samples of vaginal secretion of 20 women with chronic recurrent genital vaginosis, the mean colony-forming capacity of S. epidermidis, S. aureus, E. coli, Enterococcus, S. sapphyticus and C. albicans species was determined, which amounted to 5.90±0.28 CFU, 8.16±0.30 CFU, 7.66±0.19 CFU, 1.00±0.12 CFU, 2.16 CFU AND 2.27±0.17 CFU, respectively. In the vaginal fluid samples of 22 women who underwent another preventive examination in the women's consultation and included us in the control group, the colony-forming ability of the species S. epidermidis, Entrococcus and S. sapphyticus was respectively 1.18±0.079 CFU, 0.024±0.002 CFU and 0.014 CFU, while for S. aureus, E. coli and Candida, this figure was 0. In the study of the nature of the menstrual cycle in the group of 22 healthy women normomenorrhea was established in 15 women (68.2%), oligomenorrhea – in 5 women (22.7%), hypomenorrhea – in 1 woman (4.5%), hypermenorrhea – in 3 women (13.6%), dysmenorrhea – in 3 women (13.6%) and premenstrual syndrome – in 6 women (27.3%). In the study of the presence of other diseases in the control group in 3 women (13.6%) revealed thyroid disease, 4 women (18.2%) – cholecystitis, 3 women (13.6%) – gastritis and 3 women (13.6) –cystitis. In a group of 20 patients with chronic recurrent genital candidiasis, thyroid pathology was established in 3 women (15%), gastritis – in 4 women (20%), cholecystitis – in 5 women (25%), intestinal dysbiosis – in 6 women (30%), cystitis – in 5 women (25%). Among 29 patients with recurrent bacterial vaginosis, thyroid pathology was found in 6 women (20.7%), gastritis – in 5 women (17.2%), cholecystitis – in 9 women (31%), intestinal dysbiosis – in 7 women (24.1%), cystitis – in 8 women (27.6%). Research in the group of 39 patients suffering from chronic recurrent genital candidiasis and bacterial vaginosis at the same time, showed the presence of thyroid pathology in 9 women (23,1%), gastritis – in 7 women (17.9 percent), cholecystitis in 8 women (20,5%), dysbacteriosis of the intestine in 8 women (20.5%) and cystitis – in 16 women (41%).

Conclusion. In women with genital pathologies, the incidence of various somatic diseases and menstrual disorders was higher than in healthy women.

Key words: bacterial vaginosis, genital candidiasis, somatic diseases.

Рецензент – проф. Ліхачов В. К.
Стаття надійшла 23.08.2018 року

DOI 10.29254/2077-4214-2018-3-1-145-80-83
UDC 616.36-003.826+616.61-036.12]-036.1-07-08

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CLINICAL AND PATHOGENETIC FEATURES OF NONALCOHOLIC STEATOHEPATITIS FOR COMORBIDITY WITH CHRONIC KIDNEY DISEASE AND OBESITY

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Publication relation to planned scientific research projects. This work is a fragment of the research work "Pathogenetic mechanisms of mutual burden and clinical features of non-alcoholic fatty liver disease and chronic kidney disease, justification of differentiated treatment", registration number 0117U002351 (2017-2019).

Introduction. The topicality of the problem of nonalcoholic steatohepatitis (NASH) course against the background of chronic kidney disease (CKD) consists in a significant increase in the frequency of this type of comorbidity (14-30%), which, when progressing, is accompanied by an increasing degree of endotoxicosis, an increase of nitrogen metabolism products in systemic circulation against the background of hypoalbuminemia, hyper- and dyslipidemia, activation of oxidative and nitrosative stress against the background of significant suppression of the antioxidant defense system and the natural detoxification system, inhibition of erythropoiesis (anemia of chronic disease), endothelial dysfunction, significant disorders of the peripheral and organ circulation (liver, kidneys, myocardium), activation of connective tissue system [1,2,3,4,5,6]. All these mechanisms are pathogenetic links in NASH and CKD, especially if they occur against the background of type 2 diabetes or obesity [4,7]. The prevalence of NASH among patients with type 2 diabetes and obesity is 80-100% [8,9,10]. During the autopsy NASH is detected in 18.5-26%, cirrhosis of the liver – in 9-10% of cases in patients with type 2 diabetes and obesity [10]. However, at present, the degree of these disorders and the clinical features of the course in comorbidity of NASH and CKD are unknown.

The purpose of our study was to study the changes in the functional state of the liver in patients with nonalcoholic steatohepatitis in combination with chronic kidney disease and obesity.

Object and methods of research. 140 patients with NASH were examined: 68 patients with NASH and obesity of the I degree (group 1) and 72 patients with NASH and comorbid obesity of the I degree and CKD of the I-II stages (group 2). To determine the dependence of the NASH course on the presence of CKD, the group of patients was randomized according to age, sex, degree of obesity. The average age of patients was (45.8±3.81) years.

The diagnosis of NASH was made according to a unified clinical protocol approved by the MoH of Ukraine Order No. 826 dated November 6, 2014, in the presence of criteria for the exclusion of chronic diffuse liver disease of viral, hereditary, autoimmune or medicinal origin as a cause of cholestatic or cytolytic syndromes, as well as the results of the USG examination. Diagnosis and treatment of CKD was conducted in accordance with the clinical guidelines of the SI "Institute of Nephrology of NAMS of Ukraine" (2012). The study involved patients

with CKD of the I-II stage without nephrotic syndrome with chronic uncomplicated pyelonephritis in the phase of exacerbation subsiding or with a latent course. When the patients were admitted to the hospital, the functional state of the liver and kidneys was determined according to the generally accepted list of enzymes activity, pigment and nitrogen metabolism markers, proteinogram, lipidogram, ionogram, De Ritis ratio (AST/ALT ratio) calculations, glomerular filtration rates.

The statistical analysis of the results was carried out in accordance with the type of research and the types of numerical data that were obtained. Distribution normality was verified using the Lilliefors and Shapiro-Wilk tests and by the direct visual evaluation of eigenvalues distribution histograms. Quantitative indices having a normal distribution are represented as mean (M) ± standard error (S). In the nonparametric distribution the data are presented as median (Me) as a measure of position, upper (Q75) and lower (Q25) quartiles as a measure of dispersion. Discrete indices are presented in the form of absolute and relative frequencies (percentage of observations to the total number of examined). Parametric tests with the assessment of Student's t-test, Fisher's F-test were used to compare the data that had normal distribution. The median test, Mann-Whitney Rank U-test, and Wilcoxon signed-rank test for multiple comparisons (in the case of dependent groups) were used in abnormal distribution. Statistica for Windows version 8.0 (Stat Soft Inc., USA), Microsoft Excel 2007 (Microsoft, USA) software packages were used for statistical and graphical analysis of the obtained results.

Results of the research. NASH in the examined patients clinically manifested in the following way: asthenic-vegetative (61.5%), dyspeptic (nausea, bloating, stool disorders) (78.8%) symptoms, heaviness or discomfort in the right subcostal region (32.7%), hepatomegaly (86.5%), splenomegaly (13.5%), hemorrhagic disorders (bleeding gums, nasal, uterine, hemorrhoidal bleedings, bruising, petechiae on the skin) (9.6%), cholestatic symptoms (bitter taste in the mouth, itching skin, xanthoma, xanthelasmas on the eyelids) (21.2%) and endocrine disorders: 100.0% of patients suffered from obesity of the I degree, in 86.5% impaired glucose tolerance (IGT) was diagnosed **(Table 1).** Cytolytic (100.0%), cholestatic (21.2%), mesenchymal-inflammatory syndrome (48.1%) and the hepatocellular failure syndrome (HCF) were found among biochemical syndromes in the examined patients.

The analysis of clinical manifestations of NASH shows that their frequency and intensity are likely to be higher in patients of the 2nd group. In particular, the symptoms of asthenic-vegetative syndrome were observed more often: in 1.3 times ($p<0.05$) respectively compared to patients in group 1, which was probably due to increased accumulation of metabolic products which were not removed by the liver under the conditions of concomitant CKD in the phase of exacerbation.

Manifestations of dyspepsia in patients of the 2nd group also occurred more often than in patients of the 1st group (13.7% and 20.5% respectively ($p<0.05$), which indicates disorders of digestive processes due to the secretion of bile inadequate in its composition, probable concomitant disbacteriosis and dysbiosis of the colon resulted from the repeated courses of antibiotic therapy against CKD, uroseptics. A sensation of heaviness or moderate pain with palpation in the right subcostal and lumbar regions was also recorded in patients of the 2nd group at a frequency exceeding the one in patients of the 1st group: in 2.5 times ($p<0.05$), that was probably associated with the stretching of the Glisson's capsule of the liver due to hepatomegaly, with the accompanying dysfunction of the sphincter apparatus of the biliary tract, which is often observed in obese patients, as well as in those with CKD in the exacerbation phase. Reliably hepatomegaly was detected with higher frequency in patients of group 2 (by 11.6% ($p<0.05$)), as compared to patients in group 1 **(see Table 1)** with a significant increase in the average size of the liver (by Kurlov, USG) in patients of the 2nd group ($p<0.05$). The degree of liver enlargement, in this case, may indicate an increase in the degree of liver steatosis or the degree of the inflammatory process activity, venous stasis, as well as the stage of liver fibrosis.

Table 1.

Frequency of occurrence of clinical and biochemical syndromes of non-alcoholic steatohepatitis depending on the presence of CKD, %

Syndromes	NASH+ obesity, n=68		NASH + obesity + CKD, n=72	
	Abs.	%	Abs.	%
Asthenic-vegetative	32	61.5	42	79.2
Dyspeptic	41	78.8	47	88.7
Discomfort in the right subcostal	17	32.7	45	84.9
Hepatomegaly	45	86.5	51	96.2
Splenomegaly	7	13.5	17	32.1
Hemorrhagic	5	9.6	9	17.0
Cytolysis	52	100.0	53	100.0
Cholestasis	11	21.2	19	28.3
Mesenchymal-inflammatory	25	48.1	38	71.7
Hepatocellular failure	11	21.2	24	45.3
Impaired glucose tolerance	45	86.5	49	92.5

Clinically and biochemically cholestasis syndrome was diagnosed in 20.0% of patients with NASH of group 1 and in 28.3% of patients in group 2, which was manifested by itching of the skin, bitterness in the mouth, presence of xanthomatous formations on the eyelids, hyperbilirubinemia due to direct fraction of bilirubin, increased activity of alkaline phosphatase (AP) and γ-GT **(Table 2).** A small number of patients of the 1st group had splenomegaly (13.5%), however, in patients of the 2nd group, the frequency of splenomegaly exceeded the rate in group 1 in 2.4 times ($p<0.05$) respectively. Splenomegaly syndrome completely disappeared in patients of the 1st and 2nd groups after treatment, which indicates the absence of persistent syndrome of portal hypertension.

The analysis of biochemical syndromes at NASH most frequently demonstrated an increase in the average index of ALAT activity in the blood serum, which, at an isolated course of NASH, exceeded the index in PHI by 2.3 times ($p<0.05$) and ASAT by 3.0 times ($p<0.05$))

Table 2.

Indices of biochemical blood test in patients with non-alcoholic steatohepatitis depending on the presence of CKD (M±m)

Indices, unit of measurement	PHI, n=30	Groups of examined patients	
		NASH+ obesity, n=68	NASH + obesity + CKD, n=72
Total bilirubin, μmol/l	19.23±1.11	28.2±1.25 *	35.2±1.03 */**
Direct bilirubin, μmol/l	4.52±0.25	8.6±0.23 *	10.1±0.35 */**
Indirect bilirubin, μmol/l	14.73±0.38	19.6±1.12 *	25.1±0.97 */**
ASAT, μmol/h×l	0.39±0.012	0.89±0.016 *	1.25±0.025 */**
ALAT, μmol/h×l	0.38±0.014	1.15±0.014 *	1.41±0.011 */**
De Ritis coefficient	1.03±0.018	0.77±0.005 *	0.89±0.004 */**
GGT, mmol/h×l	5.22±0.13	6.14±0.12*	6.74±0.13*/**
AP, mmol/h×l	1.23±0.02	1.43±0.01 *	1.72±0.02 */**
Bile acids, mmol/l	1.27±0.01	2.42±0.02 *	2.83±0.06 */**
Thymol test, conventional unit	2.82±0.13	3.72±0.11 *	4.33±0.13 */**
Total protein, g/l	76.13±2.12	69.27±1.96	60.31±2.17*/**
Albumins,%	59.37±2.23	53.21±2.38	43.63±2.35 */**
Globulins,%	40.63±2.62	46.79±2.14	56.37±2.21*/**

Notes: 1.* – reliable difference compared to the index in practically healthy individuals (p<0.05); 2.** – reliable difference compared to the index in patients with NASH (p<0.05); *** – reliable difference compared to the index in patients with NASH and CKD (p<0.05).

(Table 2). A case in point was a decrease in the De Ritis coefficient (ASAT/ALAT) by 25.2% (p<0.05), which, in the absence of positive viruses markers of hepatitis B and C in serum, indicates non-alcoholic dysmetabolic and inflammatory liver diseases. Positive results of biochemical screening tests confirmed this fact: Steato-test and NASH-test (p<0.05) and negative results of ASH-test (p<0.05) in the examined patients, which excludes the alcoholic character of the disease.

In patients with NASH and concomitant CKD, the cytolysis syndrome was more intense, since the activity of ALAT exceeded the index in PHI by 3.7 times (p<0.05), and the activity of ASAT – by 3.2 times (p<0.05), which led to a decrease in the De Ritis coefficient by 13.6% (p<0.05) compared to the PHI **(see Table 2).** The content of total bilirubin in patients of the 2nd group exceeded the normative indices in 1.8 times (p<0.05) versus 1.5 times in patients of group 1 (p<0.05). It should be noted that the total bilirubin rate in the blood grew due to an increase in both of its fractions: conjugated – in 2.2 time (p<0.05) versus 1.9 time (p<0.05) in group 1.

The presence of cholestasis syndrome was indicated by an increase in the AP activity in 1.4 times (p<0.05) in patients of the 2nd groups versus 1.2 times (p<0.05) in patients of the 1st group, γ-GT activity, in 1.3 times respectively versus 1.2 times (p<0.05) and the content of bile acids in blood, which exceeded the indices in the PHI in 2.2 times respectively versus 1.9 times in the 1st group (p<0.05) **(see Table 2).**

The presence of mesenchymal and inflammatory syndrome in patients with NASH in group 2 was detected by hyperglobulinemia (in 1.4 times respectively (p<0.05), an increase in the thymol test (in the 1st group – in 1.3 times (p<0.05), in the 2nd group – in 1.5 times (p<0.05)), as well as a decrease in the albumin-globulin ratio (in group 1 – in 1.2 times (p<0.05), in group 2 – in 1.9 times (p<0.05)) **(see Table 2),** which was stipulated by the CKD exacerbation.

The USG of the liver of the examined patients revealed the probable degree of hepatomegaly **(see Table 1),** medium-grained structure transformation and mosaic seals (hyperechogenicity, "irregularity") of liver parenchyma due to its inflammation, as well as a significant degree of liver steatosis (a significant percentage of dorsal fading of the echo signal).

Conclusions. Clinical course of non-alcoholic steatohepatitis in comorbidity with obesity and CKD is characterized by higher frequency and intensity of clinical and biochemical syndromes. The comorbid course of NASH with CKD is characterized by higher degree of liver steatosis (HRI is 1.3 times higher than that in the group of patients with NASH, p<0.05), and higher diagnostic threshold of the hepatorenal index values, which correlates with strong interdependence with liver steatosis degree, determined by Steato-test (r=0.87; p<0.001).

The prospect of further research in this direction is the development of effective methods for the treatment of patients with a comorbid course of NASH and CKD against the background of obesity.

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КЛІНІЧНІ ТА ПАТОГЕНЕТИЧНІ ОСОБЛИВОСТІ НЕАЛКОГОЛЬНОГО СТЕАТОГЕПАТИТА ЗА КОМОРБІДНОСТІ ІЗ ХРОНІЧНОЮ ХВОРОБОЮ НИРОК ТА ОЖИРІННЯМ

Антонів А. А.

Резюме. У статті наведено теоретичне узагальнення клінічного дослідження особливостей перебігу неалкогольного стеатогепатиту за коморбідності з ожирінням та хронічної хвороби нирок I-II стадії, який характеризується вищою частотою та інтенсивністю клінічних та біохімічних синдромів. Для коморбідного перебігу неалкогольного стеатогепатиту із хронічною хворобою нирок характерний вищий ступінь стеатозу печінки, ніж у хворих на неалкогольний стеатогепатит (p<0,05) та вищий діагностичний поріг значень гепаторенального індексу, який у сильній взаємозалежності корелює із показником Steato-test (p<0,001).

Ключові слова: неалкогольний стеатогепатит, хронічна хвороба нирок, ожиріння, клінічні синдроми, стеатоз печінки.

КЛИНИЧЕСКИЕ И ПАТОГЕНЕТИЧЕСКИЕ ОСОБЕННОСТИ НЕАЛКОГОЛЬНОГО СТЕАТОГЕПАТИТА ПРИ КОМОРБИДНОСТИ С ХРОНИЧЕСКОЙ БОЛЕЗНЬЮ ПОЧЕК И ОЖИРЕНИЕМ

Антонив А. А.

Резюме. В статье приведено теоретическое обобщение клинического исследования особенностей течения неалкогольного стеатогепатита при коморбидности с ожирением и хронической болезнью почек I-II стадии, характеризующейся высокой частотой и интенсивностью клинических и биохимических синдромов. При коморбидности течения неалкогольного стеатогепатита с хронической болезнью почек характерен более высокий степень стеатоза печени, чем у больных с неалкогольным стеатогепатитом (p <0,05) и выше диагностический порог значений гепаторенального индекса, который в сильной взаимозависимости коррелирует с показателем Steato-test (p <0,001).

Ключевые слова: неалкогольный стеатогепатит, хроническая болезнь почек, ожирение, клинические синдромы, стеатоз печени.

CLINICAL AND PATHOGENETIC FEATURES OF NONALCOHOLIC STEATOHEPATITIS FOR COMORBIDITY WITH CHRONIC KIDNEY DISEASE AND OBESITY

Antoniv A. A.

Abstract. *The purpose of our study* was to study the changes in the functional state of the liver in patients with non-alcoholic steatohepatitis in combination with chronic kidney disease and obesity.

Object and methods of research. 140 patients with NASH were examined: 68 patients with NASH and obesity of the I degree (group 1) and 72 patients with NASH and comorbid obesity of the I degree and CKD of the I-II stages (group 2). To determine the dependence of the NASH course on the presence of CKD, the group of patients was randomized according to age, sex, degree of obesity.

Results of research and their discussion. The article deals with the theoretical generalization of the clinical study of non-alcoholic steatohepatitis peculiarities in comorbidity with obesity and CKD of the I-III stage, characterized by higher frequency and intensity of clinical and biochemical syndromes, the manifestation of which is likely to increase with the occurrence of secondary arterial hypertension (portal hypertension syndromes, cholestasis, mesenchymal inflammation).

Conclusion. Comorbid course of NASH with CKD is characterized by higher degree of liver steatosis compared with that in patients with NASH (p<0.05) and higher diagnostic threshold of the hepatorenal index values, which correlates with the Steato-test index (p<0.001) with strong interdependence.

Key words: non-alcoholic steatohepatitis, chronic kidney disease, obesity, clinical syndromes, liver steatosis.

Рецензент – проф. Костенко В. О.

Стаття надійшла 08.07.2018 року