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FEATURES OF THE COLON MICROBIOCENOSIS IN PATIENTS WITH NONALCOHOLIC STEATOHEPATITIS DEPENDING ON THE PRESENCE OF CHRONIC KIDNEY DISEASE

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Key words: *nonalcoholic steatohepatitis, chronic kidney disease, microbiocenosis of the large intestine.*

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The purpose of the study*: to establish the features of the of colon cavity (CC) microbial state in patients with non-alcoholic steatohepatitis (NASH) with obesity, depending on the presence of comorbid chronic kidney disease (CKD) and its stages.*

Material and methods. *168 patients with NASH from 42 to 55 years of age were examined. All patients were distributed as follows. Group 1 consisted of 68 patients with NASH and obesity of 1st degree. Group 2 consisted of 100 patients with NASH and obesity of 1st degree with a comorbid CKD I-III stages (chronic pyelonephritis). We examined 30 practically healthy persons (PHPs), which by age and sex were not statistically significantly different from the main group and the comparison group. Microbiocenosis of CC was studied by microbiological method by sowing ten-fold dilutions of feces on differential-diagnostic nutrient media in accordance with the methodological recommendations "Microbiological diagnosis of dysbiosis" of the Ministry of Health of the USSR (1986).*

Results. *The study revealed changes in the microbial cavity content of the colon (CC) during the comorbid flow of NASH with obesity and the CKD I-III stages, characterized by the development of deep dysbiosis (II-III degree) With the appearance and prevalence of pathogenic microflora, an increase in the number of opportunistic bacteria and yeast fungi of the genus Candida, a probable deficiency of representatives of normal microbiota: lactobacilli, bifidobacteria, bacteroids.*

Conclusion. *It is established that one of the components of the pathogenesis of nonalcoholic steatohepatitis in patients with obesity and chronic kidney disease is metabolic intoxication, which arises as a result of a significant violation of the quantitative and qualitative composition of the microflora of the microbial cavity of the colon with the development of deep dysbiosis.*

Ключові слова: *неалкогольний стеатогепатит, хронічна хвороба нирок, мікробіоциноз товстої кишки.*

Клінічна та експериментальна патологія Т.17, №3 (65), С.03-08.

ОСОБЛИВОСТІ СТАНУ МІКРОБІОЦИНОЗУ ТОВСТОЇ КИШКИ У ХВОРИХ НА НЕАЛКОГОЛЬНИЙ СТЕАТОГЕПАТИТ ЗАЛЕЖНО ВІД НАЯВНОСТІ ХРОНІЧНОЇ ХВОРОБИ НИРОК

А.А. Антонів

Мета роботи *- встановити особливості стану мікробіому порожнинного вмісту товстої кишки у хворих на неалкогольний стеатогепатит (НАСГ) із ожирінням залежно від наявності коморбідної хронічною хворобою нирок (ХХН) та її стадії.*

Матеріал та методи. *Обстежено 168 хворих на НАСГ віком від 42 до 55 років. Усі хворі були розподілені наступним чином. Групу 1 утворили пацієнти із НАСГ із супутнім ожирінням I ступеня у кількості 68 осіб. Групу 2 склали хворі на НАСГ із ожирінням I ступеня із коморбідною ХХН I-III ст. (хронічний пієлонефрит) у кількості 100 осіб. Обстежено 30 практично здорових осіб (ПЗО), які за віком та статтю статистично достовірно не відрізнялись від основної групи та групи порівняння. Мікробіоценоз ПВТК вивчали мікробіологічним методом шляхом засіву десятикратних розведень випорожнень на диференційно-діагностичні живильні середовища згідно з методичними рекомендаціями "Микробилогическая диагностика дисбактериозов" МОЗ УРСР (1986).*

Результати. *Дослідження показало зміни стану мікробіому порожнинного вмісту товстої кишки (ПВТК) за коморбідного перебігу НАСГ з ожирінням та ХХН I-III ст., який характеризується розвитком глибокого дисбіозу (II-III ст.) із появою і переважанням патогенної мікрофлори, зростанням кількості умовно патогенних бактерій і дріжджових грибків роду Candida, вірогідним дефіцитом представників нормальної мікробіоти: лактобактерій, біфідобактерій, бактероїдів.*

Висновки. *Встановлено, що одним із компонентів патогенезу неалкогольного стеатогепатиту у хворих на ожиріння та хронічної хвороби нирок є метаболічна інтоксикація, яка виникає внаслідок істотного порушення кількісного та якісного складу мікрофлори стану мікробіому порожнинного вмісту товстої кишки із розвитком глибокого дисбіозу.*

Ключевые слова: *неалкогольный стеатогепатит, хроническая болезнь почек, микробиоциноза толстой кишки.*

Клиническая и экспериментальная патология Т.17, №3 (65), С.03-08.

ОСОБЕННОСТИ СОСТОЯНИЯ МИКРОБИОЦИНОЗА ТОЛСТОЙ КИШКИ БОЛЬНЫХ НА НЕАЛКОГОЛЬНИЙ СТЕАТОГЕПАТИТ В ЗАВИСИМОСТИ ОТ НАЛИЧИЯ ХРОНИЧЕСКОЙ БОЛЕЗНЬИ ПОЧЕК

А.А. Антонив

Цель работы *- установить особенности состояния микробиома полостного содержимого толстой кишки у больных на неалкогольный стеатогепатит (НАСГ) с ожирением в зависимости от наличия коморбидной хронической болезнью почек (ХБП) и ее стадии.*

Материал и методы*. Обследовано 168 больных НАСГ в возрасте от 42 до 55 лет. Все больные были распределены следующим образом. Группу 1 составили пациенты с НАСГ с сопутствующим ожирением I степени в количестве 68 человек. Групу 2 составили больные НАСГ с ожирением I степени с коморбидной ХБП I-III ст. (Хронический пиелонефрит) в количестве 100 человек. Обследовано 30 практически здоровых лиц, которые по возрасту и полу статистически достоверно не отличались от основной группы и группы сравнения. Микробиоценоз ПВТК изучали микробиологическим методом путем посева десятикратных разведенных стула на дифференциально-диагностические питательные среды в соответствии с методическими рекомендациями "Микробилогическая диагностика дисбактериозов" МЗ УССР (1986).*

Результаты. *Исследование показало изменения состояния микробиома полостного содержимого толстой кишки (ПВТК) за коморбидного течении НАСГ с ожирением и ХБП I-III ст., который характеризуется развитием глубокого дисбиоза (II-III вв.) с появлением и преобладанием патогенной микрофлоры, ростом количества условно-патогенных бактерий и дрожжевых грибков рода Candida, вероятным дефицитом представителей нормальной микробиоты: лактобактерий, бифидобактерий, бактероидов.*

Выводы*. Установлено, что одним из компонентов патогенеза неалкогольного стеатогепатита у больных ожирением и хронической болезни почек является метаболическая интоксикация, возникающая вследствие существенного нарушения количественного и качественного состава микрофлоры состояния микробиома полостного содержимого толстой кишки с развитием глубокого дисбиоза.*

Introduction

The comorbidity of non-alcoholic steatohepatitis (NASH) and chronic kidney disease (CKD) on the background of obesity is often recently drawn to the attention of both practitioners and researchers [1, 2, 4]. Recent developments in the field of internal medicine point to the significant role of the violation of the quantitative and qualitative composition of the microbial cavity of the colon (CC) in the development of metabolic disorders (the exchange of bile acids, carbohydrates, lipids, oxidative-reduction reactions), endogenous intoxication syndrome, obesity pathogenesis [13, 14] and non-alcoholic fatty liver disease (NAFLD). More and more researchers admit that the microbe increases the propensity to develop nonalcoholic steatohepatitis (NASH) and transform it into cirrhosis of the liver [4, 11, 12]. As the portal system of the liver receives venous blood mainly from the large intestine, in the first place, the liver is exposed to the microorganisms and products of their vital functions [4]. In violation of digestive processes, the permeability of the intestinal wall increases and a possible bacterial translocation can cause chronic inflammation and fibrosis of the liver [9, 10].

The presence of dysbiosis in CC can have a negative effect on the urinary system and, in particular, on the course of chronic kidney disease (CKD) (chronic pyelonephritis) in patients with NASH, where contamination of pathogenic microflora in the CC can become a source of endogenous infection and inflammation of the cup-bowl system and parenchyma of kidneys [2, 3], and repeated courses of antibacterial drugs and uroseptics lead to the emergence and progression of CC dysbiosis, and may have negative hepatotoxic effects. These circumstances determine the feasibility of conducting research in this direction.

The purpose of the study: to establish the features of the microbial state of the colon cavity in patients with NASH with obesity, depending on the presence of a comorbid CKD and its stages.

Material and methods of research

168 patients with NASH, 42 to 55 years of age were examined. All patients were distributed as follows. Group 1 consisted of 68 patients with NASH and obesity of 1st degree. Group 2 consisted of 100 patients with NASH and obesity of 1st degree with a comorbid CKD I-III stages (chronic pyelonephritis). 30 practically healthy persons (PHP) were examined, which by age and sex were not statistically significantly different from the main group and the comparison group. The diagnosis of NASH was established in accordance with the unified clinical protocol, approved by the order of the Ministry of Health of Ukraine No. 826 from 06.11.2014, in the presence of criteria for the exclusion of chronic diffuse liver disease of the viral, hereditary, autoimmune or medicinal genesis as causes of cholestatic or cytolytic syndromes, as well as

the results of the USG survey. Diagnosis and treatment of CKD were performed according to the recommendations of the clinical guidelines of the State Institute "Institute of Nephrology, NAMS of Ukraine" (2012) [3]. The study included patients with CKD stage I-III without a nephrotic syndrome with chronic uncomplicated pyelonephritis in the phase of stiffening of exacerbation or with a latent course.

When the patients were admitted to the hospital, markers of liver parenchyma damage were determined according to the generally accepted list of enzymes (alanine aminotransferase, aspartate aminotransferase, de Rhithis coefficient, gamma-glutamyltransferase, alkaline phosphatase), bilirubin content in the blood; markers of the functional state of the liver (albumin content, bilirubin fractions, prothrombin time), functional renal states (blood creatinine, cystatin, urea, glomerular filtration rate), lipidograms, ionograms, glycemic blood profiles, indexes of insulin resistance. Microbiocenosis of CC was studied by microbiological method by sowing ten-fold dilutions of feces on differential-diagnostic nutrient media in accordance with the methodological recommendations "Microbiological diagnosis of dysbiosis" of the Ministry of Health of the USSR (1986). The main markers allowed to make conclusions about dysbiotic changes were: the type of belonging of aerobes and anaerobes, quantitative characteristic (concentration) and the frequency of growth of sown colonies. Verification of the severity of dysbiosis was carried out on the basis of the classification of I. B. Kuvaevo, K. S. Ladodo (1991) [7].

The statistical analysis of the results was carried out in accordance with the type of research carried out and the types of numerical data that were obtained. Distribution normality was verified using Liliefors, Shapiro-Uilka tests and the direct visual evaluation of eigenvalues distribution histograms. Quantitative indices having a normal distribution are represented as mean (M) ± standard deviation (S). In a nonparametric distribution, the data is presented as median (Me) as position, upper (Q75) and lower quartile (Q25) as a measure of scattering. Discrete values are presented in the form of absolute and relative frequencies (percentage of observations to the total number of surveyed). For comparisons of data that had a normal distribution pattern, parametric tests were used to estimate the Student's t-criterion, Fisher's F-criterion. In the case of abnormal distribution, the median test, Mann-Whitney Rank U-Score, and Wilcox's T-criterion (in the case of dependent groups) were used for multiple comparison. To measure the relationship between variables, Pearson's correlation analysis using parametric distribution and the Spirman rank correlation coefficient were used in the case of a distribution of indicators that significantly differed from the normal one. To compare discrete values in independent groups, the criterion $\chi 2$ of maximum probability (log-likelihood) (MP $\chi 2$) was used; for calculating the pairs of discrete values, the calculation of the modification of Fisher's exact criterion (mid-p) was used. To predict the course of NASH and CKD, the determination of the diagnostic significance of the indicators used the ROC-analysis with the calculation of the area, limited by the ROC curve (AUC). 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 and their discussion

In clinical analysis, it was found that in patients in 2nd group the incidence of symptoms of intestinal dyspepsia increased with the progression of dysbiotic changes in the CC and was greater compared to those in patients in 1st group. Thus, defecation disorders with predominance of diarrhea in patients of the 2nd group were observed in 47.0% versus 26.5% ($p < 0.05$) in 1st group; the frequency of abdominal distension was also significantly different: 73.0% vs. 35.3% ($p < 0.05$), respectively. Such a clinical picture of NASH with CKD can be explained by the deepening of CC dysbiosis.

The data of microbiological examination of excrement indicate that the main signs of dysbiosis in this cohort of patients is a marked decrease in obligatory autochthonous microorganisms: bifidobacteria, lactobacilli, bacteroids (Table 1), and an increase in the frequency of sowing conditionally pathogenic and pathogenic types of microbial associations - the appearance of Escherichia with hemolytic properties , pathogenic strains of staphylococci, sulfide-reducing clostridia, and fungi of the genus Candida.

In particular, in patients of 1st group, the number of bifidobacteria was 1.8 times lower ($P < 0,05$), and in patients of 2nd group - 2.3 times ($p < 0.05$) with the presence of intergroup difference, which indicates that the number of representatives of autochthonous microbiota in patients with NASH on the background of CKD is 1.3 times less than that of patients with NASH. Similar changes were also observed in relation to the quantitative indices of lactobacilli in the groups of patients with NASH: in patients of 1st group the number of lactobacilli was lower than the index in PHPs in 2,0 times ($p < 0,05$), and in patients of 2nd group - in 2,9 times ($p < 0,05$) with the presence of intergroup difference (Table 1). In 1st group patients with NASH, the number of bacteroids was 1.5 times lower than that of PHPs ($p < 0,05$), and in patients with 2nd group - 2,0 times ($p < 0,05$) with the presence of intergroup difference.

Thus, there was a probable decrease in the number of autochthonous microbiota with an increase in the number of comorbid diseases. Instead, the number of colonies of conditionally pathogenic bacteria and fungi in feces increased significantly with comorbidity with CKD. In particular, the number of peptococci in patients in 1st group was 1.5 times higher than in the PHP ($p < 0,05$), and in 2nd group patients - 1,8 times ($p < 0,05$) with the presence of intergroup difference (Table 1). The number of sulfide-reducing clostridia, representative of the putrefactive microbiota also significantly increased in comparison with the PHP: in group 1 - in 1,5 times ($p < 0,05$), and in patients in 2nd group - 1,7 times ($p < 0,05$) with the presence of intergroup differences, which explains the presence of flatulence and weakening of the feces in patients with NASH. Also, in our opinion, an analysis of the ratio of the

Table 1

Condition of microbiocenosis of the colon cavity in patients with non-alcoholic steatohepatitis depending on the presence of CKD (lg NCU/g; M ± m)

Microorganisms	PHP, n=30	GROUP 1, n=68	GROUP 2, n=100
Bifidobacteria	9,8±0,09	5,6±0,10*	4,2±0,05*/**
Bacteroids	9,4±0,20	6,4±0,17*	4,7±0,12*/**
Lactobacillus	9,1±0,10	4,5±0,05*	3,1±0,06*/**
Peptococci	5,3±0,28	8,2±0,09*	9,3±0,10*/**
Clostridium sulfide reducing	5,4±0,48	7,9±0,12*	9,1±0,10*/**
Escherichia (N)	3,5±0,08	7,8±0,04*	8,9±0,08*/**
Staphylococci	0	7,4±0,02*	8,6±0,01*/**
Fungi of the genus Candida	0	6,3±0,05 *	8,7±0,03 */**
Enterobacter	0	7,6±0,15*	8,5±0,14*/**
Escherichia (hemolysis +)	0	7,1±0,10*	8,7±0,12*/**
Zitrobakter	0	8,0±0,03*	9,5±0,05*/**
Serrations	0	6,4±0,04*	8,1±0,05*/**
Hafnium	0	7,1±0,06*	9,6±0,05*/**
Prevotes	0	6,2±0,04*	7,8±0,07*/**

Note. * - the difference is probable in comparison with the index in PHP ($p < 0,05$);
** - the difference is probable compared with the indicator in patients in group 1 ($p < 0,05$).

representative of the autochthonous microbiota of the colon, in particular, bifidobacteria, and the representative of the conditionally pathogenic flora - clostridia (B/C), depending on the comorbidity with the CKD, was also important. Thus, the average value of the coefficient B/C in the PHPs was 1.81, in patients of 1st group - 0.71, and in patients of 2nd group - 0.46 ($p < 0.05$).

In addition, it was found that in patients with NASH, with the growth of the stage of CKD, the degree of violation of the microecology of CC was increased (Table 2).

Consequently, the maximum number of patients with NASH with the CKD 1st stage, had dysbiosis of 1st degree (42.5%), which in patients with CKD 2nd and 3rd stage was found to be 1.7 and 5.9 times less frequently ($p < 0.05$). The maximum number of patients with NASH and CKD 2nd stage, had dysbiosis of the 2nd degree (40.6%), which in patients with CKD 1st and 3rd was found 8.6% and 12.9% less ($p > 0.05$). At the same time, the maximum number of patients with NASH and CKD of the 3rd stage, had a dysbiosis of CC of the 3rd degree (57.1%), which in patients with CKD 1st and 2nd stage was found to be 2.9 and 1.7 times less frequently ($p < 0.05$).

Table 2

Degree of dysbiosis of the colon in patients with non-alcoholic steatohepatitis depending on the stage of CKD (%)

Dysbiosis degree / CKD stage	Stage I. CKD, (n=40)	Stage II. CKD (n=32)	Stage III. CKD (n=28)
I degree, %	42,5	25,0	7,2
II degree, %	37,5	40,6	35,7
III degree, %	20,0	34,4	57,1

Note: Data is presented as a percentage of the number of patients.

Conclusions

Thus, for the comorbid flow of non-alcoholic steatohepatitis in patients with obesity and chronic kidney disease, there is a significant violation of the quantitative and qualitative composition of the microflora of the colon cavity with the development of deep dysbiosis (II-III st.), Which is accompanied by the appearance and predominance of pathogenic ammonia, rotten microflora, growth of the number conditionally pathogenic bacteria and yeast fungi of the genus Candida, probable deficiency of representatives of normal microbiota: lactobacillus, bifidobacteria and bacteroids.

The prospect of further research in this direction is the development of methods for the prevention and correction of established changes in the microbiota of the cavity of the colon in patients with non-alcoholic stecohepatitis with comorbid obesity and chronic kidney disease.

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