Level of cellular reactivity of organism and extent of intoxication severity in patients with acute and exacerbation of chronic pancreatitis depending on genes polymorphism CFTR, PRSS1, IL-4 and TNF-α

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Introduction. Acute pancreatitis (AP) and the exacerbation of chronic pancreatitis still remain one of the most actual medical problems, which attract the attention of both surgeons and gastroenterologists, because the danger of the heavy course or pancreonecrosis always remains. The question of defining the criteria of severity of the patient's condition and disease prognosis to prevent complications interest many scientists. Therefore, based on the fact that peripheral blood is one of the major carriers of information of the processes occurring in tissue structures and immune competent cells (ICC) are highly sensitive to the changes in the environment and temporary stay, many researchers study the level of cellular reactivity of organism of patients with acute or exacerbation of chronic pancreatitis, and explore the absolute and relative number of basic populations of ICC of peripheral blood [2, 3, 4, 6, 12, 15, 17].

In addition, cytokines which are synthesized by ICC, purposefully regulate the interaction with other cells of the human body, and each other, correlating with the mode of pancreas inflammation and the severity of intoxication [1, 8, 9, 16].

However, despite the significant function of ICC, the questions of cell reactivity and severity of intoxication in patients with AP and ECP depending on genes polymorphisms are not studied and, therefore, require further research.

The aim of the research. To investigate the levels of cellular reactivity and intoxication severity in patients with acute and exacerbation of chronic pancreatitis depending on the genes polymorphism CFTR (*ΔF508*, rs 113993960), PRSS1

(*R122H,* rs 111033565), IL-4 (*C-590T,* rs 2243250) and TNF-α (*G-308A*, rs 1800629).

Materials and methods. The study included 123 patients with exacerbation of CP and AP (edematous form), admitted to the Local Emergency hospital (Chernivtsi, Ukraine) during last 4 years. The Diagnosis of AP was exhibited according to the existing national MOH Ukraine order [5] and the recommendations of the European Societies of diagnosis and treatment of acute pancreatitis [11]. All patients signed an informed consent of the patient to participate in the study, followed by complex examinations: clinical, laboratory and instrumental. Among the patients were 23 (18.7%) women and 100 (81.3%) men. The patients' averaged age was 45,1 ± 5,19 years for males and 53,2 ± 7,07 years for women (23 to 77). The control group was made up of 40 healthy individuals matched for age and sex.

Molecular-genetic study, which included the definition of polymorphic variants of four genes: IL-4 (C-590T), TNF-α (G-308A), PRSS1 (R122H) and CFTR (delF508), were performed at the laboratory of the State institution «Reference centre of molecular diagnostics of the Ministry of Health of Ukraine» (Kyiv) and at the laboratory of Medical Biology and Genetics Department of Bukovinian State Medical University. The polymorphic variants of analysed genes were studied by polymerase chain reaction (PCR) method using oligonucleotide primers of the company «Metabion» (Germany) according to the modified protocols [10, 13, 14]. Amplification products of DNA fragments of genes were digested by hydrolysis using restriction enzyme («Thermo Scientific», USA): enzyme PmlI (Eco72I) for gene PRSS1, AvaII — the gene for IL-4, NcoI — gene for TNFα. The resulting fragments were analysed in agarose gel with the addition of ethidium bromide, molecular weight marker GeneRuler 50 bp (DNA Ladder, «Thermo Scientific», USA), and further visualization by using transilluminator and Vitran software.

The calculation of haematological indexes and ratios: leukocyte index of intoxication (LII) according to Kalf-Kalif, LII according to Reis, LII according to Ostrovsky’s modification, the haematological intoxication index (HII) according to Vasilyev, core index of endotoxicosis degree (CIED), core shift index (CSI),

neutrophil/monocyte ratio (NMR), lymphocyte/monocyte ratio (LMR), immune reactivity index (IRI), allergisation index (AI) [7] were conducted on the basis of the extended general clinical blood test, which was performed on the haematology analyser CELL-DYN 3700 SL (manufacturer — «Abbott Laboratories», USA).

The statistical analysis was performed using applications MYSTAT 12 (Systat Software Inc., USA) and Scout 2008 Version 1.00.01 (USA Environmental Protection Agency, USA). The reliability of data for independent samples was calculated according to t-test Student (with the distribution of ranges close to normal), or U-criterion Wilcoxon-Mann-Whitney (with uneven distribution). The analysis of qualitative features was performed according to the χ^2 criterion. The difference was considered reliable at $p<0.05$.

Results and Discussion. The results of the data calculations of the parameters, which characterize the cellular reactivity level of patient's organism with AP considering the polymorphic variants of the gene CFTR, are shown in Table 1.

Table 1

The cellular reactivity level in patients with acute pancreatitis considering the ***ΔF508*** polymorphism of gene CFTR

	Parameter	Control group, n=40	Genotype of gene CFTR, n=101	
			NN, n=98	NM, n=3
1	Leukocyte index of intoxication according to Kalf-Kalif	1.31±0.04	14.37±1.02; $p_c<0.001$	11.88±0.65; $p_c<0.001$; $p_{NN}<0.05$
2	Leukocyte index of intoxication according to Reis	1.61±0.05	4.88±0.31; $p_c<0.001$	4.33±0.28; $p_c<0.001$
3	Leukocyte index of intoxication according to Ostrovsky's modification	1.64±0.05	4.82±0.31; $p_c<0.001$	3.50±0.25; $p_c=0.001$; $p_{NN}<0.01$
4	The haematological intoxication index according to Vasilyev	0.17±0.008	47.31±6.87; $p_c<0.001$	11.88±0.98; $p_c<0.001$; $p_{NN}<0.01$
5	Core index of endotoxicosis degree	0.20±0.04	0.62±0.09; $p_c<0.01$	0.31±0.05; $p_c<0.01$; $p_{NN}<0.01$
6	Core shift index	0.06±0.009	0.48±0.08; $p_c=0.01$	0.26±0.04; $p_c<0.01$; $p_{NN}<0.05$
7	Neutrophil/monocyte ratio	7.36±0.21	23.31±2.15; $p_c<0.001$	19.50±1.47; $p_c<0.001$

8	Lymphocyte/monocyte ratio	3.36±0.29	4.65±0.72	3.25±0.51
9	Immune reactivity index	3.57±0.32	5.08±0.68; $p_c<0.05$	3.50±0.41; $p_{NN}<0.05$
10	Allergisation index	0.79±0.05	0.51±0.03; $p_c<0.01$	0.41±0.03; $p_c=0.001$; $p_{NN}<0.05$

Notes. p_c — the reliability of indexes difference in comparison with control group; p_{NN} — the reliability of indexes difference in comparison with the carriers of NN-genotype.

In the carriers of NN-genotype of gene CFTR were observed the higher levels of cellular reactivity (Kalf-Kalif LII) to 20.96%, than in those with genotype-NM ($p<0.05$). Increasing of Kalf-Kalif LII indicates the presence of bacterial intoxication, which was heavier in NN-genotype. The definition of Reis LII also, showed in NN-genotype carriers the increasing by 12.7% ($p>0.05$) more than in NM-genotype. Ostrovsky's modification LII, that most reliably reflects the degree of exo- and endotoxemia, was higher by 37.71% ($p<0.01$) in the carriers of NN-genotype of gene CFTR compared with the owners of NM-genotype.

According to Vasilyev HII in the carriers of NN-genotype of gene CFTR was observed 3.98 times higher ($p<0.01$) endotoxicosis level than in carriers of NM-genotype. That is, in the carriers of NN-genotype of gene CFTR, occurred more expressed intoxication output beyond interstitial space and manifestation of endotoxicosis at peripheral blood, indicating a less favourable AP course prognosis.

The results of the influence of the polymorphism of gene CFTR (genotype NN and NM) indicate that in patients with AP carriers of NN-genotype of gene CFTR has a place a higher level of cellular reactivity and endointoxication that is confirmed by the growth of CIED, in the NN-genotype carriers 2 times ($p<0.01$) compared with NM-genotype and CSI to 84.62% ($p<0.05$), respectively. The last parameters point to the cells disintegration of the patient's organism with AP, which can serve as an indicator of the early stages of destructive AP and testify less favourable course in NN-genotype carriers.

The NMR index growth indicates at the increasing of the endogenous intoxication level and reflects the increase of exogenous intoxication caused by bacterial toxins (exo- and endotoxins). On the activity of this process affects CFTR

gene polymorphism: for NN-genotype by 19.54% higher than NM-genotype. The last indicates that for NN-genotype more effectively increases microphage activity and less — macrophage part of nonspecific resistance of patients with AP. That is, for the NN-genotype exists the bigger need for anaerobic macrophages than for NM-genotype, which is, probably, due to a greater area of hypoxia or destruction. LMR index, which characterizes the relationship of affector and effector parts of the immunological process, was by 24% higher in NN-genotype carriers.

We know that on the course and severity of the disease significantly affect the intoxication degree and immune reactivity (the mechanisms of non-specific protection and specific immune response of the immune system) of the patient's organism. It was found out, that immunological reactivity, which aims at the neutralization of toxic substances, increases only if the NN-genotype of gene CFTR is present, by 42.30% ($p<0.05$) compared to controls, and by 45.14% compared to the carrier of NM-genotype. The last does not cause similar changes of immune reactivity and, in fact, promotes the limiting of the immune response. Both genotypes of gene CFTR assist deallergisation of the organism of patients with AP, but more passive inhibitor of the immune system hypersensitivity is NN-genotype (by 24.39% ($p<0.05$)) than NM-genotype.

In summary, it is worth to notice that the carrier of NN-genotype of gene CFTR promotes the increase of cellular reactivity level more effectively than NM-genotype. Along with that, the developing of the immune system hyperactivity is being limited with both genotypes with a significant advantage in this with NM-genotype carriers.

The results of the study of cell reactivity of organism of patients with AP based on PRSS1 (G365A) gene polymorphism are shown in Table 2.

In the patients with AP — carriers of GA-genotype of gene PRSS1, compared with the GG-genotype, there are higher levels of LII: Kalf-Kalif LII — 3.72 times ($p<0.001$), Reis LII — 2.59 times ($p<0.001$), Ostrovsky's modification LII — 3.0 times ($p<0.001$); the growth of Vasilyev HII — 10.38 times ($p<0.001$), CIED — 6.54 times ($p<0.01$), CSI — 7.29 times ($p<0.01$), index NMR — 4 times ($p<0.001$), LMR

index — by 9.17%, that indicates at the formation of higher degree exo- and endointoxication in the GA-genotype carriers of the gene PRSS1.

The IRI in carriers of the GA-genotype of gene PRSS1 — patients with AP, was by 20.48% higher than in carriers of GG-genotype, while, as in the last one the AI, on the contrary, was by 70% higher ($p<0.01$). That is, the GA-genotype has a more positive effect on the immune system, limiting the development of its hypersensitivity to antigens which circulate in the body of patients with AP, than GG-genotype.

Table 2

Cellular reactivity level in patients with acute pancreatitis based on polymorphic variants of gene PRSS1 (G365A)

	Parameter	Control group, n=40	Genotype of gene PRSS1, n=123	
			GG, n=117	GA, n=6
1	Leukocyte index of intoxication according to Kalf-Kalif	1.31±0.04	12.92±0.67; $p_c<0.001$	48.00±3.41; $p_c<0.001$; $p_{GG}<0.001$
2	Leukocyte index of intoxication according to Reis	1.61±0.05	4.58±0.24; $p_c<0.01$	11.86±0.97; $p_c<0.001$; $p_{GG}<0.001$
3	Leukocyte index of intoxication according to Ostrovsky's modification	1.64±0.05	4.43±0.23; $p_c<0.001$	13.30±1.21; $p_c<0.001$; $p_{GG}<0.001$
4	The hematological intoxication index according to Vasilyev	0.17±0.008	33.85±2.72; $p_c<0.001$	348.48±17.92; $p_c<0.001$; $p_{GG}<0.001$
5	Core index of endotoxicosis degree	0.20±0.04	0.50±0.07; $p_c<0.01$	3.27±0.65; $p_c<0.01$; $p_{GG}<0.01$
6	Core shift index	0.06±0.009	0.38±0.06; $p_c<0.01$	2.77±0.58; $p_c<0.01$; $p_{GG}<0.01$
7	Neutrophil/monocyte ratio	7.36±0.21	20.77±1.57; $p_c<0.001$	83.00±5.08; $p_c<0.001$; $p_{GG}<0.001$
8	Lymphocyte/monocyte ratio	3.36±0.29	4.58±0.64	5.00±0.72; $p_c<0.05$
9	Immune reactivity index	3.57±0.32	4.98±0.69	6.00±0.87; $p_c<0.05$
10	Allergisation index	0.79±0.05	0.51±0.03; $p_c<0.01$	0.30±0.02; $p_c<0.001$; $p_{GG}<0.01$

Notes. p_c — reliability of indexes difference in comparison with control group; p_{GG} — reliability of indexes difference in comparison with carriers of GG-genotype.

Thus, in patients with AP — GA-genotype carriers there is a "better" cellular reactivity increasing as response to exogenous (bacterial toxins) and endogenous (breakdown products of own cells) toxic substances and greatly limited the development of allergic reactions.

Cellular reactivity level of the organism of patients with AP depending on the polymorphic variants of the gene IL-4 (C-590T) are presented in Table 3.

Polymorphism of gene IL-4 affects the cellular reactivity level of the organism of patients with AP and development of intoxication symptoms in different ways.

So, in the T-allele carriers there are higher levels of cellular reactivity of organism in accordance with LII data: Kalf-Kalif LII — by 2.1% (CT-genotype) and 67.59% ($p<0.01$) (TT-genotype), Reis LII — by 4.12% and 95.23% ($p<0.05$) respectively, Ostrovsky's modification LII — by 2.42% and 99.46% ($p<0.01$) respectively. According to the Vasilyev HII, there unidirectional changes were not detected, decrease by 21.3% for CT-genotype and increase by 7.43% in the TT-genotype carriers.

Table 3

Association of C-590T polymorphism of gene IL-4 with cellular reactivity levels of the organism of patients with acute pancreatitis

	Parameter	Control group, n=40	Genotype of gene IL-4, n=101		
			CC, n=58	CT, n=34	TT, n=9
1	Leukocyte index of intoxication according to Kalf-Kalif	1.31±0.04	13.79±1.45; $p_c<0.001$	14.08±1.56; $p_c<0.001$	23.11±2.01; $p_c<0.001$; $p_{CC}<0.01$; $p_{CT}<0.01$
2	Leukocyte index of intoxication according to Reis	1.61±0.05	4.61±0.38; $p_c<0.001$	4.80±0.55; $p_k<0.01$	9.00±1.93; $p_c<0.01$; $p_{CC}<0.05$; $p_{CT}<0.05$
3	Leukocyte index of intoxication according to Ostrovsky's modification	1.64±0.05	4.55±0.41; $p_c<0.001$	4.66±0.52; $p_c<0.01$	9.03±1.04; $p_c<0.001$; $p_{CC}<0.01$; $p_{CT}<0.01$
4	The haematological intoxication index according to Vasilyev	0.17±0.008	50.34±11.57; $p_c<0.01$	39.62±6.37; $p_c<0.01$	54.08±5.18; $p_c<0.001$

5	Core index of endotoxicosis degree	0.20±0.04	0.83±0.16; p_c<0.01	0.36±0.08; p_{CC}=0.01	0.25±0.05; p_{CC}<0.01
6	Core shift index	0.06±0.009	0.65±0.13; p_c<0.01	0.27±0.06; p_c<0.01; p_{CC}=0.01	0.18±0.05; p_c<0.05; p_{CC}<0.01
7	Neutrophil/monocyte ratio	7.36±0.21	18.66±2.48; p_c<0.01	29.36±4.10; p_c<0.01; p_{CC}<0.05	17.98±2.01; p_c<0.01; p_{CT}<0.05
8	Lymphocyte/monocyte ratio	3.36±0.29	2.84±0.20	7.19±1.77; p_c<0.05; p_{CC}<0,05	0,8±0,05; p_c<0.001; p_{CC}<0.001; p_{CT}<0.01
9	Immune reactivity index	3.57±0.32	3.10±0.22	7.84±1.91; p_c<0.05; p_{CC}<0.05	1.01±0.02; p_c<0.001; p_{CC}<0.001; p_{CT}<0.01
10	Allergisation index	0.79±0.05	0.47±0.03; p_c<0.01	0.57±0.07; p_c<0.05	0.25±0.03; p_c<0.001; p_{CC}<0.01; p_{CT}<0.01

Notes. p_c — reliability of indexes difference in comparison with control group; p_{CC} — reliability of indexes difference in comparison with carriers of CC-genotype; p_{CT} — reliability of indexes difference in comparison with carriers of CT-genotype.

CIED that bordered with norm parameters for the TT-genotype, increased by 44% for CT-genotype carriers and 3.32 times for the SS-genotype. A similar trend was observed on CSI: the increasing 1.5 times in the CT-genotype carriers and 3.61 times for the CC-genotype.

In the owners of TT-genotype were observed the lowest indices of NMR, LMR, immune reactivity and allergisation which grew in CC- and CT-genotypes carriers. Accordingly, the index NMR — by 3.78% and 63.29%, the index LMR — 3.55 and 8.99 times, the IRI — 3.07 and 7.76 times, the AI — by 88% and 2.28 times.

That is, in the TT-genotype carriers there was a heavy degree of intoxication as compared to medium in the carriers of CC- and CT-genotypes. On this background the reduction of LMR index ($p<0.01$) and the total immunological reactivity of the organism of patients with AP indicates at the immune system hyporeactivity in the TT-genotype owners. Although all genotypes (CC, CT, TT) of gene IL-4 promote the limitation of the immune system hypersensitivity to exo- and endotoxins as well of bacteria as to substances of destroyed own cells, but most of it is shown with TT-genotype.

Along with the fact, the stimulation of immune reactivity of the organism of patients with AP is observed for CT-genotype, when with other genotypes (CC and TT), conversely, there is a reduction. Also CT-genotype is associated with increased LMR index, in other words the activity of effector link of immunological process.

The results of the changes of the cellular reactivity level of the organism of patients with AP depending on the polymorphic variants of the gene TNF-α (G-308A) are shown in Table 4.

TNF-α — inflammatory cytokine produced by immune cells of different populations (monocytes/macrophages, B- and T-lymphocytes), is characterized by differing vectors of effects depending on its concentration. At low concentrations TNF-α affects at the functional activity of neutrophils, increases the synthesis of other cytokines by T-helpers/inductors and stimulates the growth of B-lymphocytes. At large concentrations TNF-α leads to inhibition of the lipoprotein lipase of adipose tissue, reducing the fatty acids utilization, which leads to cachexia, and also causes the development of endotoxin-induced septic condition; promotes the proliferation of T- and B-lymphocytes, activation of natural killers, monocytes/macrophages; increases the production of prostaglandins E_2 and I_2, which realize many toxic effects of TNF-α; it enhances the production of other (IL-4, IL-6) cytokines. This multidirectional action of tumor necrosis factor-alpha in inflammatory process attracted the attention in our studies to establish the impact of gene polymorphism which determines the synthesis of this cytokine, which undoubtedly has influence on the course and severity of AP.

Table 4

Cellular reactivity level of the organism of patients with acute pancreatitis based on the G-308A polymorphism of gene TNF-α

	Parameter	Control group, n=40	Genotype of gene TNF-α, n=11	
			GG, n=9	GA, n=2
1	Leukocyte index of intoxication according to Kalf-Kalif	1.31±0.04	14.31±1.59; p_c<0.001	11.88±1.47; p_c<0.001
2	Leukocyte index of intoxication according to Reis	1.61±0.05	5.61±0.61; p_c<0.001	4.33±0.47; p_c<0.01

3	Leukocyte index of intoxication according to Ostrovsky's modification	1.64±0.05	5.48±0.64; p_c<0.01	3.50±0.43; p_c<0.01; p_{GG}<0.05
4	The haematological intoxication index according to Vasilyev	0.17±0.008	64.06±9.69; p_c<0.001	11.88±1.19; p_c<0.001; p_{GG}<0.01
5	Core index of endotoxicosis degree	0.20±0.04	0.34±0.07	0.31±0.03; p_c<0.05
6	Core shift index	0.06±0.009	0.27±0.06; p_c<0.01	0.26±0.03; p_c<0.01
7	Neutrophil/monocyte ratio	7.36±0.21	18.54±0.83; p_c<0.001	19.50±0.84; p_c<0.001
8	Lymphocyte/monocyte ratio	3.36±0.29	2.43±0.37	3.25±0.38
9	Immune reactivity index	3.57±0.32	2.65±0.38	3.50±0.42
10	Allergisation index	0.79±0.05	0.35±0.02; p_c<0.001	0.41±0.05; p_c<0.01

Notes. p_c — reliability of indexes difference in comparison with control group; p_{GG} — reliability of indexes difference in comparison with carriers of GG-genotype.

The received data show, that the genotypes GG and GA of gene TNF-α are associated with the increased cellular reactivity of the organism of patients with AP, but limit the general immune reactivity of patients' organism, and particularly it was connected with "wild" GG-genotype. Thus, in the GG-genotype carriers have been observed higher, in comparison with the GA-genotype, levels of LII: Kalf-Kalif — by 20.45%, Reis — by 29.56%, Ostrovsky's modification — by 56.57%; HII according to Vasilyev — 5.39 times, CIED — by 9.68%.

The difference in value of CSI for GG- and GA-genotypes was practically absent. But in the owners of GA-genotypes were observed higher rates of indices NMR by 5.18%, LMR — by 33.74%, IRI — by 32.08%, AI — by 17.14%.

So, the GA-genotype does not influence the general immune reactivity level of the organism of patients with AP, and GG-genotype promotes the development trends in the limitation of immunological reactivity of organism. In the process of suppression of patient's organism allergisation to exo- and endoantigens (toxins) the profitable effect is observed for GG-genotype.

Conclusions. 1. In the patients with AP — carriers of the NN-genotype of gene CFTR there is a higher level of cellular reactivity by 20.96% ($p<0.05$) and endointoxication that is confirmed by the growth of Ostrovsky's modification LII by

37.71% ($p<0.01$), HII according to Vasilyev — 3.98 times ($p<0.01$), CIED — 2 times ($p<0.01$) and CSI by 84.62% ($p<0.05$) in comparison with NM-genotype, and indicates a less favourable course of AP in the NN-genotype carriers and can serve as an indicator of the destructive process beginning.

2. In patients with AP — GA-genotype carriers of gene PRSS1 is observed the forming of higher degree of exo- and endointoxication, as affirmed by the LII growth: Kalf-Kalif — 3.72 times ($p<0.001$), Reis — 2.59 times ($p<0.001$), Ostrovsky's modification — 3.0 times ($p<0.001$); HII according to Vasilyev — 10.38 times ($p<0.001$) CIED — 6.54 times ($p<0.01$), CSI — 7.29 times ($p<0.01$), index NMR — 4 times ($p<0.001$) with a significant limitation of allergic reactions.

3. In patients with AP — TT-genotype carriers of the gene IL-4 takes a place the most difficult intoxication level with hyporeactivity and the maximum limitation of immune system hypersensitivity to exo- and endotoxins.

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Level of cellular reactivity of organism and extent of intoxication severity in patients with acute and exacerbation of chronic pancreatitis depending on genes polymorphism CFTR, PRSS1, IL-4 and TNF-α

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The level of cellular reactivity of organism and extent of intoxication severity depending on genes polymorphism CFTR (*ΔF508,* rs 113993960), PRSS1 (*R122H,* rs 111033565), IL-4 (*C-590T,* rs 2243250) and TNF-α (*G-308A,* rs 1800629) were investigated in 123 patients with acute and exacerbation of chronic pancreatitis (edematous form). It has been established that higher level of cellular reactivity by 20,96% ($p<0,05$) and endointoxication occurs in the carriers of NN-genotype of the gene CFTR, thus showing less favourable clinical course of pancreatitis. The higher degree of exo- and endointoxication formation has been observed in the carriers of GA-genotype of the gene PRSS1 on the background of considerable limitation of allergic reactions development. In the carriers of TT-genotype of the gene IL-4 there is the most serious degree of intoxication on the background of hyporeactivity and maximum limitation of immune system hypersensitivity to exo- and endotoxins.