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IMMUNE SYSTEM PARAMETERS IN PATIENTS WITH CHRONIC OPISTORCHIASIS BASED ON GENETIC POLYMORPHISM ASSOCIATED WITH CARBOHYDRATE AND LIPID METABOLISM DISORDERS

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Abstract. A study assessing differences in the immunopathogenesis of chronic opisthorchiasis with or without genetic polymorphisms in patients associated with predisposition to type II diabetes mellitus and lipid metabolism disorders was carried out. Venous blood samples from 89 patients were collected to analyze immunological parameters and genetic polymorphisms by using pyrosequencing. In the presence of mutations affecting regulation of carbohydrate metabolism, patients with opisthorchiasis had less pronouncedly increased phagocytic activity, a lower monocyte count, higher total T-lymphocyte count, lower T-cytotoxic cell and B-lymphocyte counts, lower IgA, IgG but higher IgM concentration. This indicates a moderately compromised nonspecific resistance, imbalanced effector T- and B-immunity, but in most cases (PPARG, TCF7L2 rs12255372, CDKAL1, CDKN2A/2B, SLC30A8) aggravated humoral immune reaction to invasion particularly revealed by lower B-lymphocyte count. The presence of polymorphisms that alter lipid metabolism regulation bidirectionally affects the parameters of immune response. An increased B-lymphocyte count and other indicators of humoral immune activation to invasion, which are detected in groups with mutations in the APOE (rs429358), PCSK9, ABCA1, APOC3 rs2854117 genes, can contribute to a more effective response to sustained antigenic stimulation. Changes in the T-lymphocytes subpopulations, characteristic of opisthorchiasis invasion, are aggravated in the presence of mutations in the PCSK9, ABCA1, and APOC3 rs2854117 genes. Mutations in the genes APOC3 rs5128, LPL rs268 activate patients' nonspecific resistance, although this effect may also be associated with exhaustion of neutrophil bactericidal reserve. In general, minor alleles of the APOE (rs429358), APOC3 rs2854117, LPL rs268, LPL rs328, PON1 rs662 genes can be considered "protective" for the immunopathogenesis of chronic opisthorchiasis. Thus, patients with chronic opisthorchiasis with different genotypes predisposing to carbohydrate and lipid metabolism disorders had significant differences in immune system parameters, which can also affect the disease course. Mutations in different loci of the PCSK9, ABCA1, APOE, APOC3, and PON1 genes have opposite effects on the analyzed immune parameters. In the presence of mutations in other genes (PPARG, TCF7L2 rs12255372, CDKAL1, CDKN2A/2B, SLC30A8, LPL), opisthorchiasis invasion leads to more pronounced alterations in immune response;

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mutations in the lipoprotein lipase gene may have some “protective” immune-related effect in opisthorchiasis. The effect of all studied genetic polymorphisms associated with a predisposition to developing type II diabetes mellitus was predominantly negative.

Key words: *immune system indicators, chronic opistorchiasis, genetic polymorphisms, lipid metabolism disorders, diabetes mellitus type II, innate immunity, adaptive immunity.*

ПОКАЗАТЕЛИ ИММУННОЙ СИСТЕМЫ У БОЛЬНЫХ ХРОНИЧЕСКИМ ОПИСТОРХОЗОМ В ЗАВИСИМОСТИ ОТ ГЕНЕТИЧЕСКИХ ПОЛИМОРФИЗМОВ, АССОЦИИРОВАННЫХ С НАРУШЕНИЯМИ УГЛЕВОДНОГО И ЛИПИДНОГО ОБМЕНА

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Резюме. Проведено исследование различий в иммунопатогенезе хронического описторхоза при наличии и отсутствии у больных генетических полиморфизмов, связанных с предрасположенностью к сахарному диабету II типа и нарушениям обмена липидов. В образцах венозной крови 89 пациентов определяли комплекс иммунологических показателей, генетические полиморфизмы выявляли методом пиросеквенирования. При наличии мутаций, изменяющих регуляцию углеводного обмена, у больных описторхозом выявлены: менее выраженное повышение фагоцитарной активности, меньшее количество моноцитов, большее общее количество Т-лимфоцитов, меньшее количество Т-цитотоксических клеток и содержание В-лимфоцитов, меньшая концентрация IgA, IgG и большая — IgM. Это свидетельствует об умеренной недостаточности неспецифической резистентности, дисбалансе эффекторного Т- и В-звеньев иммунитета, но в большинстве случаев (PPARG, TCF7L2 rs12255372, CDKAL1, CDKN2A/2B, SLC30A8) — об усугублении реакции гуморального иммунитета на инвазию, в частности, меньшем числе В-лимфоцитов. Наличие полиморфизмов, нарушающих регуляцию липидного обмена, разнонаправленно влияет на показатели иммунного ответа. Повышенное количество В-лимфоцитов и другие показатели активации гуморального звена иммунитета в ответ на инвазию, которые выявляются в группах с наличием мутаций в генах APOE (rs429358), PCSK9, ABCA1, APOC3 rs2854117, могут способствовать более эффективной реакции на постоянную антигенную стимуляцию. Изменения субпопуляционного состава Т-лимфоцитов, характерные для описторхозной инвазии, усугубляются при наличии мутаций в генах PCSK9, ABCA1, APOC3 rs2854117. Мутации в генах APOC3 rs5128, LPL rs268 активируют неспецифическую резистентность больных, хотя этот эффект может быть связан и с истощением бактерицидного резерва нейтрофилов. В целом, «протективными» для иммунопатогенеза хронического описторхоза можно считать минорные аллели генов APOE (rs429358), APOC3 rs2854117, LPL rs268, LPL rs328, PON1 rs662. Таким образом, у больных хроническим описторхозом с разными генотипами, предрасполагающими к нарушениям углеводного и липидного обмена, выявлены существенные различия в показателях функций иммунной системы, что может влиять и на течение болезни. Мутации в разных локусах генов PCSK9, ABCA1, APOE, APOC3 и PON1 оказывают противонаправленное воздействие на исследованные показатели иммунного ответа. При наличии мутаций в других генах (PPARG, TCF7L2 rs12255372, CDKAL1, CDKN2A/2B, SLC30A8, LPL) описторхозная инвазия приводит к более выраженным отклонениям иммунного реагирования; мутации в гене липопротеиновой липазы, возможно, оказывают некоторый «протективный» эффект на иммунную систему больных описторхозом. Эффект всех исследованных генетических полиморфизмов, связанных с предрасположенностью к развитию сахарного диабета II типа, оказался преимущественно негативным.

Ключевые слова: *показатели иммунной системы, хронический описторхоз, генетические полиморфизмы, нарушения липидного обмена, сахарный диабет II типа, врожденный иммунитет, адаптивный иммунитет.*

Introduction

In previous studies, we identified the features of the immune response during opisthorchiasis invasion. Among the indicators of nonspecific resistance are: an increase in the concentration in the blood serum of total circulating complexes; increased activity of the enzyme myeloperoxidase (MP) of neutrophils; increased activity of bactericidal systems of neutrophils in a spontaneous test with nitroblue tetrazolium (NBT), increased relative and absolute number of eosinophils. In patients with chronic opisthorchiasis (CO), the relative and absolute number of lymphocytes and cytotoxic ($CD3^+CD8^+$) lymphocytes, B-lymphocytes ($CD3^-CD19^+$) and DN-T-lymphocytes decreases; the relative number of T helper cells ($CD3^+CD4^+$) (and, accordingly, the $CD4^+/CD8^+$ index), as well as T lymphocytes with a late activation

marker ($CD3^+HLA\text{-}DR^+$), increases, and interleukin balance is disrupted [6]. Relationships have been found between indicators of the functioning of the immune and hepatobiliary systems, reflecting the degree of activity of the pathological process and immune reactions caused by invasion [1]. Conducted studies [2, 5] suggested the influence of genetic polymorphisms associated with a predisposition to the development of non-infectious diseases on the response of the immune system and metabolic processes of patients with CO to invasion. In this work, in order to test this assumption, we studied polymorphisms associated with disorders of carbohydrate and lipid metabolism (the development of type II diabetes mellitus (T2DM) and atherogenesis), which, according to the literature, also affect immunopathogenetic processes.

In particular, the expression of the SLC30A8 gene can be suppressed by cytokines such as IL-1β and IFNγ [18]. The PPARG gene product is an antagonist of nuclear transcription factors that regulate gene expression during the cell's response to external influences, including the immune response, which underlies their anti-inflammatory and potentially anti-atherosclerotic activity [17, 22, 29]. PPARG ligands reduce the expression of proinflammatory cytokines by T lymphocytes, reduce IL-2 production, and reduce inflammation in the intestine by switching from a Thl- to Th2-response. PPARG selectively controls the activity of Th17 cells, stimulates the transformation of effector T cells into regulatory ones, and is expressed in B lymphocytes [28]. Apolipoprotein E (APOE) suppresses inflammatory activation of phagocytes. Expression of APOE reduces the polarization of macrophages towards the pro-inflammatory M1 phenotype, characterized by the production of the cytokines IL-1β, IL-6, TNFα, and increases their polarization towards the anti-inflammatory M2 phenotype, characterized by the production of the cytokines IL-4, IL-10. Apolipoproteins (including APOB) are acute phase proteins [9]. Paraoxonase-1 (PON1) hydrolyzes oxidized phospholipids of the plasma membrane of macrophages with the formation of lipolactones (modulators of the local inflammatory process and stimulators of reverse cholesterol transport) [4]; weakens phagocytosis and necrotic death of macrophages, suppresses their proinflammatory reactions [14].

The purpose of the study was to identify differences in the immunopathogenesis of CO in the presence and absence of genetic polymorphisms in patients associated with a predisposition to T2DM and lipid metabolic disorders.

Materials and methods

A comprehensive study of immunological parameters was carried out in venous blood samples of 89 patients diagnosed with opisthorchiasis, chronic phase of the disease.

The study was conducted with the voluntary informed consent of the patients. The study was approved by the ethical committee of the Tyumen Research Institute of Regional Infectious Pathology of Rospotrebnadzor (protocol No. 2 of 02/01/2023).

Phagocytic activity of neutrophils (PAN) was determined by the ability of cells to absorb latex particles with d = 10 μm (DIAEM LLC, Moscow) — the percentage of neutrophils out of 200 analyzed containing latex particles. The metabolic activity of neutrophils was determined by the cytochemical method of reducing nitroblue tetrazolium to diformazan (NBT test, spontaneous and stimulated with a 10% pyrogenal solution) [10]. The spontaneous NBT test reflected the degree of activation of oxygen-dependent metabolism and the associated production of free radicals, while the stimulated version (in vitro) characterized the functional reserve [10]. The stimulation index is the ratio of the % of positive cells in the stimulated NBT test to the % of positive cells in the spontaneous NBT test (NBTstim./NBTspont.). The level of neutrophil myeloperoxidase was detected by spectrophotometry [13]. The study of lymphocyte phenotype was carried out by flow cytometry of whole peripheral blood using monoclonal antibodies (Beckman Coulter, USA) labeled with FITC (fluorescein isothiocyanate), PE (phycoerythrin), ECD (phycoerythrin-Texas Red-X) and PC5 (phycoerythrin-cyanin5) on flow cytometer "Cytomics FC-500" (Beckman Coulter, USA). Three-color immunophenotyping panels were used: CD3/CD4/CD45, CD3/CD8/CD45, $CD3/CD16^+56$/CD45, CD3/HLA-DR/CD45 and CD3/CD19/CD45. Main lymphocyte phenotypes: T lymphocytes ($CD3^+CD19^-CD16/56^-CD45^+$), T helper cells ($CD3^+CD4^+CD45^+$), cytotoxic T lymphocytes ($CD3^+CD8^+CD45^+$), NK cells ($CD3^-CD16/56^+CD45^+$), activated T-lymphocytes ($CD3^+HLA\text{-}DR^+CD45^+$), B-lymphocytes ($CD3^-CD19^+CD45$). The number of DN-T cells ($CD45^+CD3^+CD4^-CD8^-$) was determined by subtracting the relative number of $CD4^+$ and $CD8^+$ lymphocytes from the relative number of $CD3^+$ lymphocytes) [11].

Absolute values were obtained using dual-platform technology using the results of hematological analysis. The concentration of immunoglobulins M, G, A, and E (IU/ml) in blood serum was determined by the enzyme immunoassay method using commercial kits "Immunoscreen-G, M, A-ELISA-BEST" and "IgE-total-ELISA-BEST" (Vector-Best, Russia). The concentration of cytokines (IFNγ, IL-4, IL-8, IL-10 (pg/ml)) was determined by enzyme immunoassay using commercial kits "Gamma-interferon-ELISA-BEST", "Interleukin-4-ELISA-BEST", "Interleukin-8-ELISA-BEST", "Interleukin-10-ELISA-BEST" (Vector-Best, Russia).

Isolation of total human DNA from blood samples was carried out using the commercial AmpliPrime DNA-sorbB kit. Genetic polymorphisms were identified by pyrosequencing using the PyroMark24 genetic analysis system and commercial reagent kits

"AmpliCenc Pyroscreen": "DIABET-2-screen" and "DIABET-2D-screen", "LIPO-screen-B" and "LIPO-screen-D", designed to assess genetic predisposition to the development of type II diabetes mellitus by detecting polymorphisms in the loci:

– rs5219 of the KCNJ11 gene (ATP-dependent potassium channel);
– rs1801282 of the PPARG2 gene (receptor gamma transcription factor);
– rs7903146 and rs12255372 of the TCF7L2 gene (transcription factor 7);
– rs7756992 of the CDKAL1 gene (cyclin-dependent kinase);
– rs10811661 of the CDKN2A/2B gene (cyclin-dependent kinase inhibitors);
– rs1111875 of the HHEX gene (transcription factor);
– rs4402960 of the IGF2BP2 gene (growth factor regulator);
– rs13266634 of the SLC30A8 gene (zinc ion transporter),

and also to assess genetic predisposition to hereditary forms of lipid metabolism disorders by detecting polymorphisms in loci:

– rs429358 and rs7412 of the APOE gene (apolipoprotein E);
– rs5742904 and rs754523 of the APOB gene (apolipoprotein B);
– rs11206510 of the PCSK9 gene (serine protease);
– rs2230806 ABCA1 gene (ABCA1 transporter);
– rs2854116, rs2854117 and rs5128 of the APOC3 gene (apolipoprotein C3);
– rs268 and rs328 of the LPL gene (lipoprotein lipase);
– rs854560 and rs662 of the PON1 (paraoxonase-1) gene.

Statistical processing of the results was carried out using the on-line calculator https://www.statskingdom.com. For each of the studied indicators and identified polymorphisms, groups with the presence and absence of minor alleles were compared using tests for independent groups: with a normal distribution confirmed by the Shapiro–Wilk test, the Student's T-test (T-test) was used, taking into account the assessment of equality of variances using the F-test (indicate the mean and standard error of the mean); otherwise, the nonparametric Mann–Whitney Test (U-test) was used (the median value and IQR were indicated — the interquartile range between the 1st and 3rd quartiles). "n" means number of patients in the group. A significance level of $p < 0.05$ was taken as statistically significant differences.

Results

The identified significant differences in the studied parameters between the groups of CO patients with and without minor alleles for individual polymorphisms are shown in Table.

For the rs5742904 polymorphism of the APOB (apolipoprotein B) gene, no mutant alleles were found among the examined patients; for the rs754523 polymorphism, on the contrary, they were detected in all patients except one. This does not make it possible to compare the values of immunological parameters in groups with and without mutations, but suggests that these mutations can affect the body's vulnerability to infection by the opisthorchiasis pathogen.

In patients with the rare T allele of the rs5219 polymorphism of the KCNJ11 gene, a significantly lower percentage of cytotoxic T lymphocytes ($CD3^+CD8^+$) was detected than in homozygotes for the normal allele.

In the group with the rare G allele for the rs1801282 polymorphism of the PPARG gene, the level of immunoglobulin A was significantly lower.

In the group with the rare T allele for the rs12255372 polymorphism of the TCF7L2 gene, a lower relative number of B-lymphocytes ($CD3^-CD19^+$) and a higher relative number of T-lymphocytes ($CD3^+$) were detected compared to the group of patients without the mutation

Table. Immunological parameters in patients with chronic opisthorchiasis with different genotypes for polymorphisms associated with predisposition to carbohydrate and lipid metabolism disorders (mean±standard error of the mean or median (IQR), n — quantity in group)

Group / Polymorphism indicator, unit of measurement	Without mutation genotype	With mutation genotype	Comparison of groups without and with mutation, p
KCNJ11 rs5219 C > T	CC (n = 15)	TC and TT (n = 25)	
$CD3^+CD8^+$, %	33 (24.5–38.5)	22 (19–29)	0.020 U-Test
PPARG rs1801282 C > G	CC (n = 34)	GC and GG (n = 7)	
IgA, mg/ml	2.4 (1.48–3.09)	1.5 (1.23–1.66)	0.019 U-Test
TCF7L2 rs 12255372 G > T	GG (n = 30)	TG and TT (n = 15)	
$CD3^-CD19^+$, %	11.17±0.80	8.33±1.01	0.040 T-test
$CD3^+$, %	75±1.25	80.8±1.18	0.008 T-test
CDKAL1 rs7756992 A > G	AA (n = 29)	AG and GG (n = 36)	
Monocytes, cells/μl	276 (192–354)	205.5 (137.2–277.5)	0.047 U-Test

Group / Polymorphism indicator, unit of measurement	Without mutation genotype	With mutation genotype	Comparison of groups without and with mutation, p
$CD3^-CD19^+$, cells/μl	185.6 (141.6–241.9)	140.1 (122.2–195.6)	0.045 U-Test
CDKN2A/2B rs10811661 T > C	TT (n = 48)	TC and CC (n = 16)	
IgG, mg/ml	17.55 (11.38–21.26)	11.25 (8.94–14.41)	0.015 U-Test
IGF2BP2 rs4402960 G > T	GG (n = 32)	TG and TT (n = 28)	
FAN, %	83.4±1.12	79.7±1.49	0.046 T-test
SLC30A8 rs13266634 C > T	CC (n = 24)	TC and TT (n = 40)	
IgM, mg/ml	1.69 (1.22–2.24)	2.06 (1.69–2.88)	0.042 U-Test
APOE rs429358 T > C	TT (n = 44)	TC and CC (n = 14)	
$CD3^-CD19^+$, cells/μl	158.4 (122.4–231.7)	226.5 (176.3–240.6)	0.033 U-Test
$CD3^-CD19^+$, %	9.56±0.60	12.14±1.08	0.038 T-test
Ig E, mg/ml	10.5 (4–27)	40 (19.25–76.75)	0.012 U-Test
DN-T, cells/μl	41 (0–62.3)	57.7 (42.2–103.1)	0.048 U-Test
PCSK9 rs11206510 T > C	TT (n = 18)	TC and CC (n = 3)	
$CD3^+CD8^+$, cells/μl	450.3 (324.5–535.1)	288 (253.4–309.4)	0.035 U-Test
CD4/CD8 ratio	1.90±0.21	2.78±0.08	0.001 T-test
$CD3^-CD19^+$, %	9.5±1.09	16.3±1.76	0.025 T-test
ABCA1 rs2230806 G > A	GG (n = 38)	AG and AA (n = 18)	
$CD3^+CD8^+$, cells/μl	477.7 (344.8–610.7)	375.9 (289.4–440.6)	0.048 U-Test
$CD3^+HLA\text{-}DR^+$, cells/μl	168.3 (113.7–291.7)	109.3 (75.7–180.4)	0.029 U-Test
$CD3^+$HLA-DR+, %	10 (7–14.5)	8 (6–9)	0.032 U-Test
IL-8, pg/ml	1.15 (0.35–3.38)	3 (1–6)	0.044 U-Test
$CD3^-CD19^+$, %	9.2±0.66	12±1.13	0.027 T-test
APOC3 rs2854116 C > T	CC (n = 5)	TC and TT (n = 35)	
Myeloperoxidase, a.u.	923 (856–1708)	608 (366–894.5)	0.022 U-Test
NBT stimulated/NBT spontaneous	3 (2.56–3.3)	2 (1.37–2.62)	0.019 U-Test
$CD3^+HLA\text{-}DR^+$, %	11 (11–13)	8 (6–11)	0.034 U-Test
IgA, mg/ml	2.6±0.26	1.92±0.12	0.041 T-test
APOC3 rs2854117 C > T	CC (n = 12)	TC and TT (n = 27)	
NBT stimulated/NBT spontaneous	1.8±0.14	2.39±0.19	0.017 T-test
$CD3^+CD8^+$, %	21.5 (20.25–22.75)	26 (21–33)	0.039 U-тест
IgA, mg/ml	1.95±0.29	2.16±0.13	0.033 T-test
APOC3 rs5128 G > C	GG (n = 10)	GC and CC (n = 47)	
NBT spontaneous, %	13.7±1.45	20.5±1.10	0.009 T-test
NBT stimulated/NBT spontaneous	3.2 (2.5–3.4)	2.1 (1.4–2.75)	0.003 U-тест
$CD3^+CD16/56^+$, %	18 (12–20)	11 (8–15)	0.049 U-тест
DN-T, cells/μl	17.4 (0–42.3)	51.9 (31.8–89.8)	0.040 U-тест
LPL rs268 A > G	AA (n = 47)	AG and GG (n = 9)	
NBT stimulated, %	39.2±1.32	48.8±1.52	0.0001 T-test
$CD3^+HLA\text{-}DR^+$, cells/μl	125.6 (93.2–186.3)	190.8 (153.9–346.3)	0.025 U-тест
DN-T, %	3 (2–5)	0 (0–2.5)	0.042 U-тест
DN-T, cells/μl	52.5 (33.1–78.2)	0 (0–38.2)	0.004 U-тест
LPL rs328 C > G	CC (n = 31)	CG and GG (n = 26)	
NBT spontaneous, %	19 (15.5–27.5)	16.5 (11.25–21)	0.045 U-тест
NBT stimulated/NBT spontaneous	2 (1.37–2.56)	2.64 (2.16–3.08)	0.005 U-тест
PON1 rs854560 A > T	AA (n = 22)	AT and TT (n = 36)	
FAN, %	78.7±1.77	83.0±1.19	0.041 T-test
NBT spontaneous, %	19.4 (13.1–24.1)	12.7 (10.6–21)	0.048 U-тест
PON1 rs662 A > G	AA (n = 28)	AG and GG (n = 30)	
$CD3^+CD4^+$, cells/μl	764.6 (612.5–879.8)	856.7 (763.4–1053.9)	0.044 U-тест

In the group with the CDKAL1 gene mutation (rs7756992), lower absolute numbers of monocytes and B-lymphocytes ($CD3^-CD19^+$) were found.

In the presence of a mutation in the CDKN2A/2B gene, lower production of total immunoglobulin G is observed.

The presence of a mutation in the IGF2BP2 gene leads to less phagocytic activity of neutrophils in patients with opisthorchiasis.

In patients with the SLC30A8 gene mutation, a higher concentration of total immunoglobulin M was detected than in the group with the normal allele.

If the genotype contains a rare allele for the first polymorphism rs429358 T > C of the apolipoprotein E gene, the relative and absolute numbers of B-lymphocytes ($CD3^-CD19^+$), the concentration of total immunoglobulin E and the absolute number of DN-T-lymphocytes are significantly higher.

In patients who are carriers of the minor allele of the serine protease gene (PCSK9 rs11206510), a higher relative number of B-lymphocytes and an even greater decrease in the absolute number of cytotoxic T-lymphocytes were found than in patients with CO without this mutation, while the CD4/CD8 index is naturally higher.

When patients with opisthorchiasis have a minor T allele in the ABCA1 transporter gene (ABC1 rs2230806), a lower absolute number of cytotoxic lymphocytes, an absolute and relative number of T lymphocytes with a marker of late activation ($CD3^+$HLA-DR^+), and a higher relative number of B lymphocytes, as well as IL-8 levels.

The presence of a minor allele in the APOC3 gene (rs2854116) leads to significantly lower values of neutrophil myeloperoxidase enzyme activity, stimulation index in the NBT test, relative number of activated T lymphocytes, and total immunoglobulin A during invasion. Patients with another APOC3 mutation (rs2854117) have a significantly higher neutrophil stimulation index in the NBT test, as well as the number of cytotoxic T-lymphocytes and immunoglobulin A concentration. In patients with the APOC3 rs5128 mutation, the spontaneous NBT test index is higher, and the stimulation index in the NBT-test below; the relative content of natural killer cells ($CD3^+CD16/56^+$) is lower, the absolute number of DN-T lymphocytes is higher.

In patients who are carriers of the G allele in the lipoprotein lipase gene LPL (rs268), the bactericidal activity of neutrophils in the stimulated version of the test with nitroblue tetrazolium is significantly higher, as well as the absolute number of T-lymphocytes with a marker of late activation, and the absolute and relative number of DN-T-lymphocytes is lower. In the presence of a mutation in another polymorphism of the same gene (rs328), the bactericidal activity of neutrophils in the spontaneous version of the NBT test is lower than in patients without this mutation, but the stimulation index is higher.

When the function of the PON1 gene is impaired due to the presence of the minor allele rs854560 in patients with opisthorchiasis, an increase in the absorption activity of neutrophils is observed, but at the same time the rate of the stimulated NBT test decreases. The presence of a minor allele in another locus of this gene (rs662) leads to a significant increase in the absolute number of $CD3^+CD4^+$.

Discussion

When studying immunological parameters, it was found that significant deviations of their values in groups of patients with opisthorchiasis with the presence of rare alleles for various genes associated with the risk of diabetes mellitus and lipid metabolism disorders from the values in groups without mutations can both bring the indicators closer to normal values and aggravate changes caused by invasion in comparison with a group of healthy individuals.

The lower percentage of cytotoxic T lymphocytes in patients with the KCNJ11 rs5219 mutation may be due to the fact that with defects in the ATP-dependent potassium channel, opisthorchiasis invasion is characterized by a more significant decrease in the activity of the effector cell component of immunity.

In the presence of a mutation in the rs1801282 polymorphism of the PPARG gene, which enhances the negative effect of chronic opisthorchiasis invasion on the activity of alpha-amylase and bile secretion parameters [2], a lower level of immunoglobulin A was detected, that is, the humoral link of adaptive immunity in CO reacts with an even greater decrease in its activity. This may be due to the expression of PPARG in B lymphocytes and the effect on lymphocyte proliferation, as well as their antigen-specific response during inflammation [28].

A lower relative number of B-lymphocytes and a higher relative number of T-lymphocytes in the group with the rare T allele for the rs12255372 polymorphism of the TCF7L2 gene (this mutation is associated with both T2DM and obesity and markers of inflammation [7]) indicates an even more pronounced activation cellular immunity and decreased humoral immunity. The TCF7L2 gene product is a component of the Wnt-dependent signaling pathway, the abnormal activation of which is associated with tumor development in colorectal carcinoma [23].

Lower absolute numbers of monocytes and B-lymphocytes in the group with the CDKAL1 gene mutation (rs7756992) may be due to the fact that the mutation aggravates the immune system's response to invasion and has an unfavorable effect: a decrease in the number of monocytes can lead to immunological deficiency, because one of the most important functions of cells of the monocyte-macrophage link — antigen presentation. A smaller number of B-lymphocytes under conditions of high antigenic load in opisthorchiasis may be caused by

enhanced transformation into plasma cells or a decrease in proliferative potential under the influence of mutation. CDKAL1 expression in immune cells, especially $CD4^+$ and $CD19^+$ lymphocytes, has been shown to be downregulated when they are activated by proliferation signals [26].

In the presence of a CDKN2A/2B gene mutation, the response of the humoral immune system to invasion is probably less pronounced, since a lower concentration of total immunoglobulin G is detected.

Since neutrophils constitute the first line of defense against the penetration of infectious agents and are responsible for the elimination of damaged cells [8], their lower absorption activity in the presence of a mutation in the IGF2BP2 gene in patients with opisthorchiasis is unfavorable, but the absolute value of the differences is small (4.4%), it can be assumed that it does not make a significant contribution to the change in nonspecific resistance in patients with the mutation.

A higher concentration of total immunoglobulin M in patients with the SLC30A8 gene mutation may indicate some impairment in B-lymphocyte differentiation [12].

So, in the presence of the mutations we studied that alter the regulation of carbohydrate metabolism, patients with opisthorchiasis revealed various changes in the immune system (less pronounced increase in phagocytic activity, lower number of monocytes, higher total number of T-lymphocytes, lower number of T-cytotoxic cells and B-lymphocytes, a lower concentration of IgA, IgG and a higher concentration of IgM), which indicate a moderate lack of nonspecific resistance, an imbalance of the effector T- and B-links of immunity, but in most cases (PPARG, TCF7L2 rs12255372, CDKAL1, CDKN2A/2B, SLC30A8) aggravate reaction of humoral immunity to invasion, in particular, a decrease in the number of B-lymphocytes.

If the genotype contains a rare allele for the first polymorphism rs429358 of the APOE gene, there appears to be a positive change in the adaptive humoral immune response to invasion (a higher number of B-lymphocytes and the concentration of total immunoglobulin E). A larger number of DN-T lymphocytes can also be considered a protective change, since this is a minor subpopulation of highly effective suppressor cells and regulators of the intensity of the immune response, which suppress proliferation, change the metabolism, characteristics, effector functions of CD4-T-lymphocytes and shift the CD4-T-lymphocyte phenotype. Lymphocytes towards the resting one, thereby inducing peripheral tolerance [16], which is important for preventing autoimmune complications (probably including opisthorchiasis). There is also evidence in the literature [25] that APOE can suppress cellular immunity by exerting an antiproliferative effect on mitogen-stimulated lymphocytes.

In patients who are carriers of a minor allele of the serine protease gene (PCSK9 rs11206510), which is involved in the regulation of immune system functions [27], disturbances in the subpopulation composition of T-lymphocytes characteristic of CO are aggravated, and the humoral component of immunity apparently tends to restore.

In the presence of a mutation in the ABCA1 transporter gene (involved, in particular, in the mechanism of action of tumor necrosis factor on cells [24]), changes in the parameters of the cellular part of the immune system, characteristic of patients with CO, deepen — there are even fewer effector cells of adaptive immunity, and activated T-lymphocytes are reduced to a level lower than in the whole group of patients with CO, which is not justified under conditions of sufficient antigenic load. The humoral component of the adaptive immune response (relative number of B lymphocytes) and nonspecific resistance (IL-8 level) are activated.

Mutations in different loci of the APOC3 gene (the level of expression of which depends on cytotoxic T cells and varies significantly in tumor tissues [30]) have different effects on immunogram parameters in patients with CO. The differences identified in patients with the APOC3 rs2854116 mutation may indicate that their innate immune response is less pronounced, the potential of neutrophils is depleted, and the reactions of the cellular and humoral components of the adaptive immune response are reduced. In patients with the APOC3 rs2854117 mutation, the bactericidal potential of neutrophils is higher than in patients without the mutation (and than in the general group of patients with CO), changes in the number of cytotoxic T-lymphocytes and the concentration of immunoglobulin A are characteristic of the activation of cellular and humoral immunity, apparently this demonstrates the protective effect of this mutation on immune response parameters. In patients with the APOC3 rs5128 mutation, NBT test indicators indicate activation of the bactericidal ability of neutrophils, and a low number of natural killer cells, on the contrary, indicates a decrease in innate resistance. A higher number of DN-T lymphocytes (leading to the development of tolerance [16]) can also be considered a protective change to prevent autoimmune complications of opisthorchiasis, as with the APOE rs429358 mutation.

In patients with the LPL rs268 mutation, NBT test indicators indicate stimulation of nonspecific resistance, and a greater number of T lymphocytes with a late activation marker indicate a greater participation of adaptive cellular immunity. An increased reaction of these components of the immune response may be associated, among other things, with a lower absolute and relative number of DN-T lymphocytes, which can lead to hyperstimulation of the immune response (as well as autoimmune diseases) [16]. In the presence of a mutation in another LPL poly-

morphism (rs328), apparently, with a slightly lower bactericidal activity of neutrophils, their potential bactericidal activity has a certain reserve. This suggests a "protective" effect for the immune response to opisthorchiasis invasion of this "antiatherogenic" minor allele of LPL, associated with favorable changes in lipid composition (lowered triglyceride levels and increased HDL levels [19, 21]), as well as with lipid-associated macrophages [20] and inflammatory processes [15].

In CO patients with the PON1 rs854560 mutation, the bactericidal activity of neutrophils is reduced and an increase in the absorption activity of these cells can be considered as a compensatory mechanism. Perhaps such effects are associated with the involvement of paraoxanase-1 in the functions of innate immunity noted in the literature: it is believed that it protects against bacterial infection by destroying signaling molecules that produce gram-negative bacteria for invasion into human tissues and the formation of colonies [3, 4]. The presence of a minor allele in another PON1 locus (rs662) leads to a higher number of T helper cells, approaching those of the control group of practically healthy people. The immune response in chronic opisthorchiasis is generally characterized by an increase in the relative number of T-helper cells.

Thus, the presence of polymorphisms that disrupt the regulation of lipid metabolism has a multidirectional effect on the parameters of the immune response, possibly shifting the development of the immune response in different directions (T-helper cells type 1 or 2, etc.). At the same time, the approach of indicators of different parts of the immune system to the "normal" level in the presence of chronic parasitic invasion cannot always be interpreted as a positive effect of one or another polymorphism due to possible compensatory shifts in different parts of the immune system. However, an increased number of B-lymphocytes and other indicators of activation of the humoral immune system in response to invasion, which are detected in groups with mutations in the APOE (rs429358), PCSK9, ABCA1, APOC3 rs2854117 genes, may contribute to a more effective response to constant antigenic stimulation. Changes in the subpopulation composition of T-lymphocytes, characteristic of opisthorchiasis invasion, are aggravated in the presence of mutations in the PCSK9, ABCA1, APOC3 rs2854117 genes. Mutations in the genes APOC3 rs5128, LPL rs268 activate nonspecific resistance of patients with CO, although this effect may also be associated with depletion of the bactericidal reserve of neutrophils. In general, minor alleles of the genes APOE rs429358, APOC3 rs2854117, LPL rs268, LPL rs328, PON1 rs662 can be considered "protective" for the immunopathogenesis of CO.

As a result of the study, significant differences in the indicators of immune system function were identified in patients with chronic opisthorchiasis with different genotypes predisposing to disorders of carbohydrate and lipid metabolism, which may also affect the course of the disease. Mutations in different loci of the PCSK9, ABCA1, APOE, APOC3 and PON1 genes have opposite effects on the studied parameters of various components of the immune response. When mutations cause dysfunction of a number of proteins (PPARG, TCF7L2 rs12255372, CDKAL1, CDKN2A/2B, SLC30A8, LPL), opisthorchiasis invasion leads to more pronounced deviations in the immune response; mutations in the lipoprotein lipase gene may have some kind of "protective" effect on the immune system of patients with opisthorchiasis. At the same time, the effect of all studied genetic polymorphisms associated with a predisposition to the development of T2DM turned out to be predominantly negative.

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