standardised assessments of fibrosis that combine detailed historical and clinical informations (14).

The disease can run a remarkably variable course, from decades of viremia with little fibrosis, to rapid onset of cirrhosis in 10-15 years.

The standardised serum biological markers of liver damage in HCV have been under wide investigations (15, 16, 17, 18, 19), but the fluctuating values of aminotransferase levels during the course of HHC make their relation to inflammatory activity and a degree of fibrosis (stage) uncertain.

Chronic Hepatitis C virus infections progress to cirrhosis in 20% of cases and 1-4% of cirrhotic patients develop hepatocelular carcinoma each year. Controle of infection, fibrosis progression and therapeutical trials for fibrose reversion in human are under active investigation (20, 21, 22, 23).

Improvement in the detection of factors which initiate and influence the deposition in extracellular matrix responsible for fibrosis show that those processes are more reversibile than we once thought (24).

Our aim was to demonstrate histomorphological changes which follow elevated serum ALT and AST values in the patients with HHC in the time when "null biopsy" was performed.

The results point to a spectrum of morphological changes and specially fibrotic stages in the course of HHC: 78.02% of patients had fibrosis and among them 3 had cirrhosis in the time of "null" biopsy of the liver. This result is in extreme opposite to the findings of Forns and co-workers who discovered HHC in early phases of a dissease in 80% of their cases (25).

We have shown a striking differences in individual tendency to fibrosis of the liver during the course of HHC. A large number of patients with fibrosis in this investigation can be explained by the fact that HHC have a mild subjective symptomatology , as well as by the absence of reliable tests for discovering the fibrosis aside from liver biopsy. Although there are developed systems for detection of serum parameters which point out to fibrosis in the liver, they are not widely used and are not reliable enough (26) and a liver biopsy remains a principal method for detection of liver damage, especialy of fibrosis in hepatitis (27). The need for liver biopsy in patients with permanently normal levels of ALT is still under debate (28, 29). In our group of patients there were 5 with normal AST levels and none of them with normal ALT levels two weeks before biopsy. Our results show significant correlation of the fibrose stage and serum values of ALT and AST. The AST/ALT relation is < 1 even in the cases of cirrhosis, what is in contrast to other findings (30) and in concordance with the report by Reedy DW (31).

Conclusion

According to the results gained we can reach a conclusion that in the chronic hepatitis C, the fibrosis is a very common diagnosis in the zero liver biopsy with extreme individual differences in ratio to a degree of fibroses. Index of histological activity is in correlation with a degree of fibroses. AST and ALT serum levels are in significant mutual dependence ratio to a degree of fibroses, so they are recommended for taking care of the disease and a degree of fibroses.

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NIVOI SEUMSKIH TRANSAMINAZA I STEPEN FIBROZE U NULTOJ BIOPSIJI JETRE U HRONIČNOM C HEPATITISU

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Kratak sadržaj: *Infekcija virusom hepatitisa C doprinosi oštećenju i zapaljenju jetre koje je odgovorno za nastanak fibroze u jetri. Prirodna istorija fibroze je povezana sa zapaljenjem u i oko portnog prostora kao imunološki događaj, čiji uticaj na fibrogenezu nije rasvetljen. Markantna odlika hroničnog hepatitisa C (HHC) je blaga simptomatologija i često, diskrepanca laboratorijskih pokazatelja funkcije jetre i morfoloških promena, što je razlog otkrivanju bolesti u odmaklim morfološkim fazama. Cilj ovog rada je utvrđivanje korelacije vrednosti serumskih transaminaza sa stepenom histološke aktivnosti i fibroze u vreme analize nulte biopsije jetre. Istraživanje obuhvata 23 pacijenta sa HHC kojime su podvrgnute aspiracionoj biopsiji jetre. Analiza obuhvata: put i način infekcije, starost, pol, vrednosti serumske aspartat amino transferaze (AST), alanin amino transferaze (ALT), stepen histološke aktivnosti (HAI) i stepen fibroze u momentu uzimanja nulte biopsije jetre. Rezultati su pokazali da oko 50% ispitanika ima samo blago povišene vrednosti AST, kao i normalne vrednosti ovog parametra u pet pacijenata. Vrednosti ALT su u svih pacijenata povišene. HAI je pokazao izrazite varijacije intenziteta, dok samo pet osoba nije imalo fibrozu. Ciroza je prisutna u tri pacijenta. Pacijenti bez fibroze imaju vrednosti AST u normalnim granicama i one su bile statistički značajno niže nego u osoba sa fibrozom i cirozom ($p<0,05$). Vrednosti ALT su najviše u osoba sa uznapredovalom fibrozom i analiza pokazuje statistički signifikantan odnos vrednosti ALT i fibroze u ispitivanoj grupi pacijenata sa HHC ($p<0,01$). Rezultati su pokazali prisustvo fibroze kao značajne posledice HHC u jetri pri nultoj biopsiji. Odnos međuzavisnosti vrednosti transaminaza, posebno ALT, prema HAI i stepenu fibroze preporučuju ih za praćenje toka bolesti i predviđanje razvoja fibroze.*

Ključne reči: *Hepatitis C, ALT, AST, fibroza*