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STRUCTURE OF ANAEMIC CONDITIONS COMORBID TO ALCOHOLIC AND NON-ALCOHOLIC STEATOHEPATITIS

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Abstract

The retrospective analysis of 378 medical records of inpatients with steatohepatitis (SH) depending on its etiology was performed to identify and study the type of anaemic conditions (AC). Among patients with SH of mixed (including alcoholic) etiology anaemia was found in 32.2% of cases, in patients with alcoholic (ASH) - in 36.3%, in patients with non-alcoholic SH (NASH) - in 22.0 % of cases. Macrocytic, hyperchromic anaemia prevailed in patients with anaemia of all groups: in patients with SH of mixed etiology - in 47.9%, in patients with ASH - 56.8%, NASH - 71.4%. Normocytic, normochromic anaemia was registered in 52.1% with mixed etiology of SH, in patients with ASH - 43.2%, NASH - 28.6%.

The prospective study of 125 patients with SH showed that anaemia was found in 40.0% of patients with ASH, among patients with SH of mixed (including alcoholic) etiology anaemia was found in 32.0%, among patients with NASH the result was 21.7%. The following types of anaemia were found in ASH: vitamin B12 - deficient - in 17.5% of cases, anaemia of chronic disease - in 10.0% of cases and Zieve's syndrome - in 12.5% of cases. Three types of anaemia were found in patients with SH of mixed etiology: vitamin B12 - deficient - in 16.0% of cases, anaemia of chronic disease - in 8.0% and Zieve's syndrome - in 8.0% of patients. The structure of anaemias in patients with NASH accompanied by obesity of I-II degrees is as follows: B12 - deficient anaemia - in 15.0% of cases, anaemia of chronic disease - in 6.7% of people. In patients with NASH, H. pylory contamination was present in 84.6% of patients with anaemic syndrome (AS), including 100% of patients with B12-deficient anaemia. With ASH, H. pylory contamination was present in 80.0% with anaemia, including 100% of patients with B12-deficient anaemia. In patients with SH of mixed etiology, H. pylory contamination was present in 100.0% of people with AS.

Key words: alcoholic steatohepatitis; non-alcoholic steatohepatitis; anaemia; H.pylory.

The topicality of the problem of comorbidity of steatohepatitis of alcoholic (ASH) and non-alcoholic etiology (NASH) with anaemic conditions (AC) and the need for their differentiated correction are determined by the significant frequency of ASH and NASH in the world and Ukraine and the presence of burdening syndrome [1, 5-9, 21, 22, 28]. Anaemia contributes to the progression of steatohepatitis of various etiologies to liver cirrhosis (LC), in which AC is often a manifestation of hypersplenism with the increased destruction of erythrocytes in the spleen, as well as frequent complications of LC by posthaemorrhagic anaemia with decreased venous iron stores, stomach, hemorrhoidal veins against the background of increasing the degree of portal hypertension against the background of reduced biosynthesis of coagulation factors by the liver [1-2, 5-6, 10-18, 23-26]. The causes of anaemia in LC may include impaired regulation of erythropoiesis (due to the decreased synthesis of erythropoietin by hepatocytes and kidneys on the background of hepato-renal syndrome at the terminal stage of LC), impaired synthesis of traspherin in hepatocytes, impaired iron accumulation [17, 22, 23, 24, 30-32]. Anaemia in alcoholic LC can be the result of colonic dysbiosis, maldigestion, malabsorption, vitamin B12 deficiency and other important nutrients involved in hematopoiesis, especially in cases of insufficiency of exocrine function of the pancreas in comorbid acidosis and alcoholic pancreatitis. food, the presence of

worm infestations, as well as contamination of H. pylori, which can cause atrophic gastritis and deficiency of Castle factor synthesis, etc. [1, 2, 18-20, 24, 29, 32-35]. In the pathogenesis of alcoholic LC and ASH there is a direct toxic lesion of the bone marrow with ethanol and its metabolic products [18, 20, 28]. However, the work on the results of a comprehensive study of the causes, structure of anaemic conditions on the background of steatohepatitis of various etiologies, is quite limited. According to Noskova KK et al., who studied the frequency and structure of AS in patients with chronic diffuse liver disease of various etiologies, anaemia was detected in 21.2% of cases [5]. In the category of patients with ASH anaemia was found in 19.7% of cases, with hepatitis of unknown etiology - in 16.5%, NASH - in 9.3%. Among patients with alcoholic liver cirrhosis (LC), anaemia was registered in 35% of cases, LC of mixed (alcoholic and viral) etiology - in 23.9%, with primary biliary cholangitis - in 19.7% of people [5]. Regarding the structure of anaemias depending on the colour index and size of erythrocytes, 60% of patients have normochromic, normocytic anaemia, 21% of patients - hypochromic, microcytic anaemia, 19% of patients - macrocytic hyperchromic anaemia [5]. At the same time, no other information on studies comparing the structure of AS depending on the etiology of steatohepatitis has been found in the available literature.

The aim of the study was to establish the frequency and structure of comorbid anaemic conditions depending on the etiology of steatohepatitis**.**

Material and methods of research. The retrospective analysis of 378 medical records of inpatients with steatohepatitis of alcoholic and nonalcoholic etiology, who were treated inpatiently in the gastroenterology department of Regional municipal noncommercial enterprise Chernivtsi emergency medical hospital (RMNCE Chernivtsi emergency medical hospital) within the period f the years 2015-2020 to determine the frequency of comorbid anaemic syndrome and its nature. Among 378 cases, the diagnosis of steatohepatitis of mixed (including alcoholic) etiology was established in 149 cases, ASH - in 102 patients, NASH - in 127 patients.

The open prospective study accompanied by the examination of 125 patients with steatohepatitis, including 60 on NASH against the background of obesity of I-II degrees and 65 patients with SH of alcoholic and mixed etiology (25 patients of mixed, including alcoholic) and 40 patients with ASH), 25 practically healthy individuals (PHIs) of the corresponding age and sex. The examinations were conducted in the gastroenterological and therapeutic departments of the RMNCE Chernivtsi emergency medical hospital in 2016-2020. Among the examined patients with NASH, there were 15 male patients (25.0%) and 45 female patients (75.0%). The mean age of the examined patients was (46.3 ± 5.2) years.

Among the examined patients with ASH, there were 56 male patients (86.2%) and 9 female patients (13.8%). The mean age of patients with ASH was (47.4 ± 5.1) years. The control group consisted of 25 practically healthy individuals (PHIs): male - 11 (44.0%) and female - 14 (56%). The mean age of PHIs was (41.3 ± 2.1) years. The diagnosis of NASH and ASH was established according to the unified clinical protocol approved by the order of the Ministry of Health of Ukraine № 826 from 06.11.2014, in the presence of the criteria for the exclusion of chronic diffuse liver disease of viral, hereditary, autoimmune or drug genesis as a cause of cytolytic, cholendoma-cholestatic-melestatic, as well as the results of ultrasonography (USG) of the liver with shear wave elastography, Steato-test, ASH-test, NASH-test, Fibro-test (BioRedictive, France). Additionally, in the diagnosis of steatohepatitis of alcoholic origin, anamnestic data on daily consumption of toxic doses of alcohol, consultation with a narcologist, the presence of records in the drug dispensary were taken into account [18].

The diagnosis of obesity was established according to the classification of the WHO International Working Group on Obesity (1997). Patients were measured for height and body weight, calculated body mass index (BMI) according to the Kettle formula (1):

BMI = weight (kg) / height2 (m) (1)

The diagnosis of obesity was established when the BMI value is more than 30 kg / m2.

The diagnosis of anaemia was established according to the unified clinical protocol of primary and secondary (specialized) medical care "Iron deficiency anaemia" (Order of the Ministry of Health of Ukraine of November 2, 2015 № 709), and the Order of the Ministry of Health of Ukraine of June 30, 2010 № 647 protocols for providing medical care to patients in the specialty "Haematology".

The number of erythrocytes was calculated by counting cells in the Goryaev chamber, hemoglobin was determined by haemoglobin cyanide method. The content of iron in blood plasma, ferritin, transferrin, unsaturated iron binding capacity (UIBC) was studied by the ferrosine method (LLC SPE "Philisit-Diagnostics", Ukraine). The transferrin saturation (TS) was also calculated (1).

TS = Iron/Transferrin × 3,9 (1) [8].

Normal plasma iron levels were 9.5 - 29.9 μmol / l, UIBC - 44.8-76.1 μmol / l, transferrin saturation - up to 30%.

The state of erythropoietin-synthesizing function of the kidneys was assessed by the level in the serum of erythropoietin. The latter was studied by enzyme-linked immunosorbent assay using a set of reagents Erythropoetin (EPO) manufactured by Biomerica (Russia). The range of 4.3 - 32.0 mO / ml for serum EPO was considered normal. The concentration of vitamin B12 in the serum was determined by enzyme-linked immunosorbent assay using a kit produced by DAI (USA).

Statistical analysis of the results was performed according to the type of study and the types of numerical data that were obtained. The normality of the distribution was checked using Liliefors, Shapiro-Wilk tests and the method of direct visual evaluation of histograms of the distribution of eigenvalues. Discrete values are presented in the form of absolute and relative frequencies (percentage of observations to the total number of subjects). For comparisons of data that had a normal distribution, we used parametric tests with the assessment of Student's t-test, Fisher's F-test. In the case of abnormal distribution, used: median test, calculation of the Mann-Whitney rank U-test, for multiple comparison - Wilcoxon T-test (in the case of the study of dependent groups). For statistical and graphical analysis of the obtained results we used software packages Statistica for Windows version 8.0 (Stat Soft inc., USA), Microsoft Excel 2007 (Microsoft, USA).

Research results and their discussion. Analysis of 378 medical records of inpatients with steatohepatitis of alcoholic and non-alcoholic etiology for the period 2015-2020 indicates the following frequency and structure of anaemic syndrome among patients with steatohepatitis (Table 1).

Table 1 - Frequency and structure of anaemic syndrome in patients with steatohepatitis depending on the etiology of steatohepatitis, erythrocyte size and colour index (n, %)

№	Anaemic syndrome (AS)	SH Mix (with alcoholic), n=149	ASH, n=102	NASH, n=127	OR, CI 95%
1.	Present AS	48 (32,2 %)	37 (36,3 %)	28 (22,0 %)	1.2,10* [1,39-3,18] 2. 1,75* [1,08-2,86] 3. 3,54* [2,17-5,75]
	Normocytic, normochromic	25 (52,1 %)	16 (43,2 %)	8 (28,6 %)	1. 4,04* [2,46-6,62] 2. 4,06* [2,20-7,49] 3. 12,38* [5,78-26,49]
	Macrocytic, hyperchromic	23 (47,9 %)	21 (56,8 %)	20 (71,4 %)	1. 4,40* [2,65-7,29] 2. 3,09* [1,76-5,44] 3. 4,95* [2,89-8,49]
	Microcytic, hypochromic	-	-	-	
2.	Absent AS	101 (67,8 %)	65 (63,7 %)	99 (78,0 %)	

Note: 1. OR, CI 95% - an indicator of the ratio of the chances of anaemic condition in patients with SH of mixed etiology (*p <0,05); 2. OR, CI 95% - an indicator of the ratio of the chances of developing AS in patients with ASH (*p <0,05); 3. OR, CI 95% - an indicator of the ratio of the chances of AS in patients with NASH on the background of obesity (*p <0,05).

In particular, among 149 patients with steatohepatitis of mixed (including alcoholic) etiology, anaemia was registered in 48 cases (32.2%), among 102 patients with ASH - in 37

(36.3%), among 127 patients with NASH - in 28 cases (22.0%) ($p<0.05$) with the maximum risk of AS in patients with ASH ($p <0.05$) (Table 1). According to archival data of medical records of treated patients with steatohepatitis, patients of all groups were dominated by macrocytic, hyperchromic anaemia: in patients with SH of mixed etiology - in 47.9%, patients with ASH - 56.8%, NASH - 71.4% ($p<0.05$). At the same time, the remaining anaemic conditions were represented by normocytic, normochromic anaemia - respectively in 52.1% of SH of mixed etiology, in patients with ASH - 43.2%, NASH - 28.6% ($p<0.05$). According to the data in the table, no signs of microcytic, hypochromic anaemia were registered after the patients' examination (Table 1). The pathogenetic explanation of a significant proportion of macrocytic, hyperchromic anaemia in NASH, ASH and SH of mixed etiology is the formation of vitamin B12, folate-deficient anaemia, which occurs under conditions of decompensated dysbiosis of the colon of III degree, maldigestion, malabsorption due to the secretion of defective bile composition and insufficiency of activating factors (bile acids) of proteolytic, lipolytic enzymes with the formation of vitamin B12 and folic acid deficiency, which catalyze DNA replication reactions, regulate cell division processes, in particular 2, 5-9, 11-15, 18-22, 27, 29, 32-35]. Prominent in the etiopathogenesis of B12-deficient anaemia is also the contamination of H. pylori, which can cause atrophic gastritis and deficiency of Castle factor synthesis, necessary for the assimilation of B12, etc. [6, 24]. The causes of normochromic, normocytic anemia in SH should be considered the causes of chronic disease anaemia, among which the leading mechanism is the presence of low-intensity systemic inflammation with the release of proinflammatory cytokines that inhibit hematopoiesis, reduce erythropoietin synthesis by hepatocytes and kidneys, acupuncture, haemorrhage [2, 11, 14-17, 30-32]. The pathogenesis of the formation of normochromic, normocytic anaemia in ASH should take into account the direct toxic damage to the bone marrow by ethanol and its metabolic products, as well as the formation of Zieve's syndrome, which is acquired hemolytic anaemia on the background of chronic alcohol intoxication. [18, 24, 25].

A prospective study of patients with SH, depending on the indicators of clinical blood tests, namely the presence of AS, indicated two categories of patients - with AS and no AS. Among patients with ASH - anaemia was found in 16 patients (40.0%), among patients with SH of mixed (including alcoholic) etiology anaemia was found in 8 patients (32.0%), among patients with NASH - in 13 patients (21.7%) (Table 2). The analysis of red blood cells in patients with ASH revealed three types of anaemia, namely vitamin B12 - deficient - in 7 people (17.5%), anaemia of chronic disease - in 4 people (10.0%) and acquired hemolytic anaemia associated with with alcohol abuse (Zieve's syndrome) - in 5 people (12.5%).

Assessment of quantitative indicators of haemoglobin in the blood indicates that 10 people had a mild degree of anaemia (62.5%), 6 people - moderate anaemia (37.5%).

Table 2 - Distribution of examined patients with steatohepatitis depending on the etiology of steatohepatitis, the presence and type of anaemic syndrome (n,%)

№	Anaemic syndrome	PHIs, n=25	SH Mix (with alcoholic), n=25	ASH, n=40	NASH, n=60
1.	Present	-	8 (32,0 %)	16 (40,0 %)	13 (21,7 %)
	B12 deficiency anaemia	-	4 (16,0 %)	7 (17,5 %)	9 (15,0)
	Anaemia of chronic disease	-	2 (8,0 %)	4 (10,0 %)	4 (6,7 %)
	Hemolytic anaemia (Zieve's syndrome)	-	2 (8,0 %)	5 (12,5 %)	-
2.	Absent AS	25 (100%)	17 (68,0 %)	24 (60,0 %)	47 (78,3 %)

In patients with SH of mixed (including alcoholic) etiology, 3 types of anaemia were found, namely vitamin B12 - deficient - in 4 people (16.0%), anaemia of chronic disease - in 2 people (8.0%) and acquired hemolytic anaemia associated with alcohol abuse (Zieve's syndrome) - in 2 people (8.0%). Estimation of quantitative indicators of haemoglobin in the blood indicates that 5 people had a mild degree of anaemia (62.5%), 3 people - moderate anaemia (37.5%).

The structure of AS in patients with NASH with obesity differed slightly. In particular, B12 - deficiency anaemia was found in 9 people (15.0%), anaemia of chronic disease in 4 people (6.7%). The analysis of haemoglobin levels in the blood indicates that 10 patients with NASH had a mild degree of anaemia (76.9%), 3 people - moderate anaemia (23.1%).

Examination of patients with steatohepatitis of various etiologies for H. pylory contamination using a stool test revealed the following results: in patients with NASH - H. pylory contamination was present in 11 (84.6%) of 13 people with anaemic syndrome, including 100% of patients with B12-deficient anaemia. Among patients with ASH, H. pylory contamination was present in 32 (80.0%) of 40 people with anaemic syndrome, including 100% of patients with B12-deficient anaemia. Among patients with mixed SH (including alcohol etiology) - H. pylory contamination was present in 100.0% of people with anaemic syndrome.

Thus, the combination of these etiological factors and multiple links of pathogenesis contributes to the development of anaemic conditions on the background of SH of different origins and necessitates their adequate correction, in particular, treatment of the underlying disease (weight loss, IR, elimination of alcohol, drugs, anti-inflammatory, hepatoprotective, metabolic therapy), restoration of the endogenous pool of vitamin B12 by increasing its intake, improving its absorption, eliminating dysbiosis of the colon, eradication of H.pylory.

Conclusions

1. According to the retrospective analysis of medical records of inpatients with steatohepatitis of mixed (including alcoholic) etiology, anaemia was found in 32.2% of cases, in patients with ASH - in 36.3%, in patients with NASH - in 22 , 0% of cases. Macrocytic, hyperchromic anaemia predominated in patients with anaemia of all groups: in patients with SG of mixed etiology - in 47.9%, in patients with ASH - 56.8%, NASH - 71.4%. Normocytic, normochromic anaemia was registered in 52.1% of patients with mixed etiology of steatohepatitis, in patients with ASH the result was 43.2%, in those with NASH it showed 28.6%.

2. Among the examined patients with alcoholic steatohepatitis - anaemia was found in 40.0%, among the patients with steatohepatitis of mixed (including alcoholic) etiology anaemia was found in 32.0%, among patients with non-alcoholic steatohepatitis - in 21.7% .

3. The following types of anaemia were found in ASH: vitamin B12 - deficient - in 17.5% of cases, anaemia of chronic disease - in 10.0% of cases and acquired hemolytic anaemia associated with alcohol abuse (Zieve's syndrome) - in 12 , 5% of cases. The estimation of the quantitative indicators of haemoglobin content in the blood indicates that 62.5% of patients had a mild degree of anaemia, 37.5% of patients were examined for moderate anaemia.

4. In patients with steatohepatitis of mixed (including alcoholic) etiology, three types of anaemia were found, namely vitamin B12 - deficient - in 16.0% of cases, anaemia of chronic disease - in 8.0% and Zieve's syndrome - in 8.0% of patients. Mild anaemia was registered in 62.5% of cases, moderate anaemia in 37.5%.

5. The structure of the anaemic syndrome in patients with NASH with obesity of I-II degrees is as follows: B12 - deficiency anaemia was detected in 15.0% of cases, anaemia of chronic disease in 6.7% of people. The severity of anaemia was distributed as follows: 76.9% of patients had mild anaemia, 23.1% had moderate anaemia.

6. In patients with NASH, H. pylory contamination was present in 84.6% of patients with anaemic syndrome, including 100% of patients with B12-deficient anaemia. With ASH, H. pylory contamination was present in 80.0% with anaemia, including 100% of patients with B12-deficient anaemia. In patients with mixed SH (including alcoholic etiology), H. pylory contamination was present in 100.0% of people with anaemic syndrome.

Prospects for further research in this area are to develop methods for the correction of established anaemic conditions in patients with steatohepatitis of different etiology.

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