DOI 10.26724/2079-8334-2022-1-79-94-98
UDC 616.36+616.36-004

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CLINICAL AND LABORATORY MANIFESTATIONS OF ALCOHOLIC LIVER DISEASE AT THE CIRRHOSIS STAGE ASSOCIATED WITH NON-ALCOHOLIC FATTY LIVER DISEASE DEPENDING ON DISEASE COMPENSATION

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The purpose of the study was to clarify the features of course of alcoholic liver disease at the stage of cirrhosis in combination with fatty liver disease. Clinical, laboratory and instrumental examinations were performed for 204 patients with alcoholic liver cirrhosis. It was found that all patients systematically took toxic doses of alcohol that caused clinical manifestations of the disease and a violation of the functional state of the liver. Somatometric indices significantly differed in all patients depending on the degree of compensation. The thickness of the skin and fat fold are reliable indicators that reflect the state of the fat depot of the body; the circumference of shoulder muscles is a reliable indicator of the reduction of the somatic protein pool, accompanied by a decrease in the synthetic function of the liver, especially in patients associated with fatty liver disease. Therefore, when examining patients with alcoholic liver cirrhosis, along with general clinical and laboratory-instrumental examinations, it is recommended to evaluation the trophological status to predict the course of liver cirrhosis.

Key words: alcoholic liver disease; fatty liver disease; cirrhosis; functional liver tests; nutritional status.

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КЛІНІКО-ЛАБОРАТОРНІ ПРОЯВИ АЛКОГОЛЬНОЇ ХВОРОБИ ПЕЧІНКИ НА СТАДІЇ ЦИРОЗУ У ПОЄДНАННІ З НЕАЛКОГОЛЬНОЮ ЖИРОВОЮ ХВОРОБОЮ ПЕЧІНКИ ЗАЛЕЖНО ВІД КОМПЕНСАЦІЇ ЗАХВОРЮВАННЯ

Метою дослідження було вивчення особливостей перебігу алкогольної хвороби печінки на стадії цирозу у поєднанні з жировою хворобою печінки. Проведено загальноклінічні та лабораторно-інструментальні обстеження 204 пацієнтів з алкогольним цирозом печінки. Виявлено, що всі хворі систематично вживали токсичні дози алкоголю, які спричинили клінічні прояви захворювання та порушення функціонального стану печінки. Соматометричні показники відрізнялися у всіх хворих залежно від ступеня компенсації. Товщина шкірно-жирової складки є достовірним показником, що відображає стан жирових депо організму, обвід м'язів плеча – достовірним показником зменшення соматичного білкового пулу, що супроводжується зниженням синтетичної функції печінки, особливо у хворих при поєднанні з жировою хворобою печінки. Отже, при обстеженні пацієнтів на алкогольний цироз печінки поряд із загальноклінічними та лабораторно-інструментальними обстеженнями рекомендовано оцінювати трофологічний статус для прогнозування перебігу цирозу печінки.

Ключові слова: алкогольна хвороба печінки; жирова хвороба печінки; цироз; функціональні печінкові тести; трофологічний статус.

The work is a fragment of the research project "Structural and functional changes of internal organs in chronic non-communicable diseases: the possibility of drug correction", state registration No. 0121U108893.

Over the last few decades, attention has been drawn to the increase of incidence of so-called non-infectious diseases, resulting from the combination of genetic, physiological, environmental and behavioural factors, which are usually modified. These include the use of tobacco, lack of physical activity, inappropriate nutrition, and alcohol abuse [8]. Others, not less important factors include metabolic factors: increased blood pressure, excess body weight/obesity, hyperglycaemia, hyperlipidemia [1, 11]. Among non-infectious diseases that arise from the influence of such risk factors, an important place belongs to diseases of the digestive system in connection with the increase in mortality [6, 9]. A significant contribution to mortality from this class of causes make fibrosis and liver cirrhosis (LC), alcoholic and non-alcoholic liver diseases, which account for more than 50 % of those who died of the digestive system diseases. The reasons for this are the progressive growth of the quantitative and qualitative composition of such patients, frequent chronic diseases, prolonged and severe course, unfavourable close and distant consequences of the disease, prevailing affection of people of working age, which is associated with medical and socio-economic factors [8].

The main causes of liver damage are alcohol, viruses, non-alcoholic fatty liver disease (NAFLD). NAFLD is one of the most common liver diseases. It is registered in 20–35 % of the adult population, both in industrialized countries and in developing countries. The disease has a long asymptomatic course [3, 4, 5]. The initial manifestations of NAFLD are fatty hepatosis and steatohepatitis. However, under adverse conditions, the pathological process is transformed into a LC and can lead to hepatocellular carcinoma [2,

10]. The basis of the development of the LC is the processes of fibrosis, necrosis, angiogenesis, which realize the steady progression of pathology through the cascade of systemic metabolic and immune-inflammatory reactions and lead to endotoxemia, the restructuring of the normal structure of the parenchyma and the vascular system of the liver with the formation of pseudo lobules, regeneration nodes, and the development of multiple organ failure [7] When treating patients with LC, it is particularly important to evaluate the cause of progression and severity of the disease, that directly affects further treatment tactics and life expectancy [1, 12].

The purpose of the study was to clarify the features of the course of alcoholic liver disease at the stage of cirrhosis in combination with fatty liver disease.

Materials and methods. The study included 204 patients with diagnosed LC who underwent inpatient treatment in the gastroenterology department of the Ivano-Frankivsk Regional Clinical Hospital. Among them, 78 patients were diagnosed with ALD (Group I) and 126 patients had a combination of ALD with NAFLD (Group II). Among the patients in Group I, there was 24 women and 54 men (53.2±7.6) years old; among patients of Group II – 22 women and 104 men (47.8±6.4) years old. Patients of Groups I and II were subgrouped depending on the LC compensation classes according to the *Child*-Pugh criteria: IA (17 persons), IB (38 persons), IC (23 persons); IIA (44 persons), IIB (48 persons), IIC (34 persons). Diagnosis was verified using clinical and laboratory-instrumental methods in accordance with the order of the Ministry of Health of Ukraine No. 826 dated November 6, 2014, of the adapted clinical guidelines "Non-Alcoholic Fatty Liver Disease", adapted clinical guidelines "Alcoholic Liver Disease", 2014, adapted clinical guidelines "Liver Cirrhosis", 2017 (State Expert Center of the Ministry of Health of Ukraine, Ukrainian Gastroenterology Association, Kyiv), recommendations of the European Association for the Study of Liver, Diabetes and Obesity (EASL-EASD-EASO, 2016).

A general-clinical examination and ultrasound examination of the abdominal cavity, esophagogastroduodenoscopy was performed. The evaluation of the trophological state of patients included the determination of somatometric parameters: the thickness of the skin-fat fold was determined using the Betap Clipper over Triceps (TSFF); upper arm circumference (UAS) using a flexible measuring tape; shoulder muscles circumference (SMC) was calculated by the formula: SMS (cm)=UAS (cm)–3.14xTSFF (cm); the body mass index (BMI) was calculated according to the formula: BMI=weight (kg)/height ($м^2$). The ratio of waist and hips circumference was not performed due to the presence of ascite in some patients. To detect the alcoholic aetiology of the disease we took into account the recommendations of the World Health Organization: using more than 2 doses of alcohol (1=standard dose of 10 grams of ethanol) per day for women and more than 4 doses for men. Cage, AUDIT, PAS questionnaires, LeGo network was also used. The functional state of the liver was evaluated according to the activity of aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), total bilirubin (TB), thyme sample rate; the protein-synthetic function of the liver was determined by the level of albumin, fibrinogen in the blood, prothrombin index (PI) and international normalized ratio (INR); the activity of the inflammatory process – by the content of C-reactive protein (CRP), which was determined by standard methods. As a method of non-invasive evaluation of the aetiology of alcoholic and non-alcoholic liver damage it was used the Code ANI (alcoholic liver disease/non-alcoholic liver disease index, calculated as follows: ANI (for women)= 58.50+0.637×(MCV)+3.91×(ASAT/ALAT)–0.406×(BMI) and ANI (for men)= 58.50+0.637×(MCV)+ 3.91×(ASAT/ALAT)–0.406×(BMI)+6.35. ANI takes into account the content in the blood of ASAT and ALAT, the average volume of erythrocytes (MCV)). The control group included 20 practically healthy persons who were matched according to age and sex.

Exclusion criteria were hepatic cirrhosis of the viral, toxic and autoimmune genesis, metabolic disorders of the liver, oncological diseases, lack of individual consent of the patient to conduct the study.

Statistical processing of the obtained results was carried out using the software package Statistica v. 12.0, StatSoft, USA and Microsoft Excel. The parameters of parametric statistics were used – the arithmetic average (M) and the standard deviation (SD). To determine the significance of the differences between groups in the distribution, close to normal, t-criterion Student was used. Statistically significant differences were considered at $p<0.05$.

Results of the study and their discussion. The Cage questionnaire revealed that positive results (2 or more points) in patients of Group I were noted in 64.7 %, 82.6 %, and 100.0 % of individuals (with stages A, B and C according to *Child*-Pugh criteria respectively), and in patients of Group II – 54.5 %, 56.2 %, 76.5 % (with stages A, B and C, respectively). Patients in Group I have more positive answers depending on the degree of disease compensation compared with patients in Group II. This indicates that these patients recognize their alcohol dependence more often. Patients in IIA, IIB and IIC groups indicate problems with alcohol use less frequently.

According to the results of the AUDIT questionnaire, in both groups there were more than 15 points, indicating the systematic use of hazardous doses of alcoholic beverages. In patients in the Group I (Classes A, B, C, according to *Child*-Pugh criteria respectively) the indicator was by 1.03, 1.07 and 1.07 times higher in comparison with those in Group II, but there was no significant difference between the groups ($p>0.05$).

The use of the PAS questionnaire and the assessment of the physical signs of chronic alcohol intoxication through the LeGo network allowed confirmation of regular abuse of alcohol in both groups of patients, which led to the development of symptoms of chronic alcohol intoxication. When comparing the indicators according to the PAS questionnaire, depending on the compensation of the disease, no significant difference was found between the indices of patients in Groups I and II ($p>0.05$). Patients in Group II had some more signs in accordance with the LeGo network, but the obvious difference between the groups was not noticed ($p>0.05$).

Results of Cage, AUDIT, PAS questionnaires, and LeGo network indicate the systematic use of patients in both groups of toxic doses of alcohol and the consequences of such use, which led to the clinical manifestations of alcohol intoxication.

We studied anthropometric indicators in patients of groups I and II. The analysis of BMI showed a significant difference between the indicators in Groups I and II depending on the stage of compensation ($p<0.05$). Assessing the trophological status of patients, there was a significant reduction of the upper arm circumference from IA to IB, IC and from IIA to IIB, IIC groups. There is a probable difference between the parameters in groups IA and IIA, IB and IIB, IC, and IIC ($p<0.05$). The parameters of SMS as an integral index reflecting the somatic protein pool have a probable difference between IA, IB, IC and between IIA IIB and IIC groups ($p<0.05$). Parameters in IIB, IIC groups are significantly lower than in IB and IC groups respectively ($p<0.05$). The parameter reflecting the state of body fat depots is TSFF. Its numerical values are reduced from IA and IIA groups of patients to IB, IC and IIB, IIC groups, respectively. With the development of decompensation, there is a significant difference between the indices of the groups of stages A and B ($p<0.05$); between the indices of the IC and the IIC groups, no differences were found ($p>0.05$). Somatometric indices in patients with alcoholic cirrhosis of the liver, when combined with NAFLD, are characterized by a proportional decrease in somatic protein and depletion of the fat depot of the body in the progression of the disease.

Somatometric indices significantly differed in patients when combined with NAFLD, accompanied by higher body mass values and BMI, as well as larger circumference of the upper arm. Along with such changes in patients with alcoholic cirrhosis of the liver, in combination with NAFLD, there was a more pronounced violation of the synthetic function of the liver, accompanied by a greater decrease in somatic protein. TSFF as an indicator reflecting the state of body fat depots, decreased with the progression of the disease in patients of both groups. In patients with the stage of compensation and subcompensation, the TSFF was significantly different in Groups I and II, and in patients of the class C this figure did not differ.

Analyzing the data of the clinical examination, it was found that the signs of astheno-vegetative, pain, dyspeptic, hepatorenal, hepatopulmonary syndromes, jaundice, medically uncontrolled ascite, and manifestations of hepatic encephalopathy were shown more often in patients in Group II.

After analyzing the complaints of the examined patients, it was found that itching and sleep disturbances were more often in patients of group II. At examination of the II group patients there were more often the scratches on skin, vascular asterisks, subicteric, splenomegaly, platypnoe and hydrothorax.

The results of the biochemical study (table 1-2) showed that the parameters of the liver functional state deteriorate with increasing decompensation of the disease.

Patients in groups IIA, IIB and IIC had increased levels of TB, ASAT, ALAT, thymol samples, CRP in comparison with patients of Group IIA (IIA – by 31.6 %, 39.1 %, 25.8 %, 18.6 %, 27 %, IIB – by 21.4 %, 23.5 %, 24.7 %, 13.1 %, 38.6 %, IIC – by 25.6 %, 28.7 %, 28 %, 17.0 %, 55.2 % respectively, all $p<0.05$). This is accompanied by a more pronounced decrease in the synthetic function of the liver compared to patients in Group I, which is reflected in lowering the albumin content in the blood, fibrinogen and PI (IIA – by 9.1 %, 9.1 %, 5.5 %, 13.4 %, IIC – by 12.5 %, 19.2 %, 9.6 %, 15.1 %, IIC – by 16.1 %, 14.3 %, 9.1 %, 9.9 % respectively, all $p<0.05$).

In the calculation of the ANI index as an integral indicator of the differentiation of the etiological factor of the occurrence of ALD and NAFLD, it was found that in healthy subjects (KG) the ANI index was (-17.59±0.68) in men and (-23.76±0.79) in women; in patients with alcoholic LC, it was greater than (11.62±0.72/5.59±0.48), and in patients with a combination of alcoholic LC and NAFLD greater than (4.72±0.12/-0.42±0.03). In all patients' disease progression, the magnitude of the ANI index increased. Moreover, the value of the ANI index in patients of Group I exceeded the following indices of patients

in Group II by 2.5; 2.2; 1.4 times in men and 14.3; 13.3; 1.9 times in women of compensating classes of LC, A, B, C respectively ($p<0.05$). Lower values of the ANI index in patients of Group II compared to patients in Group I of the corresponding class are related to the higher values of the fat depot index in patients with combined alcohol and NALFD. The following changes are especially obvious in people with stages A and B, when fat depots are not exhausted. Comparing the indices in Groups I and II, depending on the *Child*-Pugh class, an increase in the value of the ANI index and the systemic inflammatory response was found, as well as a decrease in the synthetic function of the liver and, consequently, a decrease in the somatic protein pool with an increase in the decompensation of the alcoholic LC in combination with NAFLD.

Table 1

Features of the hepatic functional ability in patients with alcoholic liver disease at the stage of cirrhosis, M±m

Parameters	Control, n=20	Stage of liver cirrhosis by *Child*-Pugh criteria					
		Group IA	Group IIA	Group IB	Group IIB	Group IC	Group IIC
		n=17	n=44	n=38	n=48	n=23	n=34
Total protein, g/l	74.67±4.27	62.12±5.74	59.92±3.56*	56.46±3.24▲	52.72±4.16•ʁ	46.35±2.71■	42.18±1.53#□
Albumin, g/l	47.83±4.26	43.37±2.86	39.43±1.09*	34.61±1.75▲	30.28±1.58•ʁ	28.82±1.74■	24.17±1.65#□
Thymol test, units	2.36±0.63	4.33±0,28	5.49±0.25*	6.13±0.49▲	7.93±0.33•ʁ	6.78±0.37■	8.17±0.67#□
TB, umol/l	13.52±1.28	21.65±1.83	28.49±2.16*	42.27±2.54▲	51.33±3.87•ʁ	126.14±11.72■	158.37±14.58#□
ASAT, unit/l	18.4±1.59	69.72±3.92	79.42±5.48*	86.39±5.87▲	95.26±6.83•ʁ	176.43±11.79■	197.59±13.24#□
ALAT, unit/l	19.6±1.84	37.46±2.54	52.72±3.76*	47.73±4.56▲	72.52±6.61•ʁ	97.54±10.42■	156.42±12.97#□

Notes: 1) * – probability of parameters difference between the IA and IIA groups ($p<0.05$); 2) ● – probability of parameters difference between the IB and IIB groups ($p<0.05$); 3) # – probability of parameters difference between the IC and IIC groups ($p<0.05$); 4) ▲ – the probability of parameters difference between the IA and IB groups ($p<0.05$); 5) ■ – probability of parameters difference between the IB and IC groups ($p<0.05$); 6) ʁ – probability of parameters difference between the IIA and IIB groups ($p<0.05$); 7) □ – probability of parameters difference between the IIB and IIC groups ($p<0.05$).

Table 2

Changes of the ANI index, C-reactive protein and indicators of synthetic liver function in patients with alcoholic liver disease at the stage of cirrhosis, M±m

Parameters	Control, n=20	Stage of liver cirrhosis by *Child*-Pugh criteria					
		Group IA	Group IIA	Group IB	Group IIB	Group IC	Group IIC
		n=17	n=44	n=38	n=48	n=23	n=34
ANI, m/f	-17.59±0.68/-23.76±0.79	11.62±0.72/5.59±0.48	4.72±0.12*/-0.42±0.03*	12.73±0.64▲/7.18±0.31▲	5.69±0.022•ʁ/0.54±0.02•ʁ	14.56±0,86■/8.62±0.53■	10.19±0.74#□/4.64±0.25#□
CRP, ml/l	3.4±0.42	6.19±0.57	9.56±0.59*	9.26±0.62▲	16.83±0.97•ʁ	11.85±0.74■	23.39±1.65#□
Fibrinogen, g/lл	3.66±0.27	2.74±0.15	2.49±0.17*	2.14±0.12▲	1.73±0.14•	1.61±0.13■	1.38±0.11#□
PI, %	88.52±5.73	75.58±2.34	71.43±2.47*	62.27±2.99▲	56.32±1.58•ʁ	38.18±2.86■	34.71±2.42□
INR	1.21±0.08	1.34±0.07	1.52±0.12*	1.85±0.11▲	2.13±0.09•ʁ	2.51±0.14■	2.76±0.10#□

Notes: 1) * – probability of parameters difference between the IA and IIA groups ($p<0.05$); 2) ● – probability of parameters difference between the IB and IIB groups ($p<0.05$); 3) # – probability of parameters difference between the IC and IIC groups ($p<0.05$); 4) ▲ – probability of parameters difference between the IA and IB groups ($p<0.05$); 5) ■ – probability of parameters difference between the IB and IC groups ($p<0.05$); 6) ʁ – probability of parameters difference between the IIA and IIB groups ($p<0.05$); 7) □ – probability of parameters difference between the IIB and IIC groups ($p<0.05$).

Thus, according to Cage, AUDIT, PAS questionnaires, LeGo network, both groups systematically used toxic doses of alcohol that caused clinical manifestations of astheno-vegetative, painful, dyspeptic, hepatotoxic and hepatopulmonary syndromes, jaundice, medically uncontrolled ascite, hepatic encephalopathy, and a violation of the functional state of the liver. Such manifestations were more pronounced in patients when combined with NAFLD. These results are consistent with studies of Y.H. Paik et al. [6].

A separate aspect of the examination of patients with ACP in combination with obesity to identify disorders of protein-energy metabolism is the study of somatometric indicators. In their work, S. C. Bischoff et al. recommend a differentiated approach to the regulation of protein-energy metabolism depending on the stage of liver cirrhosis and the presence of excess body weight and obesity [1]. In our

study to assess the trophological status depending on the stage of liver cirrhosis and the presence of excess body weight and obesity, we showed the feasibility of using indicators of SMS, UAS and TSFF.

An important stage in predicting the course of liver cirrhosis is to establish the factors of occurrence and progression of the disease. In their work Cerović I. et al. described the use of the ANI index to assess the alcoholic and non-alcoholic origin of steatohepatitis [3]. We found that the ANI index was higher in men than in women. In patients of Group II, it was lower than that in Group I, due to the combination of alcoholic LC and NAFLD. With worsening liver cirrhosis, the value of the ANI index increased in all patients. Determining the ANI index in clinical practice is easy to perform and available for use by physicians in different medical care levels. Therefore, it can be further included in the routine diagnosis of liver cirrhosis both to clarify the etiological factor of the disease and to predict the course of the disease.

Conclusions

1. Determination of indicators according to Cage, AUDIT, PAS questionnaires, LeGo network and ANI index allows differentiating the alcoholic ethology of liver cirrhosis and the combination with non-alcoholic liver disease, which justifies their use in the comprehensive examination of such patients.

2. Results of the study of somatometric indices in patients with alcoholic liver disease at the stage of cirrhosis in combination with non-alcoholic fatty liver disease determine the obligatory study of trophological status in such patients for timely correction of detected violations of protein-energy metabolism.

3. The combination of ALC with NAFLD was accompanied by more pronounced clinical manifestations, changes in somatometric indices, a decrease in the synthetic function of the liver, a violation of its functional status, and more significant manifestations of the systemic inflammatory response.

Prospects for further research in this area are the studies of the relationship between metabolic disturbances, synthetic liver function and systemic inflammatory response associated with a combination of alcoholic liver cirrhosis and non-alcoholic fatty liver disease.

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Стаття надійшла 15.01.2021 р.