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Evaluation of Small Intestinal Permeability in Patients with Overlap Syndrome (Autoimmune Hepatitis/Primary Biliary Cholangitis)

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Aim: to evaluate the state of small intestine permeability by the "double sugar test" in patients with overlap syndrome (autoimmune hepatitis / primary biliary cholangitis (AIH / PBC)).
Materials and methods. Prospectively, 56 people were included in the study. Of these, 26 were diagnosed with AIH/PBC, 30 were in the control group. The diagnosis was made in accordance with the current recommendations. The average age of patients was 49.7 ± 13.8 years, healthy volunteers — 48.6 ± 9.2 years. The determination of the permeability of the small intestine was carried out by a "double sugar test" (the ratio of lactulose/mannitol in urine), using the method of high-performance liquid chromatography — mass spectrometry.
Results. In patients with AIH/PBC, an increase in intestinal permeability was found — 0.20 [0.09; 0.30] ($p < 0.001$) compared with the control group 0.01 [0.01; 0.02]. We divided patients at the stage of liver damage. An increased small intestinal permeability was revealed: hepatitis stage — 0.19 [0.13; 0.30] ($p < 0.001$), liver cirrhosis stage — 0.18 [0.09; 0.30] ($p < 0.05$) compared with the control group. In the early stages of disease (1 month from the onset of the disease) had an increased lactulose/mannitol ratio — 0.13 [0.05; 0.26] ($p < 0.001$) compared to the control group. In the presence of portal hypertension (PH), small intestinal permeability was increased — 0.18 [0.09; 0.30] ($p < 0.001$) compared with the control group.
Conclusions. An increase in small bowel permeability was found in patients with overlapping syndrome. All patients had increased intestinal permeability (regardless of the presence of extrahepatic manifestations).
Keywords: small intestine permeability, "double sugar test", overlap syndrome, autoimmune hepatitis / primary biliary cholangitis (AIH/PBC), extrahepatic manifestations
Conflict of interest: the authors declare no conflict of interest.

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Оценка тонкокишечной проницаемости у пациентов с синдромом перекреста (аутоиммунный гепатит / первичный билиарный холангит)

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Цель исследования: изучить состояние проницаемости тонкой кишки «двойным сахарным тестом» у пациентов с синдромом перекреста аутоиммунный гепатит / первичный билиарный холангит (АИГ/ПБХ).
Материалы и методы. В проспективное исследование были включены 56 человек. Из них 26 пациентов – с диагнозом АИГ/ПБХ, 30 человек — группа контроля. Диагноз устанавливали в соответствии с актуальными рекомендациями. Средний возраст пациентов составил 49,7 ± 13,8 года, у здоровых добровольцев — 48,6 ± 9,2 года. Определение проницаемости тонкой кишки проводилось «двойным сахарным тестом» (отношение «лактулоза/маннитол» в моче) с использованием метода высокоэффективной жидкостной хроматографии — масс-спектрометрии.
Результаты. У пациентов с АИГ/ПБХ было выявлено повышение тонкокишечной проницаемости — 0,20 [0,09; 0,30] ($p < 0,001$) по сравнению с группой контроля 0,01 [0,01; 0,02]. При разделении пациентов на стадии поражения печени было выявлено повышение тонкокишечной проницаемости как на стадии гепатита — 0,19 [0,13; 0,3] ($p < 0,001$), так и на стадии ЦП — 0,18 [0,09; 0,30] ($p < 0,05$) при сравнении с группой контроля.

На ранних стадиях у пациентов с синдромом перекреста (1 месяц от начала заболевания) было выявлено повышение отношения лактулоза/маннитол — 0,13 [0,05; 0,26] ($p < 0,001$) по сравнению с группой контроля. Тонкокишечная проницаемость была повышена при активной форме заболевания — 0,205 [0,088; 0,284] ($p < 0,001$), неактивная форма — 0,140 [0,086; 0,316] ($p < 0,001$) по сравнению с группой контроля. При наличии портальной гипертензии тонкокишечная проницаемость была повышена — 0,18 [0,09; 0,30] ($p < 0,001$) по сравнению с группой контроля.

Выводы. У пациентов с синдромом перекреста (АИГ/ПБХ) было выявлено повышение проницаемости тонкой кишки. Вне зависимости от клинических проявлений, длительности, наличия внепеченочных проявлений у всех пациентов была повышена тонкокишечная проницаемость.

Ключевые слова: проницаемость тонкой кишки, «двойной сахарный тест», синдром перекреста, аутоиммунный гепатит / первичный билиарный холангит (АИГ/ПБХ), внепеченочные проявления

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Currently, the question of the triggering mechanisms of the development of autoimmune liver diseases (ALD), the features of their progression, and the possibilities of effective therapy are being actively studied [1]. In addition to classical ALD such as autoimmune hepatitis (AIH), primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC), with their own diagnostic criteria, there is a combination of AIH and cholestatic liver diseases (PSC, PBC) [2–5]. This immunopathological condition is called overlap syndrome [2, 6–8]. Overlap syndrome is not a separate nozological form of autoimmune nature, it represents various variants of the manifestation of clinical phenotypes that are characteristic of patients with ALD [2, 9–11].

It is well known that people with one autoimmune disease are more likely to develop other autoimmune diseases. These patients have immunological dysfunction, and the interaction between genetic, immunological, environmental and hormonal factors which plays a role in the development of the disease [2, 6, 7]. Among extrahepatic immune disorders in AIH, the most common are autoimmune thyroid diseases (AIT)- Hashimoto's thyroiditis, Graves' disease and unspecified autoimmune thyroiditis [12–14]. P.L. Bittencourt et al. [15] showed that extrahepatic immune-mediated disorders, designated as concomitant autoimmune disorders, occur in approximately 22–46 % of cases with type 1 AIH, and in 20–34 % of cases with type 2 AIH [16].

The close relationship between the liver and intestine affects the development and progression of parenchymal liver diseases. The liver receives about 75 % of its blood reserves from the intestine [17]. Kupfer cells in the liver serve as the most important protective system that removes toxins and pathogenic microorganisms entering the portal vein from the intestine [18, 19]. Changes in the intestinal mucosa of a structural and functional nature can increase its permeability. Among the structural disorders that lead to an increase in the permeability of the small intestine, portal hypertension and a decrease in the villi/crypt ratio should be mentioned [19]. One of the most sensitive methods for assessing the permeability of the small intestine is the "double sugar test" [20].

The aim of the study was to evaluate the state of permeability of the small intestine by a "double sugar test" in patients with overlap syndrome AIH/PBC.

Material and methods

The prospective study included 56 people, 26 of them with a diagnosis of overlap syndrome AIH/PBC (98 % of women and 2 % of men) and 30 people in the control group. The average age of patients was 49.7 ± 13.8 years, in the group of healthy volunteers — 48.6 ± 9.2 years.

The study was approved by the Local Ethics Committee of the Kazan State Medical University of the Ministry of Health of the Russian Federation (extract from Protocol No. 10 of December 23, 2020) and the State Medical Institution "RCH of the Ministry of Health of the Republic of Tatarstan". All procedures carried out in human studies complied with the ethical standards of the National Research Committee, as well as the Helsinki Declaration of 1964 and its later amendments.

The criteria for inclusion in the study were: the age of patients over 18 years old; signed informed consent to participate in the study; reliable clinical and laboratory data confirming the diagnosis of overlap syndrome. Exclusion criteria from the study: the presence of markers of viral hepatitis; Wilsons disease; non-alcoholic steatohepatitis; alcoholic liver

disease; drug hepatitis; pregnancy and lactation; refusal of the patient to participate in the study; the presence of active or chronic infections in the acute stage; an undesirable reaction to mannitol and / or lactulose.

The control group was represented by 30 volunteers who did not have diseases of the digestive system and closest relatives with ALD, and also did not take any medications.

Patients with overlap syndrome were examined by doctors: internist, gastroenterologist, endocrinologist, rheumatologist. The diagnosis was established in accordance with the recommendations of AIH — IAIHG (2011) [7], PBC — EASL (2017) [21] and AASLD (2019) [22].

The determination of small intestine permeability by the "double sugar test" (lactulose/mannitol) was carried out in patients with overlap syndrome (AIH/PBC) and in a group of healthy volunteers. Before starting the study, urine was taken from patients. Then they drank a mixture solution containing 5 g of lactulose, 10 g of mannitol and 40 g of sucralose dissolved in 100 ml of clean water. The patients collected urine for the next 6 hours. The urine of each subject was stored in a container containing thimerosal as a preservative. The urine was mixed, the volume was accurately measured, each sample was frozen and transported on dry ice to the laboratory. Prior to the laboratory analysis, the samples were stored at a temperature of –20 °C. The results on colon permeability (sucralose level) (nmol/L) are not reflected in this article.

The double sugar test was performed by high-performance liquid chromatography — mass spectrometry on an Agilent 1260 Infinity chromatograph (Agilent Technologies, Inc., USA) coupled with an ABSciex 5600 mass spectrometer (AB Sciex, USA).

Statistical processing and analysis of the obtained results was carried out using the program SPSS version 28, Statistica version 12.5 (Statsoft) and Microsoft Excel 2013. The distribution of the studied parameters was different from normal, so the description of the features is presented in the form of Me [Q1; Q3], where Me is the median, Q1 and Q3 are the first and third quartile, respectively. The Mann — Whitney criterion was used for paired comparison. The differences obtained were considered statistically significant at $p < 0.05$. Nonparametric statistical methods were used. The mean value and 95 % confidence interval were determined.

Research results

In clinical manifestations in patients with overlap syndrome jaundice was observed in 57.7 % of cases, abdominal discomfort in 53.8 %, joint syndrome in 55 %, autoimmune thyroiditis (AIT) in 42.3 %. In 30.7 % of patients were at the stage of liver cirrhosis.

In the study of small intestinal permeability in patients with overlap syndrome (AIH/PBC) was found an increase in small intestinal permeability — the lactulose/mannitol ratio was

Table 1. Laboratory parameters of patients
Таблица 1. Лабораторные показатели пациентов

Parameter Показатель	In the beginning of disease Дебют	
	M ± SD	95% CI 95% ДИ
Hemoglobin, g/L Гемоглобин, г/л	110.0 ± 7.4	94.67–125.33
ALT, U/L АЛТ, Ед/л	125.10 ± 13.72	95.80–153.31
AST, U/L АСТ, Ед/л	118.60 ± 13.82	90.08–147.13
Alkaline phosphatase, U/L Щелочная фосфатаза, Ед/л	489.85 ± 67.30	350.62–629.08
GGT, U/L ГГТП, Ед/л	381.70 ± 58.95	258.31–505.09
Total bilirubin, umol/L Общий билирубин, мкмоль/л	31.17 ± 5.40	19.98–42.35
Albumin, g/L Альбумин, г/л	46.95 ± 0.63	45.58–48.33
Total IgG, mg/ml Общий IgG, мг/мл	17.60 ± 1.22	14.81–19.87
Gamma globulin, g/L Гамма-глобулин, г/л	25.35 ± 0.91	23.38–27.32

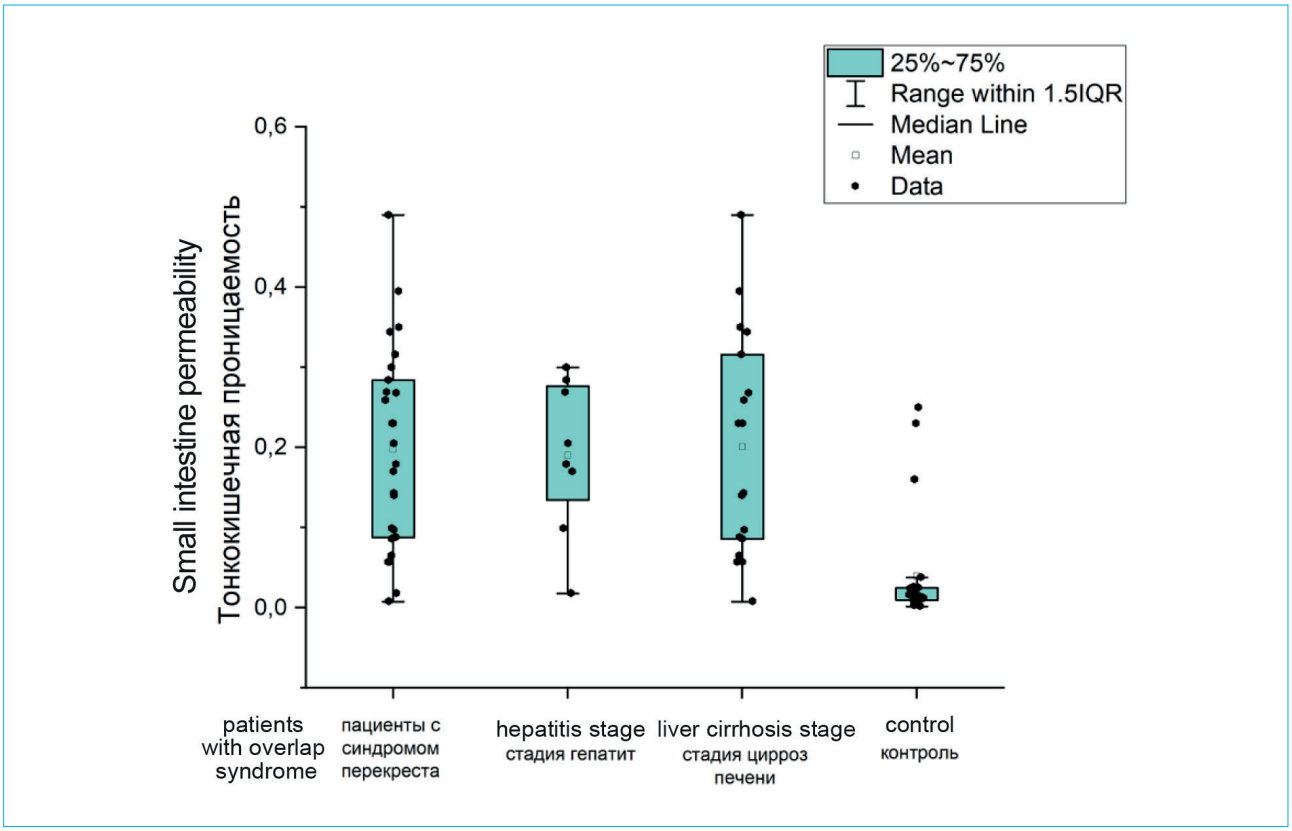

Fig. 1. Lactulose/mannitol ratio in patients with overlap syndrome (AIH/PBC)

Рис. 1. Отношение лактулоза/маннитол у пациентов с синдромом перекреста АИГ/ПБХ

0.2 [0.088; 0.3] ($p < 0.001$), in the control group 0.013 [0.01; 0.025]. When separating patients at the stage of liver damage it was revealed that at the stage of hepatitis was 8 (30.7 %) patients with overlap syndrome (AIH/PBC), the small intestinal permeability was increased — 0.19 [0.13; 0.3] ($p < 0.001$) — compared with the control group, in 18 (69.3 %) patients with liver cirrhosis — 0.18 [0.086; 0.3] ($p < 0.05$) — in comparison with the control group, an increase in small intestine permeability was also observed (Fig. 1).

The state of small intestinal permeability was analyzed depending on the duration of the course of the overlap syndrome (AIH/PBC). An interesting fact turned out to be that already in the early stages (1 month from the onset of the disease), the lactulose/mannitol ratio was increased in patients with overlap syndrome (AIH/PBC) — 0.13 [0.05; 0.261] ($p < 0.001$). With a duration of up to 6 months — 0.268 [0.097; 0.284] ($p < 0.001$), from 6 months to 1 year — 0.114 [0.072; 0.245] ($p < 0.001$), more than 1 year — 0.205 [0.099; 0.3] ($p < 0.001$) compared with the control group (Fig. 2).

Regardless of the Child — Pugh class the lactulose/mannitol ratio was increased in the studied group of patients (Table 2).

When assessing the activity of the overlap syndrome (AIH/PBC) the permeability of the small intestine was increased in patients with an active form of the disease in 88.5 % of cases — 0.205 [0.088; 0.284] ($p < 0.001$), and in patients with an inactive form of the disease in 11.5 % of cases — 0.14 [0.086; 0.316] ($p < 0.001$) compared to the control group (Table 2).

Portal hypertension (PH) was observed in 31 % of cases in patients with overlap syndrome (AIH/PBC). Regardless of the presence or absence of PH the small intestinal permeability was increased in each group of patients — 0.18 [0.09; 0.304] ($p < 0.001$) and 0.19 [0.065; 0.28] ($p < 0.001$) respectively (Table 2).

In 55 % of patients with overlap syndrome (AIH/PBC) with joint syndrome the small intestinal permeability was increased — 0.17 [0.099; 0.27] ($p < 0.05$) compared with the control group. In 42.3 % of cases of patients with overlap syndrome (AIH/PBC) with AIT the small intestinal permeability was also increased — 0.17 [0.097; 0.3] ($p < 0.05$) compared with the control group (Table 2).

An increase in small intestinal permeability was detected regardless of the therapy with ursodeoxycholic acid (UDCA) or glucocorticosteroids (GCS).

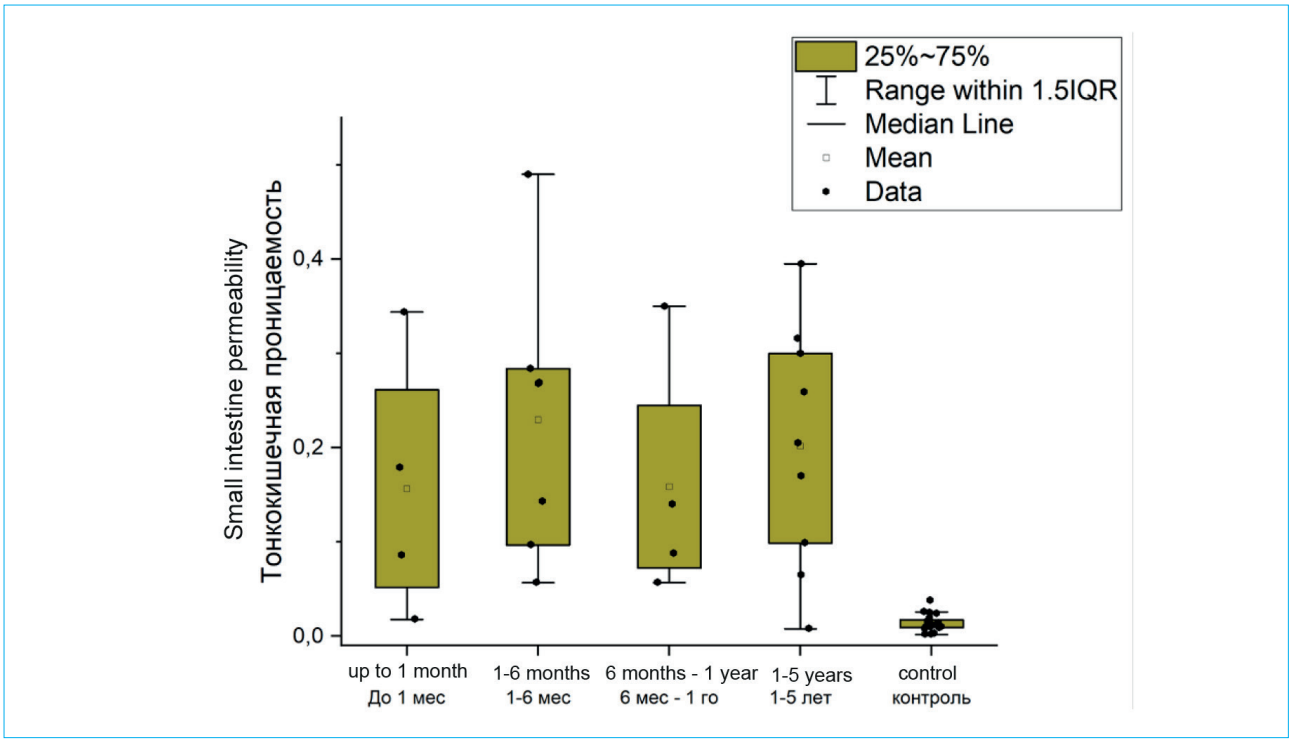

Fig. 2. The ratio of lactulose / mannitol in patients with overlap syndrome (AIH/PBC) depending on the duration of the disease

Рис. 2. Отношение лактулоза/маннитол у пациентов с синдромом перекреста в зависимости от длительности заболевания

Discussion

In our study, an increase in small intestinal permeability was revealed in patients with overlap syndrome (AIH/PBC) (0.2 [0.088; 0.3] ($p < 0.001$)) compared with the control group (0.013 [0.01; 0.025]). Already at the hepatitis stage the ratio lactulose/mannitol (0.19 [0.13; 0.3] ($p < 0.001$)) was higher than in the control group. With the progression of the overlap syndrome (AIH/PBC) into cirrhosis an increase in the permeability of the small intestine also persisted (0.18 [0.086; 0.3] ($p < 0.05$)) compared to the control group. The increase in intestinal permeability did not depend on the duration of the disease ($p < 0.001$), disease activity ($p < 0.001$), portal hypertension ($p < 0.001$). An interesting fact was the detection of an increase in the lactulose/mannitol ratio in patients already at the onset of the disease (within 1 month from the moment of the appearance of the first signs of crossroads syndrome) compared with the control group.

Immune inflammatory diseases are closely associated with changes in the intestinal microbiome [23], which is associated with changes in intestinal permeability.

J. Benjamin et al. [24] were analyzing the lactulose/mannitol ratio at patients with liver cirrhosis various etiologies (alcoholic, viral) and they determined that the excretion of mannitol was increased. They expected that these results because of a damage to tight contacts and a decrease in the height of the villi as a result of portal enteropathy in patients with portal hypertension. J. Such et al. [25] found in patients with liver cirrhosis and PH syndrome structural and functional changes in the intestinal barrier (stagnation, swelling of the mucous membrane) due to the expansion of intercellular spaces. That fact can be secondary due to PH and lead to an increase intestinal permeability and, probably, to a bacterial translocation. K. Norman et al. [26] showed an increased intestinal permeability in patients with decompensated alcoholic liver cirrhosis. They expected that it happened due to the changes in tight contacts and changes in the morphology of the intestinal wall. In our study the small intestinal permeability in PH was also increased compared to the control group.

It is well known that extrahepatic autoimmune diseases are often detected in patients with ALD. AIT is most often associated with ALD [3, 14]: in 10–23 % of cases [11, 12]. In our study, a high

Table 2. Clinical features of the overlap syndrome (AIH/PBC) and intestinal permeability indicators
Таблица 2. Клинические особенности синдрома перекреста и показатели кишечной проницаемости

Sight Заболевание/признак		N	Ratio lactulose/mannitol Лактулоза/маннитол
Child – Pugh ЦП по Уайлду – Пью	A	3	0.316 [0.068; 0.37]**
	B	6	0.8 [0.14; 0.23]**
	C	9	0.09 [0.08; 0.26]**
Activity Активность	Active Активный	23	0.205 [0.088; 0.284]**
	Not active Неактивный	3	0.14 [0.086; 0.316]**
Portal hypertension Портальная гипертензия	Yes Наличие	8	0.18 [0.09; 0.304]**
	No Отсутствие	18	0.19 [0.065; 0.28]**
Extrahepatic reveals Внепеченочные проявления	With joint syndrome С артралгиями	13	0.17 [0.099; 0.27]*
	Without joint syndrome Без артралгий	13	0.2 [0.088; 0.28]*
	With autoimmune thyroid С АИТ	11	0.17 [0.097; 0.3]*
	Without autoimmune thyroid Без АИТ	15	0.2 [0.086; 0.28]*
Treatment Терапия	UDCA УДХК	11	0.2 [0.97; 0.7]**
	Steroids ГКС	14	0.18 [0.06; 0.28]**
Control group Контроль		30	0.013 [0.01; 0.025]

Note. * $p < 0.05$ compared to the control group; ** $p < 0.001$ compared to the control group.
Примечание. *$p < 0,05$ по сравнению с группой контроля; ** $p < 0,001$ по сравнению с группой контроля.

frequency of AIT was revealed in patients with overlap syndrome (AIH/PBC) – 42 % of cases. The same trend was observed in the study Q. Zeng et al. [3] – 34.9 % of cases in patients with ALD. The permeability of the small intestine was increased in AIT (was 0.17 [0.097; 0.3] ($p < 0.05$)) and in patients with joint syndrome (0.17 [0.099; 0.27] ($p < 0.05$)) compared to the control group. Q. Zeng et al. [3] it is assumed that the presence of AIT did not change the clinical course or severity of ALD. The features of the clinical course of ALD were almost the same in patients with ALD with and without AIT as evidenced by the absence of significant differences in symptoms, biochemical parameters, histological stage in patients with ALD [3]. In our study, patients with crossroads syndrome without AIT also had increased small intestinal permeability (0.2 [0.086; 0.28] ($p < 0.05$)) compared to the control group.

When evaluating the therapy in patients with overlap syndrome the small intestinal permeability was changed when taking GCS which can be explained by the presence of two autoimmune liver diseases in a patient with overlap syndrome (AIH/PBC).

Conclusions

In patients with overlap syndrome (AIH/PBC) was detected an increase in small intestinal permeability even at the onset of the disease as well as at the stages of hepatitis and liver cirrhosis regardless of the duration of the disease, activity, and the presence of extrahepatic manifestations.

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