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КЛІНІЧНІ ТА ПАТОГЕНЕТИЧНІ ОСОБЛИВОСТІ ПЕРЕБІГУ НЕАЛКОГОЛЬНОГО СТЕАТОГЕПАТИТУ ЗА КОМОРБІДНОСТІ З ВТОРИННОЮ АРТЕРІАЛЬНОЮ ГІПЕРТЕНЗІЄЮ

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CLINICAL AND PATHOGENETIC FEATURES OF THE COURSE OF NON-ALCOHOLIC STEATOGEPATITIS BY COMORBIDITY WITH SECONDARY ARTERIAL HYPERTENSION

Анотація.
Стаття присвячена дослідженню клінічних і патогенетичних особливостей перебігу неалкогольного стеатогепатиту, стану компонентів сполучної тканини, метаболічної інтоксикації, гемостазу і фібринолізу з гіпертонічної хвороби II стадії. Встановлено, що при ході неалкогольного стеатогепатиту з гіпертонічної хвороби та ожиріння прогресує висока інтенсивність гемостазіологічні розладів

Abstract.
The article is devoted to the study of clinical and pathogenetic peculiarities of nonalcoholic steatohepatitis, a condition of components of connective tissue, metabolic intoxication, hemostasis and fibrinolysis by comorbidity with stage II hypertension. It was found that in the course of comorbid nonalcoholic steatohepatitis with hypertension and obesity is a higher intensity of hemostasiological disorders.

Ключеві слова*: неалкогольний стеатогепатит, ожиріння, гіпертонічна хвороба.*
Keywords: *nonalcoholic steatohepatitis, obesity, hypertension*

The relevance of diagnosis and management of patients with non-alcoholic fatty liver disease (NAFLD) on the background of metabolic syndrome (MS), a component of which is hypertension (AH), is determined by a significant increase in recent incidence of MS [1, 2, 3, 9], high level of disability due to the development of a wide range of complications [8, 9]. The problem of the comorbid course of nonalcoholic steatohepatitis (NASH) in patients with obesity and hypertension (GC) is a cascade of interload reactions that lead to the progression of all concomitant diseases [1,4, 8]. However, studies of the effect of GC on the course of NASH, in particular on the processes of hepatic circulation, hemostasis, fibrinolysis in relation to metabolic disorders and the state of connective tissue components have not been conducted, which is the basis of the working hypothesis of our study.

The purpose of the study: to investigate the pathogenetic features of NASH on the background of obesity and GC, namely the condition of connective tissue components, metabolic intoxication, parameters of hepatic circulation, hemostasis and fibrinolysis.

Material and methods of research. 120 patients with NASH were examined: of which 60 patients with NASH of mild and moderate activity with obesity of the I degree (group 1), 60 patients with NASH of mild and moderate activity with comorbid course of GC of the II stage and obesity of the I degree (group 2).). To determine the dependence of NASH on the activity of cytolytic syndrome, each group was divided into 2 subgroups of patients: 1a - NASH of mild activity, 1c - NASH of moderate activity, 2a - NASH of GC of mild activity, 2c - NASH of GC of moderate activity, which were randomized by age, sex, degree of obesity and cytolytic syndrome activity.

The stage of liver tissue fibrosis was studied using the FibroTest, the degree of fatty degeneration of the liver was studied using the SteatoTest (BioPredictive, France). The condition of the connective tissue components was studied by the content of free oxyproline in the blood serum - by S.S. Tetyanets, protein-bound oxyproline - by MA Osadchuk. Collagenolytic activity of blood plasma was studied by the intensity of azocol lysis by enzyme-linked immunosorbent assay.

The degree of carbohydrate metabolism compensation was determined by fasting blood glucose and 2 hours after glucose loading (glucose tolerance test) by glucose oxidase method, fasting insulin content (DRG System) by enzyme-linked immunosorbent assay (ELISA) standard sets of reagents ("DanishLtd", Lviv) by the method of VA Queen. The degree of insulin resistance (IR) was determined by the value of the body

mass index (BMI): body weight (kg) / height2 (m); HOMA-IR index (D.R. Matthews et al.), which was calculated using the program HOMA CalculatorVersion 2.2 Diabetes Trials Unit University of Oxford (UK).

Total blood coagulation potential was determined by prothrombin time (PTC) and index (PTI), total plasma fibrinolytic activity (PFA), potential plasminogen activity (PAP), fibrinogen content in plasma, antithrombin III III activity, activity reagents of the company "DanushLtd" (Lviv) according to the methods of N. Titz. Enzymatic (FFA) and non-enzymatic fibrinolysis (NFA) were studied using reagents from the same company. Platelet count and aggregation capacity were studied by platelet aggregation analyzers AR 2110 (CJSC SOLAR, Belarus) on the indicators of spontaneous (SpAT) and induced platelet aggregation (IAT) using ADP as an inducer of aggregation (at a final concentration of 0.5 × 10 ×) turbidimetric method. Statistical processing of the material was carried out using parametric and nonparametric methods of variation statistics.

Research results. Comparative analysis of the frequency and intensity of clinical syndromes of NASH in patients of the 1st and 2nd groups showed that in patients of the 2nd group asthenovegetative, abdominal pain, hepatomegaly, splenomegaly, bloating and increase in size as the initial manifestations of the syndrome portal hypertension, were more common and the manifestations of the syndromes were more intense than in patients of the 1st group ($p < 0.05$). In 30.0% of patients of the 2nd group there was a hemorrhagic syndrome in the form of gingival, nasal, uterine or hemorrhoidal bleeding, the presence of hematomas in the areas of pre-injection, bruising with minimal trauma, while in patients of the 1st group these manifestations were not observed.

Table 1

Indicators of liver function, blood lipid spectrum, glycemia, reduced malonic aldehyde and glutathione content in the blood, collagenolytic activity of blood plasma, sonographic indicators of hepatic circulation, platelet hemostasis and fibrinolysis in patients with nonalcoholic steatosis moderate activity (group 1b), non-alcoholic mild steatohepatitis with obesity and stage II GC (group 2a), non-alcoholic moderate activity steatohepatitis with obesity and stage II GC (group 2c), (M ± m)

Indexes	PZO, n = 30	Group 1a, n = 30	Group 1c, n = 30	Group 2a, n = 30	Group 2c, n = 30
AST, μmol / year × l	0.4±0.01	0.9±0.03*	1,5±0,04*/**	1.1±0.02*/**/***	1.8±0.04*/**/***/#
General HS, mmol / l	4.72±0.101	6.41±0.127*	5.83±0.115*/**	6,98±0,108*/**/***	6,840,092±*/**/***
TG, mmol / l	1,47±0.033	3.18±0.019*	2,93±0,020*/**	2,72±0,032*/**/***	251±0,024*/**/***/#
LDL, mmol / l	2.59±0.028	4350.027±*	4.23±0.029*/**	4,61±0,019*/**/***	4,53±0,013*/**/***/#
Glucose h-s 2 hours.	7.51±0.531	8,75±0,193*	9.40±0.117*/**	9.95±0.153*/**/***	10.75±0.108*/**/***/#
HOMA IR	1.30±0.296	3,500.047±*	3,71±0,032*/**	4,14±0,045*/**	4,38±0,028*/**/***/#
MA er., Mmol /l	9.09±0.138	10.75±0.128*	11.95±0.139*/**	13,13±0.255*/**/***	15,16±0.127*/**/***/#
GV	0.93±0.013	0,75±0,004*	0620,003±*/**	052*0,002±/**/***	0,41±0,002*/**/***/#
NO blood, μmol / l	15.32±1.225	30.33±1.321*	36,49±1,352*/**	39.51±1.174*/**	45.14±1.142*/**/***/#
SFA, E440 / ml / year	1.68±0.022	154±0,023*	1.39±0.018*/**	1.30±0.024*/**/***	1,21±0.019*/**/***/#
The number of platelets10^9 / l	297.3±15.34	255.2±21.19	215,9,24,54±*	145.2±22.39*/**	131.5±17.19*/**/***
The degree of IAT,%	24.35±1.152	43,832,055±*	50.02±1.021*/**	35,34±2,127*/**/***	39.22±1.053*/***/#
FibroTest , USD	0.18±0.01	0.23±0.02*	0,30±0,01*/**	0.31±0.01*/**	0,36±0.01*/**/***/#
SteatoTest , USD	0.19±0.02	0.55±0.02*	0.48±0.01*/**	0.45±0.01*/**	0.37±0.02*/**/***/#
D v.v. , mm.	9.4±0.51	10.6±0.12*	11.5±0.20*/**	12.4±0.14*/**/***	12.7±0.15*/**/***
KI	0.023±0.0019	0.034±0.0013*	0.039±0.0021*	0.041±0.0019*/**	0.047±0.0018 */**/***
KLA, μM / lhgod	0.84±0.016	0.58±0.020*	0,51±0,013*/**	0.52±0.009*/**	0,48±0,017*/**
BZOP, μmol / l	41.48±3.709	64,70±7,236	73,47±6,311*	79,53±6.129*	87,05±6.138*

Notes: * - the difference is probable in comparison with the indicator in almost healthy individuals ($p < 0,05$);
** - the difference is probable in comparison with the indicator in patients of group 1a ($p < 0,05$);
** * - the difference is probable in comparison with the indicator in patients of group 1b ($p < 0.05$);
- the difference is significant in comparison with the indicator in patients of group 2a ($p < 0,05$).

Prior to treatment, a more significant increase in the content of total bilirubin in the blood of patients of group 2 was registered on average 3.8 times against 1.5 ($p < 0.05$) - in patients of group 1 with a probable intergroup difference ($p < 0.05$). The content of conjugated bilirubin in patients of the 2nd group exceeded the norm by 5.8 times against 3.4 times in group 1 ($p < 0.05$), the content of unconjugated bilirubin - 4.5 times against 2.3 times in 1 -th group, indicating a growing inability of the liver to bind bile pigment and transport it as part of

the bile micelle in the biliary tract, available cytolysis and cholestasis by comorbidity with GC. Confirmation of the higher intensity of cytolytic syndrome in patients with NASH with comorbidity with GC is a probable increase in the activity of AST and ALT in the blood of patients of group 2, and in patients of group 2a ACT activity exceeded the norm by 2.8 times (p <0,05), while in patients of group 1a - the increase was 2.3 times (p <0.05) compared with PZO; in patients of group 2b the ACT activity exceeded the normative indicators by 4.5 times (p <0.05) against 3.8 times in group 1b, with a probable intergroup difference (p <0.05).

At the same time, in patients of the 2nd group it should be noted a higher intensity of mesenchymal-inflammatory syndrome of NASH, which we assessed by the thymol test and the content of α2- and γ-globulins in the blood (p <0.05) than in patients of the 1st group. (p <0,05), as well as more significant inhibition of protein synthesizing liver function (albumin content in group 2b was lower than in PZO by 28.0% (p <0,05) against 10,7% (p> 0, 05) in group 1b) and probable inhibition of arginase activity as a marker of liver detoxification function, respectively 4.5 times (p <0.05) in group 2b and 1.7 times in group 1v (p <0.05).

Evaluating the intensity of MS and IR in the comparison groups, the level of postprandial glycemia and IR - HOMAIR (Table 1) in the comparison groups differed depending on the degree of activity of the cytolytic syndrome.

In patients of group 1a the level of glycemia in 2 h after glucose loading exceeded the index of PZO by 16.7% (p <0.05), 1b - by 25.3%, while in patients of group 2a blood glucose exceeded the indicator in PZO by 32.7% (p <0.05), in group 2 by 43.3% (p <0.05), which indicates a more significant level of IP with a probable intergroup difference (p <0.05) . The content of HbA1c in the blood before treatment in patients of group 2 was also significantly increased in the range of 18.0-22.7% (p <0.05), but did not reach the indicators that would indicate the presence of diabetes mellitus [1, 3], and in the 1st group the indicator only had a tendency to increase (10.0-14.3% p> 0.05). Fasting insulin levels before treatment were likely to be elevated in all follow-up groups, but no intergroup difference was found. At the same time, we registered probable differences in changes in the IR index - HOMA IR, which in patients with NASH2a group exceeded the index in PZO 3.2 times, 2v group - 3.4 times (p <0.05) (Table 1) , and in patients of the 1st group - respectively exceeded the norm by 2.7 and 2.8 times (p <0.05). Thus, the comorbid course of NASH with obesity and GC contributes to the early and more intensive development of carbohydrate tolerance, desensitization of insulin receptors and the development of IR syndrome.

Analyzing the indicators of lipid metabolism (Table 1) in the examined patients, it is necessary to point out some features of the established lipid imbalance in patients with NASH and NASH with GC and obesity. In particular, the content of total cholesterol in groups 1a and 1c, although higher than in PZO 1.4 and 1.2 times (p <0.05), still remained lower than similar indicators in the comparison groups, where the growth was respectively: y In group 2a - 1.5 times and in group 2b - 1.4 times (p <0.05) (Table 1). General hypercholesterolemia had the same tendency as the content of LDL in the blood, which also exceeded the maximum in the PZO in 2a and 2b groups - 1.8 and 1.7 times, respectively (p <0.05), against 1.6 and 1.5 times in groups 1a and 1b (p <0.05). It should also be noted that with increasing cytolysis activity, the content of cholesterol and LDL in the blood decreased in both groups, but with comorbidity with GC - increased, which may be an important prognostic factor in the progression of atherosclerosis in this category of patients [1, 8] . We also found a probable decrease in the level of HDL in the blood of patients of all groups compared with the maximum decrease in the 2nd group of patients (p <0.05).

An important aspect, in our opinion, aspect of the development and progression of NASH in patients with MS is the content of TG in the blood, which essentially constitute the pathogenetic basis of hepatic steatosis under conditions of obesity [3, 4]. Analysis of TG levels in the blood indicated the opposite trend relative to the content of cholesterol in the blood. Thus, in groups 1a and 1c the TG content was higher than in the PZO by 2.2 and 2.0 times, respectively (p <0.05), as well as by the indicator in the 2a and 2b groups, where the excess was 1.9 and 1.7 times (p <0.05) compared with PZO. Thus, comorbidity with GC to NASH is characterized by a likely higher hypercholesterolemia and an increase in proatherogenic LDL than in the isolated course of NASH on the background of less significant hypertriacylglycerol. It should be noted that the indicators of TG and LDL in the blood are closely interrelated with the intensity of steatosis (IC) (Steatotest) - respectively r = 0.75 (p <0.05), r = 0.69 (p <0, 05). We found the dependence of the content of TG in the blood on the degree of activity of NASH was observed for the index of IP in the comparison groups. Thus, the IC in patients 1a and 1b groups - exceeded the index in PZO, respectively, 2.9 and 2.5 times (p <0,05), while in 2a and 2b groups. Thus, the IP in patients 1a and 1b groups - exceeded the rate in PZO, respectively, 2.9 and 2.5 times (p <0,05), while in 2a and 2b groups - the intensity of steatosis was slightly lower and amounted to 2.3 and 1.9 times (p <0.05) compared with PZO.

In patients with NASH with MS, a significant intensity of metabolic intoxication was found, and all indicators were higher than comorbidities with GC. There was a significant increase in the intensity of LPS (Table 1) by increasing the content of MA in erythrocytes in patients 2a and 2b groups - by 44.3% and 66.5% (p <0.05) against 18.1% and 31.3 % (p <0.05) in groups 1a and 1b (Table 1) with the presence of a probable intergroup difference (p <0.05). Comorbidity with GC also showed a higher intensity of nitrosive stress (nitrite / nitrate content), which increased with increasing degree of activity of the cytolytic syndrome (Table 1). At the same time, the system of detoxification and antioxidant protection was damaged in patients with NASH with GC more significantly: the content of HF in erythrocytes decreased in the direction of 1a, 1c, 2a, 2c and was lower than the norm, respectively, 1.2 times, 1.5, 1 , 8 and 2.3 times (p <0.05) (Table 1).

According to the results of our studies, in the background of MS and GC, the course of NASH is accompanied by the early development of fibrosis of liver tissue. This is evidenced by the results of the Fibrotest (table 1): the average fibrosis in patients with NASH mild activity exceeds the norm by 1.3 times ($p < 0,05$), with the comorbidity of NASH with GC - 1.7 times ($p < 0.05$), with NASH of moderate activity, the indicators in groups 1b and 2b, respectively, exceed PZO by 1.7 and 2.0 times ($p < 0.05$). Investigating the causes of this phenomenon, we found a probable increase in blood levels of BZOP - a marker of collagen anabolism in the range of 1.6-1.8 times ($p < 0.05$) without a probable intergroup difference, together with a probable suppression of CLA: more significant in patients 2a and 2c groups - 1.6 and 1.8 times ($p < 0.05$), respectively, less pronounced in the 1st group of patients (1.4 and 1.6 times ($p < 0.05$)), ie the intensity of fibrosis in the 2nd group of patients occurs both due to the activation of collagen synthesis by sinusoidal star cells Ito [3] and due to the inhibition of collagen degradation by the system of matrix collagenases.

Analyzing some indicators of hemostasis, a probable decrease in the activity of the anticoagulant system was found: blood pressure III ($p < 0.05$), factor XII ($p < 0.05$), fibrinolysis (SFA, FFA, PAP ($p < 0.05$)) on the background compensatory activation of NFA and platelet aggregation ($p < 0.05$) (Table 1), which are also likely to predominate in patients of group 2 and are a significant risk factor for severe complications (stroke, heart attack), which may accompany the course of GC on background of MS.

Conclusions. 1. The clinical course of non-alcoholic steatohepatitis on the background of stage II hypertension and metabolic syndrome is characterized by the intensity of manifestations of asthenovegetative, abdominal - pain syndromes, hepatomegaly, the development of the initial manifestations of portal hypertension syndrome (splenomegaly, hyperbemagnesia, hypersmonemia stage II disease and metabolic syndrome is characterized by the predominance of the intensity of biochemical syndromes: cytolysis, mesenchymal inflammation, hepatocellular insufficiency, metabolic intoxication, activation of liver tissue fibrosis (increase in Fibro test within F1 ($p < 0.05$l), blood content bound oxyproline ($p < 0.05$), inhibition of collagenolytic activity of blood ($p < 0.05$)).

Literature

1. Успенский Ю.П. Метаболический синдром и неалкогольный стеатогепатит: причинно-следственный континуум / Ю.П.Успенский, Е.В.Балукова // Гастроэнтерол.- 2009.- №1.- С. 43-46.

2. Харченко Н.В. Неалкогольный стеатогепатит как проявление метаболического синдрома. Современные подходы к лечению / Н.В. Харченко, Е.В. Родонежская // Новости мед. и фармации.- 2007.- Тем. номер „Гастроэнтерология”.- №226.- С. 18-19.

3. Хухліна О.С. Неалкогольна жирова хвороба печінки та інсулінорезистентність: патогенез, клініка, діагностика, лікування глутаргіном // О.С.Хухліна, М.Ю.Коломоєць.- Чернівці, 2008.- 318с.

4. Bohinc B.N. MechanismsofDiseaseProgressionin NASH: NewParadigms / B.N.Bohinc, A.M.Diehl // Clin.LiverDis.- 2012.-Vol.16, №3.- P. 549-65.

5. Fujii H.Inflammationand fibrogenesisin steatohepatitis // H.Fujii, N.Kawada // J.Gastroenterol.- 2012.-Vol.47, №3.- P. 215-225.

6. NASH isan Inflammatory Disorder: Pathogenic, Prognosticand Therapeutic Implications/ Farrell G.C., vanRooyen D., Gan L., Chitturi S. // GutLiver.- 2012.-Vol.6, №2.- P.149-71.

7. Targher G.Non-alcoholicfatty liverdisease, themetabolic syndrome and the risk of cardiovasculardisease: theplotthickens / G. Targher // Diabet. Med.- 2007.- Vol.24, №1.- P.1-6.

8. Torres D.M. Features, diagnosis, and treatment of nonalcoholic Fatty liver disease / Torres D.M., Williams C.D., Harrison S.A. // Clin.Gastroenterol.Hepatol.- 2012.-Vol.10, №8.- P. 837-58.