persons. So, the obtained results allow to assess the presence of abnormal H-allele polymorphism R122H of the PRSS1 gene, as a prognostically marker of unfavorable clinical course of acute pancreatitis.

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GENETIC PROGNOSTIC MARKERS OF SEVERE ACUTE PANCREATITIS AND DEVELOPMENT OF ITS COMLICATIONS

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The character of development of acute pancreatitis (AP) and its complications depends on the ability of the mechanisms of antienzymatic protection, which realization is considerably determined by genetic factors. However, among many factors promoting the development and progressing of the disease genetically determined predictors are the least investigated. According to results of modern genetic researches a number of mutations are found which are considered as susceptibility factors to pancreatitis. A special attention among the latter ones is paid to gene transversion of cationic trypsinogen (PRSS1) and pancreatitis inhibitor of trypsin (SPINK1). They are accompanied by disorders of genetically determined mechanisms of intracellular trypsin inactivation. Although the influence of these hereditary factors on the clinical development of acute pancreatitis and its complications still remains practically uninvestigated.

According to the aim we have learnt distribution of R122H- polymorphism gene PRSS1 and N34S-polymorphism gene SPINK1 among the inhabitants of Chernivtsi region suffering from acute pancreatitis. Associative relations of the carriers of different genotype with its etiology, complications of clinical courses, morphological forms and its complications were examined.

88 persons were involved into the study including 53 (60,23%) men and 35 (39,77%) women with different forms of acute pancreatitis. The distributions of R122H-polymorphism gene PRSS1 and N34S-polymorphism gene SPINK1 were determined.

Studying distributions of genotypes R122H-polymorphism gene it was found that acute pancreatitis patients are often carriers of the R-allele (RR- and RH-genotypes 27,27% and 64,77%, respectively) in case of less quantity of pathological HH-homozygote (7,96% persons). As the result the quantity of heterozygote carriers of mutational RH-genotype was 64,77% (57 persons). The number of RR- and HH-homozygote prevailed reliably – 27,27% (24) and 7,96% (7) persons respectively ($p<0,05$).

Studying the distribution of genotype N345-polymorphism gene SPINK1 a lot of patients with acute pancreatitis demonstrated availability of favourable "wild" N-allele («wild-type» (D. Whitcomb, 2013), Wt) – 69,32% (61) persons, while the pathological "mutant" S-variant was identified in 30,68% (27) persons. Homozygote carriers of «wild» NN-genotype (N34) were 42,05% (37) persons, NS-heterozygote (N34S) – 54,55% (48) persons, but homozygote carriers of «mutant» S-allele (SS-genotype, 34S) - 3,40% (3) persons.

Genotype distribution by polymorphous variants of R122H gene PRSS1 and N24S gene SPINK1 among the examined patients with acute pancreatitis corresponded to Hardy-Weinberg equilibrium.

Performed genetic investigations formed the basis to study peculiarities of clinical development of acute pancreatitis in persons with different RH- and NS-genotypes. The examined patients with acute pancreatitis were found to have favourable R-allele of R122H-polymorphism gene of cationic trypsinogen – PRSS1 (RR- and RH-genotype – 27,27% and 64,77% persons respectively) with less quantity of pathological HH- homozygote (7,96% persons). In case patients have unfavourable H-allele of R122H-polymorphism gene PRSS1 the probability of severe clinical development of acute pancreatitis with diffuse pancreonecrosis is reliably higher than in patients with favourable R122R-genotype (55,0% persons against 17,9% persons, $\chi^2 = 9,274$, $p<0,01$). Such patients have more often pancreatogenic abscess of the peritoneal cavity – (48,3% against 21,4% persons, $\chi^2 = 4,250$, $p<0,05$) and diffuse (general) peritonitis (38,3% against 7,15% persons, $\chi^2 = 7,663$, $p<0,01$). These findings enable us to determine mutation R122H- and H122H-genotype as candidate hereditary factors of severe acute pancreatitis and its complications.

Patients with acute pancreatitis were found to be carriers of favourable N-allele of N34S-polymorphism gene of secretory pancreatitis inhibitor of trypsin more often – SPINK1 (NN-genotype – 42,05% and NS-genotype – 54,55%), with less quantity of pathological SS-homozygote (3,40%). In case patients have S34S-polymorphism of gene SPINK1 the probability of severe acute pancreatitis with diffuse pancreonecrosis development is reliably higher than in patients with favourable N34N- and N34S-genotype (100% against 21,7% persons, $\chi^2 = 5,741$, $p<0,05$). It enables to determine mutation S34S-genotype as a genetic predictor of unfavourable development of acute pancreatitis.

Identified peculiarities of the clinical course of acute pancreatitis in persons with genetically determined disorders of intracellular trypsin inactivation are the backgrounds for elaboration of two new ways to prognosticate its course and development of complications.

The main point of the first suggested method is the following: R122H-polymorphism of gene PRSS1 should be determined in patients with acute pancreatitis. In case mutational R122H- or H122H-genotypes are found severe clinical course of the disease with susceptibility to the development of diffuse necrotizing damage of the pancreas and fast formation of purulent necrotic complications can be prognosticated (patent on useful model № 68121 UA).

Another method is to investigate N34S-polymorphism of gene SPINK1. In case two mutation S-alleles are determined severe clinical course of acute pancreatitis with a high risk of development of spread infectious pancreonecrosis and early occurrence of its purulent necrosis complications can be predicted (patent on useful model № 66811 UA).

The results of the investigations conducted substantiate the reasonability to work out new diagnostic approaches, prognostication of the course and treatment of acute pancreatitis with genetically determined disorders of the intracellular trypsin inactivation.

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THE ROLE OF PROTEOLYSIS IN DEVELOPMENT OF INTESTINAL CONTRACTILITY DISORDERS

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It is known, that the proteolytic activity of blood plasma is important not only for protein metabolism, but also in maintaining of the local mechanisms of tissue protection providing protein structures fragmentation of own tissues during their life and extraneous proteins which are components of infectious agents. However, in conditions of pathological process increasing of proteolytic activity can lead to resource exhaustion, which could provide an adequate immune protection. In addition, activity changes of proteolytic systems have a huge influence on the course of the majority of biochemical processes and can affect significantly the neurohumoral regulation of the digestive system.

Proteolytic activity plays an important role not only in the mechanisms of different disorders of intestinal functions after surgical intervention, but is an essential for the regulation of regeneration processes. The growth of this index is the reflection of the proteolysis processes and it correlates with the level of the middle mass molecules which is indicative of the endotoxemia presence.

Thus, the complex assessment of proteolytic activity can be performed by means proteolysis determination using azocasein, azoalbumin and azokol.

These parameters are important not only before surgical intervention but during the postoperative period. The dynamics of these parameters may be indicative of endotoxemia severity and disorder of neurohumoral regulation of different organs and regeneration processes.

In this connection, we have studied the proteolytic activity parameters of blood plasma in 123 surgical patients who formed two groups according to the presence or absence of postoperative disorders of intestinal contractile ability.

It was established that proteolytic activity parameters differed significantly in both groups of patients before surgical treatment. The proteolytic activity by azoalbumin in the patients of the first group who had not intestinal contractility disorders after surgery was significantly lower than in the second group of patients who had postoperative intestinal paresis and postoperative ileus (1.48±0.231 vs. 1.88±0.171 E440/ml/h; $p<0.05$). This was indicative of a significant fragmentation of low molecular weight peptides in patients of the second group that manifested by expressed signs of endotoxemia as a result of excessive proteolytic activity of low molecular structures.

Postoperatively, the dynamics of this parameter was diametrically opposed to preoperative period. Proteolytic activity by azoalbumin in first group of patients had statistically improbable growth trend, while the second group of patients had a significant decrease of this parameter (from 1.88±0.171 to 1.64±0.172 E440/ml/ h; $p<0.05$). This decrease of proteolytic activity to low molecular weight structures shows effectiveness of prescribed anti-enzymatic therapy and reduces the manifestations of endotoxemia in patients of the second group which was confirmed by laboratory and other biochemical parameters.

The proteolytic activity by azocasein before surgical treatment in the second group of patients was also significantly higher than in the first group of patients (1.74±0.242 vs. 1.08 ± 0.113 E440/ml/h; $p<0.05$).

It is important that after surgical intervention in patients of the first group, this parameter was changing statistically unreliably and in patients of the second group it decreased reliably (from 1.74±0.242 to 1.22±0.151 E440/mL/h; $p<0.05$).

Reduction of high proteolytic activity to the middle molecular weight peptides in these patients can restore balance in the regulatory systems, first of all in the humoral ones, which positively affects on the recovery of motor-evacuational function of the intestine.

Proteolytic activity by azokol in both groups of patients also was differed before surgery. In the first group this parameter was significantly higher than in the second one (0.68±0.071 vs. 0.40±0.053 E440/mL/h; $p<0.05$). The decrease of proteolytic activity to collagen's structures in the second group of patients shows these pathogenic mechanisms which may be implemented in disorder of the motor-evacuational function of intestine in the postoperative period due to changes of regenerative processes in the intestinal wall.

Postoperatively, this parameter in the first group of patients was practically unchanged, while in the second group of patients it increased significantly (from 0.40±0.053 to 0.58±0.114 E440/mL/h; $p<0.05$). In our opinion, the excessive activation of proteolysis to high molecular weight peptides is one of the basic mechanisms of the neurohumoral regulation disorder of intestinal contractility. The progression of these processes in the postoperative period may lead to the development of enteroplegia.

Therefore, the studies testify the important role of proteolytic activity of blood plasma in the pathogenesis of postoperative bowel dysfunction. Excessive activation of proteolysis to low molecular weight structures can serve as a factor of endotoxemia in these patients and can provide morphofunctional disorders in the wall of the intestine. The lack of proteolytic activity is indicative of depletion of enzymatic systems caused by cascading growth of fragmentation products.