УДК 616.36-003.826:616.12-008.331.1]-056.527-036.1-092
DOI 10.11603/1811-2471.2023.v.i2.13825

THE MAIN CLINICAL AND PATHOGENETIC FEATURES OF THE COMORBID COURSE OF NON-ALCOHOLIC STEATOHEPATITIS, OBESITY AND HYPERTENSION

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SUMMARY. The incidence of nonalcoholic steatohepatitis (NASH) in the population is 20–40 %, in obese patients – 50–90 %. The presence of NASH significantly reduces the quality of life of patients. The presence of concomitant arterial hypertension in patients can cause a cascade of reactions of mutual burdens, which will lead to the progression of all comorbid diseases.

The aim – to investigate the differences between clinical and laboratory parameters in the comorbid course of NASH on the background of obesity. In addition, we studied the state of hepatic circulation and the functional state of the endothelium depending on the presence of comorbid hypertension.

Material and Methods. Systematic review with further analysis, comparison, systematization and generalization of scientific literature in MEDLINE, Cochrane and PubMed databases of relevant articles on the study of psychological characteristics of women of childbearing age diagnosed with psychogenic infertility.

Results. In recent years, NASH has increasingly been seen as an additional independent risk factor for cardiovascular disease and a predictor of its complications. The course of NASH under conditions of comorbidity with obesity in comparison with the isolated course is characterized by a predominance of hypertension of II degree (60.0 %), increased variability of systolic blood pressure (SBP) during the day with increasing duration of "pressure load" during the day. The comorbid course of NASH with obesity and hypertension (HT) there is a significant activation of the processes of liver tissue fibrosis, the content of protein-bound oxyproline in the blood, fibronectin, hexosamines, sialic acids, fucose, not bound to protein due to the activation of fibroblast growth factor, in response to which there is usually inadequate compensatory activation of collagenolysis (increase in the content of free oxyproline in the blood, which was inhibited by excessively activated proteinase-inhibitory system).

Conclusions. The comorbidity of NASH with HT and obesity is a powerful pathogenetic factor that worsens the quality of life of patients to a much greater extent than the severity of a single disease. It's crucial to have multidisciplinary approach in the treatment of people with comorbidity of HT with NASH on the background of obesity.

KEY WORDS: non-alcoholic steatohepatitis; obesity; hypertension; metabolic syndrome.

Introduction. Obesity is the most common endocrine pathology, occurring in an average of 80 % of patients with endocrine pathology and 15–40 % of the adult population in Europe and America. In addition, the WHO considers the prevalence of obesity as an epidemic. Among the complications of obesity non-alcoholic steatohepatitis (NASH) is important because its occurrence significantly reduces the quality of life of patients, contributes to the progression of impaired glucose tolerance, disorders of all types of metabolism, the development of hepatocellular insufficiency. The incidence of NASH in the population is 20–40 %, in obese patients – 50–90 %. The comorbid course of NASH in patients with obesity and hypertension (HT) is characterized by a cascade of burdening reactions that lead to the progression of all concomitant diseases. Against the background of obesity progresses metabolic syndrome (MS) with metabolic intoxication, dys- and hyperlipidemia, accumulation of neutral fat in the liver parenchyma, which activates the system of proinflammatory cytokines with accelerated cell apoptosis, formation of aseptic inflammation, necrocytic steatosis tissue with progression of liver fibrosis. Dysmetabolic changes, oxidative stress, endogenous intoxication contribute to the development of endothelial dysfunction (ED), decreased sensitivity of receptors to vasodilators and increased sensitivity to vasoconstrictors, while reducing their hydrolysis in the liver affected by steatohepatitis, which may contribute to the development of hypertension and lead to damage to target organs with the subsequent development of their dysfunction. On the other side, the complex of the above factors contributes to impaired blood flow, hyperaggregation of blood cells, which also leads to microcirculatory disorders in all organs and systems, including those involved in the regulation of blood pressure. Under conditions of background MS and HT, the course of NASH is accompanied by increased blood pressure on the circulatory system of the liver due to an increase in arterial quota of sinusoidal circulation and hypercoagulable syndrome, resulting in the development of initial manifestations of portal hypertension before liver cirrhosis. Given the high level of disability and mortality due to the development of coronary and cerebral atherosclerosis, the wide range of complications of hypertension, which are often fatal for such patients and the fact that with adequate treatment these changes are reversible, and at the same time, conventional treatments do not always approach to the problem and not always effective,

the study of the interaction of these diseases in their comorbid course and the practical application of the results obtained with each passing year is becoming increasingly important.

The aim – to investigate the differences between clinical and laboratory parameters in the comorbid course of NASH on the background of obesity, as well as the state of hepatic circulation, the functional state of the endothelium and their changes depending on the presence of comorbid hypertension.

Material and Methods. Systematic review with further analysis, synthesis, comparison, systematization and generalization of scientific literature in MEDLINE, Cochrane and PubMed databases of relevant articles on the study of psychological characteristics of women of childbearing age diagnosed with psychogenic infertility.

Results and Discussion. NASH is often associated with concomitant diseases such as obesity, hypertension, metabolic syndrome, dyslipidemia, or diabetes. Although NASH is very common in overweight individuals (body mass index ≥25 kg / m2), recent studies indicate the presence of NASH in non-obese individuals (<25 kg / m2) too [1]. In the United States, the number of NASH cases is projected to increase from 83.1 million in 2015 to 100.9 million in 2030 in adults during this interval [3]. Globally, the prevalence of NASH is estimated at about 25 % and is highest in the Middle East and South America, and lowest in Africa [4]. While NAST is commonly associated with central obesity in North America and Europe (~ 83 % of patients), in Asia a significant percentage of patients have a normal body mass index (BMI), even if BMI, the threshold for overweight in Asia (BMI>23) is lower than in North America and Europe (BMI>25) [5].

In recent years, NASH has increasingly been seen as an additional independent risk factor for cardiovascular disease and a predictor of its complications. In fact, liver disease is only the third leading cause of death in patients with NASH, after cardiovascular disease and cancer(cardiovascular disease is the most common cause of death in 48 % of patients, while diseases associated with liver damage are fatal in 7 % of patients. This is largely associated with common risk factors. Old age, as well as concomitant metabolic diseases, increase the frequency and severity of NASH. Steatosis, a hallmark of the disease, occurs when the rate of absorption of liver fatty acids from plasma and de novo synthesis of fatty acids exceeds the rate of oxidation and export of fatty acids (as triglycerides within VLDL). Hence, excessive amounts of intrahepatic triglyceride represent an imbalance between complex interactions of metabolic processes. Excess intrahepatic triglyceride (IHTG) or steatosis is chemically defined as an IHTG content >5 % of liver volume or liver weight, or histologically determined when 5 % or more of hepatocytes contain visible intracellular triglycerides (TG). The presence of steatosis is associated with a number of adverse changes in the metabolism of glucose, fatty acids and lipoproteins. Disorders of fatty acid metabolism in combination with adipose tissue, liver and systemic inflammation are likely to be key factors involved in the development of insulin resistance, dyslipidemia and other cardiometabolic risk factors associated with NASH. The course of NASH in comorbidity with obesity and hypertension is characterized by a significantly higher, compared with the course without comorbidity, the incidence and intensity of clinical syndromes, the degree of biochemical and histological activity, the degree of steatosis ballooning degeneration and hyaline-droplet dystrophy in the liver with a predominance of F2-F3 stages of fibrosis.

The course of NASH under conditions of comorbidity with obesity in comparison with the isolated course is characterized by a predominance of hypertension of II degree (60.0 %), predominant increase in systolic blood pressure (SBP) at night, increased variability of SBP during the day with increasing duration of "pressure load" during the day (4.1 time ($p<0.05$)), monotonous type of curve and inadequate reduction of systolic and diastolic blood pressure at night (predominant type "non-dipper"), tachycardia, accompanied by a hyperkinetic type of hepatic circulation with a probable increase in the diameter of the portal vein and congestive index, decrease in the linear velocity of blood flow through the portal vein, the portal-splenic venous index, which indicates an increase in resistance in the portal vein system and the redistribution of venous blood flow through the splenic vein. Systemic HT promotes an increase in the linear velocity of blood flow in the system of the common hepatic artery, an increase in the arterial quota of sinusoidal circulation. In the comorbid course of NASH with HT and obesity in comparison with the course of NASH without HT, a higher intensity of endothelial dysfunction was found (decrease in endothelium-dependent vasodilation of the brachial artery, decrease in the ratio of nitrogen monoxide and endothelium-1 in the blood due to an increase in thrombocytopenia with compensatory increase in their aggregation) and decreased activity of enzymatic fibrinolysis factors, which is interrelated with HT, decreased circulatory circulation, nitrositive stress [8].

The presence and stage of fibrosis is the clearest histological determinant of outcome in patients with NASH, but steatohepatitis is undoubtedly the driving force behind the development of fibrosis. Although the association between fibrosis and outcome is strong, there is significant collinearity between the presence of NASH and the severity of fibrosis. On ave-

rage, people diagnosed with NASH progress by one stage of fibrosis every 7 years. Overall, ~ 20 % of patients progress rapidly to severe fibrosis. Accumulation of extracellular matrix in the liver, which leads to progressive fibrosis, cirrhosis, portal hypertension, and liver failure, is the leading cause of liver-related death in patients with NASH. Fibrogenesis is driven by signaling from stressed or damaged hepatocytes and activated macrophages, which results in the activation of resident hepatic stellate cells in myofibroblasts to produce matrix proteins faster than they degrade. NASH-specific fibrogenic pathways are becoming more common [9]. Fibrosis in the liver occurs due to the activation of collagen synthesis by sinusoidal stellate Ito cells, against the background of relatively low intensity of collagen degradation by the system of matrix metalloproteinases. The degree of development of fibrotic changes in patients with NASH with comorbid HT and obesity exceeds those in groups of patients with NASH without HT. After analyzing the biochemical index of fibrosis (BIF) and markers of the main biochemical syndromes of NASH, it is obvious that there is a probable direct correlation between BIF and ALT and ALP activity, bile acid content in the blood. The intensity of fibrosing reactions in patients with NASH, which developed on the background of obesity, depends on the activity of the cytolytic syndrome and cholestasis. With the progression of the stage of fibrosis, the detoxification function of the liver decreases. The development of portal hypertension is one of the important links in the progression of NASH and decompensation of liver function, which is causally associated with diffuse fibrosis of liver tissue. Therefore, in the comorbid course of NASH with obesity and HT there is a significant activation of the processes of liver tissue fibrosis (increase in the index of liver fibrosis (2.5 times, $p<0.05$), the content of protein-bound oxyproline in the blood (2.0 times, $p<0.05$), fibronectin (1.6 times, $p<0.05$), hexosamines (1.4 times, $p<0.05$), sialic acids (1.5 times, $p<0.05$), fucose, not bound to protein (2.5 times, $p<0.05$)) due to the activation of fibroblast growth factor (3.0 times, $p<0,05$), in response to which there is usually inadequate compensatory activation of collagenolysis (increase in the content of free oxyproline in the blood (1.5 times, $p<0.05$), which was inhibited by excessively activated proteinase-inhibitory system (increase in blood content of α2-macroglobulin (2.9 times, $p<0.05$)) ($p<0.05$). In patients with NASH, which arose on the background of obesity, a significant increase in the synthesis of collagen and glycosaminoglycans, accompanied by inefficient resorption of newly formed collagen due to low levels of collagenolytic activity of blood plasma, resulting from activation of proteinase inhibitors, under conditions of concomitant HT, leads to progressive liver fibrosis and dysfunction [8].

The presence of metabolic syndrome (MetS) in people is the strongest risk factor for NASH. MetS syndrome is defined in different ways, but usually includes an increase in waist circumference (obesity), hyperglycemia, dyslipidemia, and systemic HT. The interconnection between NASH and MetS features may be bi-directional, especially especially regarding to diabetes and HT, which means that not only does MetS increase the risk of NASH, but NASH can also exacerbate some of the features and comorbidities of MetS. Thus, effective treatment of NASH may have the additional benefit of improving the properties of MetS. MetS is also an important factor in adverse cardiovascular problems and overall mortality in patients with NASH [10].

For the course of NASH on the background of HT and MetS in comparison with the course of NASH without HT is characterized by a predominance of the intensity of metabolic intoxication (increase in blood content of medium molecular weight peptides (1.5 times, $p<0.05$), malonic aldehyde (1.8 times, $p<0.05$), isolated double bonds in compounds (1.9 times), $p<0,05$) against the background of reduced activity of detoxification components and imbalance of antiradical protection factors (reduction of erythrocyte content of reduced glutathione (1.4 times, $p<0.05$), glutathione peroxidase activity (1.3 times, $p<0.05$), arginase (5.9 times, $p<0.05$), erythrocyte peroxide resistance (1.9 times, $p<0.05$), compensatory activation of catalase (1.5 times, $p<0.05$)) [8].

Conclusions. Thus, the comorbidity of NASH with HT and obesity is a powerful pathogenetic factor of mutual burden due to increasing oxidative stress, metabolic intoxication, inhibition of redox and detoxification systems, which leads to the activation of the universal mechanism of cell membrane damage due to oxidative-antioxidant imbalance, inhibits the ability of the liver and erythrocytes to resist free radical effects under conditions of metabolic syndrome. Based on the comparison of the studied material, it can be concluded that the mutual influence of NASH with obesity potentiates the negative impact of each other on the quality of life in patients with hypertension. It is the combination of nosological conditions that worsens the quality of life of patients to a much greater extent than the severity of a single disease.

Prospects of further research. Therefore, the above data indicates the necessity for a multidisciplinary approach in the treatment of people with comorbidity, and a comprehensive diagnosis of patients with HT with NASH on the background of obesity requires an assessment of quality of life, and the ability to identify the most important predictors of favorable/unfavorable course, to predict possible complications at the beginning of treatment becomes especially relevant.

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ОСНОВНІ КЛІНІЧНІ ТА ПАТОГЕНЕТИЧНІ ОСОБЛИВОСТІ КОМОРБІДНОГО ПЕРЕБІГУ НЕАЛКОГОЛЬНОГО СТЕАТОГЕПАТИТУ, ОЖИРІННЯ ТА ГІПЕРТЕНЗІЇ

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Вищий навчальний заклад «Буковинський державний медичний університет», Чернівці

РЕЗЮМЕ. Захворюваність на неалкогольний стеатогепатит (НАСГ) у популяції становить 20–40 %, у хворих на ожиріння – 50–90 %. Наявність у пацієнтів НАСГ значно знижує рівень їх життя, викликаючи розвиток глюкозотолерантності, розладів метаболізму та виникнення гепатоцелюлярної недостатності. Наявність у пацієнтів супутньої артеріальної гіпертензії може спричинити каскад реакцій взаємообтяжень, що призведе до прогресування всіх коморбідних захворювань.

Огляди літератури, ***оригінальні дослідження****, погляд на проблему, випадок з практики, короткі повідомлення*

Мета дослідження – вивчити відмінності клініко-лабораторних показників при коморбідному перебігу неалкогольного стеатогепатиту на фоні ожиріння. Крім того, ми вивчали стан печінкового кровообігу та функціональний стан ендотелію залежно від наявності супутньої гіпертензії.

Матеріал і методи. Систематичний огляд з подальшим аналізом, порівнянням, систематизацією та узагальненням наукової літератури з баз даних MEDLINE, Cochrane та PubMed відповідних статей з вивчення психологічних особливостей жінок дітородного віку з діагнозом психогенне безпліддя.

Результати. В останні роки НАСГ все частіше розглядається як додатковий незалежний фактор ризику серцево-судинних захворювань і предиктор їх ускладнень. Перебіг НАСГ за умов коморбідності з ожирінням, порівняно з ізольованим перебігом, характеризується переважанням гіпертонічної хвороби II ступеня (60,0%), підвищенням варіабельності систолічного артеріального тиску (САТ) протягом доби із збільшенням тривалості періодів навантаження тиском протягом доби. При коморбідному перебігу НАСГ з ожирінням і гіпертензією спостерігається значна активація процесів фіброзу печінкової тканини, вміст у крові білковозв'язаного оксипроліну, фібронектину, гексозамінів, сіалових кислот, фукози, не зв'язаної з білком за рахунок активації фактора росту фібробластів, у відповідь на які зазвичай відбувається неадекватна компенсаторна активація колагенолізу (підвищення вмісту в крові вільного оксипроліну, який пригнічувався надмірно активованою протеїназо-інгібіторною системою).

Висновки. Коморбідність НАСГ з гіпертензією та ожирінням є сильним патогенетичним фактором, що погіршує якість життя пацієнтів значно більшою мірою, ніж тяжкість окремого захворювання. Важливо використовувати мультидисциплінарний підхід до лікування осіб з коморбідністю гіпертензії та НАСГ на фоні ожиріння.

КЛЮЧОВІ СЛОВА: неалкогольний стеатогепатит; ожиріння; гіпертензія; метаболічний синдром.

Отримано 15.05.2023

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