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Method for Determining Clinical and Immunological Disorders in Acute Pancreatitis

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Abstract: In recent decades, the number of patients with acute pancreatitis has increased markedly in many countries of the world, and the quality of diagnosis has improved. Due to improved diagnostics, pancreatitis has become registered quite often: from 1 to 11% of all patients with acute abdominal diseases. Objective of the study: Improvement of methods for predicting surgical treatment of acute pancreatitis based on the study of clinical and immunological features of the course of the disease. Material and methods. The study was conducted in the Laboratory of Reproduction Immunology of the Institute of Human Immunology and Genomics of the Academy of Sciences of the Republic of Uzbekistan in the period from 2020 to 2023. The study included 66 patients aged 25 to 65 years with the diagnosis of acute pancreatitis of non-alcoholic origin with an abortive course (41 patients) and acute pancreatitis of non-alcoholic origin with a progressive course (25 patients). Analysis of the results and discussion. The pancreas provides secretion of hormones and synthesis of digestive enzymes and is thus both an endocrine and exocrine gland. Many factors (gallstones, alcohol, blunt abdominal trauma) adversely affect the pancreas and lead to the development of pancreatitis. A comprehensive evaluation of these clinical and laboratory markers is used in the differential diagnosis and assessment of the severity of pancreatitis. Conclusion. A clinical, instrumental and laboratory study of patients with an established diagnosis of acute pancreatitis of non-alcoholic origin with abortive and progressive course was conducted.

Keywords: Acute pancreatitis (AP), immunogenetic studies.

Relevance. In recent decades, the number of patients with acute pancreatitis has increased markedly in many countries of the world, and the quality of diagnosis has improved. Due to improved diagnostics, pancreatitis has become registered quite often: from 1 to 11% of all patients with acute abdominal diseases. Nevertheless, as many believe, pancreatitis remains the least studied, both in terms of etiology and pathogenesis, and in terms of diagnosis and treatment [1,3,5,7]. One of the formidable complications of pancreatitis is pancreonecrosis and its consequences. In recent years, the detection of acute pancreatitis in children has been reported. Acute pancreatitis most often affects elderly people and more often women. The ratio of men to women is 1:8 to 1:10 [2,4,6,8].

In parallel with the growth of morbidity, the number of surgical interventions on the organs of this zone increases, second only to the number of operations performed for acute appendicitis. However, the outcomes of treatment of pancreato-hepato-biliary zone pathology remain unsatisfactory [9,11,13,15]. Postoperative mortality in destructive and purulent-necrotic forms of pancreatitis ranges from 30 to 85% [10,12,14,16]. This is mainly due to errors in diagnosis, untimely hospitalisation, unnecessarily long conservative treatment, late operations, tactical errors during surgery and in the postoperative period.

In our country, among the large-scale measures to improve the health care system, special attention is paid to early diagnosis of diseases, reduction of the incidence of complications and prevention [18,20,22,24]. In this regard, the tasks for radical improvement of the set of measures of the health care system are outlined. On this basis, it is necessary to improve methods of predicting surgical treatment of acute pancreatitis based on the study of clinical and immunological features of the course of the disease [17,19,21,23,25].

Currently, there is a great interest in immunogenetic studies. However, it should be emphasised that publications devoted to the study of cytokine gene polymorphism and the relationship with cytokine levels in acute pancreatitis are extremely scarce. Studies at the population level to study the peculiarities of immunogenetic parameters in acute pancreatitis have not been conducted yet.

Objective of the study: Improvement of methods for predicting surgical treatment of acute pancreatitis based on the study of clinical and immunological features of the course of the disease.

Material and methods. The study was conducted in the Laboratory of Reproduction Immunology of the Institute of Human Immunology and Genomics of the Academy of Sciences of the Republic of Uzbekistan in the period from 2020 to 2023. The study included 66 patients aged 25 to 65 years with the diagnosis of acute pancreatitis of non-alcoholic origin with an abortive course (41 patients) and acute pancreatitis of non-alcoholic origin with a progressive course (25 patients). The diagnosis was established on the basis of clinical, laboratory and instrumental investigations, in accordance with the international consensus on the diagnosis and therapy of acute pancreatitis. The mean age of the examined patients was 50.1±0.91 years. The control group of immunological studies consisted of 27 healthy women and men of similar age without this pathology.

The inclusion criteria were: Age of patients from 25 to 65 years, presence of clinical, laboratory and instrumental data allowing to reliably verify the diagnosis of "acute pancreatitis", absence of severe concomitant diseases, duration of the disease not more than 2 days. Exclusion criteria were: Age of patients younger than 24 years and older than 65 years, presence of severe concomitant diseases, acute psychiatric productive symptoms (psychosis, delirium, hallucinations), suspicion of malignant neoplasms, HIV infection, pregnancy and lactation, intolerance to drugs included in treatment regimes, use of cytostatics, immunosuppressants and corticosteroids, erroneous inclusion, disease duration more than 2 days.

The concentration of proinflammatory interleukin-2, interleukin-6 (IL-2, IL-6), anti-inflammatory transforming growth factor-beta (TGFβ) in serum was determined by solid-phase enzyme-linked immunosorbent assay using test systems of Vector-Best JSC (Novosibirsk, Russia) according to the manufacturer's recommendations.

All obtained results were subjected to measurement of optical density (staining intensity) of solution in wells on ELISA-analyser "KNV ST-360 micro-plate reader" (Shanghai Kehua laboratory system CO., LTD) and on the basis of reference samples with known concentration the concentration of interleukins and growth factor in the studied samples was calculated.

Analysis of the results and discussion. The pancreas provides secretion of hormones and synthesis of digestive enzymes and is thus both an endocrine and exocrine gland. Many factors (gallstones, alcohol, blunt abdominal trauma) adversely affect the pancreas and lead to the development of pancreatitis. A comprehensive evaluation of these clinical and laboratory markers is used in the differential diagnosis and assessment of the severity of pancreatitis. To achieve the set goal, we analysed laboratory data in the history of patients of the general group with AP.

The study of the general blood analysis of patients with AP in the general group revealed a significant increase in the total number of leukocytes ($P<0.001$), haemotocrit ($P<0.05$), total number of platelets ($P<0.001$), percentage ratio of lymphocytes ($P<0.001$) and neutrophils

(P<0.001), absolute number of lymphocytes (P<0.05) and erythrocyte sedimentation rate (P<0.001) compared to the values of the control group. It was also revealed that such indicators as total number of erythrocytes and haemoglobin were not significantly significant (P>0.05).

The blood chemistry test is an important tool for diagnosing and assessing the severity of pancreatitis. This analysis provides information about the function of organs and body systems and can help in the assessment of the patient's condition. Analysis of biochemical parameters of patients with AP in the total group revealed significantly significant changes. According to literature data, the level of amylase in blood indicates pancreatic inflammation.

Total blood protein may be reduced due to impaired protein synthesis by the pancreas. Bilirubin levels elevated in acute pancreatitis are probably related to biliary tract obstruction. Elevated blood glucose levels may be associated with pancreatic dysfunction, as the pancreas plays an important role in regulating blood sugar levels. Aminotransferases (ALT and AST): These enzymes may be elevated in complicated pancreatitis when there is damage to other organs such as the liver.

Thus, the increased serum content of alpha-amylase (P<0.001), transaminases (AsAT (P<0.01), AlAT (P<0.001)), alkaline phosphotase (P<0.001), urea (P<0.001), bilirubin (total, direct, indirect (P<0.001)) was found. It was found that such parameters as total protein, glucose and creatinine were not significantly increased compared to the values of the control group (P>0.05).

The main symptoms of AP are pain, vomiting and flatulence (Mondor's triad). Typical pain syndrome occurs in acute pancreatitis always usually it is intense, persistent, not controlled by antispasmodics and analgesics. The pain usually appears suddenly, more often in the evening or at night soon after a dietary error (consumption of fried or fatty dishes, alcohol).

According to the questionnaire data, in each formed group of the present study, symptoms on examination and complaints of patients on admission to hospital were analysed.

In the 1st group of patients with non-alcoholic AP with abortive course 11 (26,7%) patients applied with pain, in the 2nd group of patients with non-alcoholic AP with progressive course - 19 (76%).

Almost simultaneously, the pain is accompanied by repeated, painful and unrelieved vomiting. Ingestion of food or water provokes vomiting. Despite the repeated nature of vomiting, the vomiting masses never have a stagnant (faecaloid) character. According to the data obtained from the analysis of anamnestic data, 17 (41.4%) people in the 1st group of patients with AP complained of vomiting, in the 2nd group - 13 (52%).

On examination of the abdomen is noted its bloating, mainly in the upper parts. In severe cases, the abdomen is uniformly bloated, sharply sensitive even with superficial palpation. At deep palpation, the pain is sharply increased, sometimes intolerable. It was also found that the majority of patients in all groups complained of flatulence. So in the 1st group with AP suffered flatulence 33 (80,5%), in the 2nd group - 15 (60%) patients. Cyanosis of face and extremities is considered to be an important and early diagnostic sign of acute pancreatitis. It should be noted that the following signs of acute pancreatitis were detected during face-to-face examination of patients when they were admitted to hospital.

Gray-Turner symptom refers to a clinical sign that may be seen in certain conditions such as pancreatitis or other abdominal diseases. This symptom involves the appearance of patches of cyanosis (livid colouration) or ecchymosis (bruising) on the lateral walls of the abdomen, usually around the lumbar region. This symptom may be an important clinical sign that helps to diagnose and assess the severity of the patient's condition. Thus, it was found that on admission to hospital this symptom was detected only in group 2 of patients with non-alcoholic AP with a progressive course in 5 (20%). Grunwald's symptom is a sign in which there is cyanosis in the perianal region in patients. In the context of acute pancreatitis, Grunwald's symptom may occasionally be observed, especially when haemorrhage around the pancreas or other complications associated

with pancreatitis develop. On reviewing the history of the patients, it was found that this symptom was not present in group 1, but in group 2, it was present in 3 (12%) patients. At palpation in the lumbar region, especially in the left rib-vertebral angle, there is a sharp soreness (Meyo-Robson's symptom). The Meyo-Robson symptom, also known as "rear diaphragm reaction", is a soreness in the left upper quadrant of the abdomen that occurs on palpation or pressure on this area. In the zone of hypersensitivity, detected by superficial palpation, stiffness of the muscles of the anterior abdominal wall is detected. Thus, the Meyo-Robson symptom was detected in all groups of patients with AP. It was found that in the 1st group of patients with non-alcoholic AP with abortive course the symptom was recorded in 12 (29.2%), in the 2nd group of patients with non-alcoholic AP with progressive course in 13 (52%). One of the signs of acute pancreatitis is the phenomenon of absence of abdominal aortic pulsation due to the increase in the size of pancreas and edema of retroperitoneal fibre - Voskresensky's symptom. Voskresensky's symptom, also known as "retroperitoneal murmur" or "lateral percussion", is a medical sign that may be observed in acute pancreatitis. The symptom consists in the fact that when percussing the lateral wall of the abdomen in the subcostal region, there is a characteristic sound resembling a drumstick, and indicates the presence of inflammation in the abdominal cavity, usually in the retroperitoneal fibres [8]. So in the 1st group of patients with AP this symptom was detected in 9 (21.9%), in the 2nd group in 14 (56%) patients. Changes in the liver in AP can be diverse and depend on the degree and nature of the inflammatory process. Instrumental examination is necessary for accurate diagnosis and assessment of the state of the liver and other organs. Ultrasonography (USG) of the abdomen is also an effective method for diagnosing acute pancreatitis. Its sensitivity, specificity and accuracy are 70.4%, 97.3% and 92.1%, respectively.

According to the obtained data of patients' anamnesis, it was found that changes in the liver condition were in all groups of patients with AP. Thus, in the 1st group 24% (10) of patients showed an increase in the size of the organ, in the 2nd group - 41.2% (10) people. Ultrasound of the pancreas plays an important role in the diagnosis of AP. In this disease, the pancreas changes its structure and size. So on ultrasound the increase in the size of the pancreas in the 1st group was revealed in 96% (39) of patients, whereas in patients with AP, and in the 2nd group - 100% enlargement of this organ was found. Also the study of indistinctness of pancreas contours in the 1st group of patients with AP of non-alcoholic origin with abortive course was found in 88% (36), in the 2nd group of patients with AP of non-alcoholic origin with progressive course in 88,2% (22) patients. The property of echogenicity is the property of tissues to reflect ultrasound waves, and increased echogenicity may indicate the presence of inflammation, oedema or other changes in the tissues of the organ. In AP, the pancreas may become more reflective to ultrasound, which may be manifested by increased echogenicity on ultrasound. In a study of this phenomenon, 100% of patients in all groups had increased echogenicity of the pancreas on ultrasound. A form of AP that is associated with problems in the biliary tract, particularly obstruction of the bile duct or the bile duct that connects to the pancreatic duct. The obstruction may be caused by gallstones, tumours, inflammation or other factors. So in the 1st group of patients with AP of non-alcoholic origin with abortive course was established in 67% (27), in the 2nd group of patients with AP of non-alcoholic origin with progressive course in 78,2% (19) of patients.

The immune system plays an important role in the regulation and recovery of acute pancreatitis. However, the impact of the disease on the immune system can be complex and depends on many factors, including the severity of the disease and its aetiology (cause). Acute pancreatitis can affect the body's immune system and, in turn, the immune system may play a role in the development and course of this disease. Comparative analysis of cytokine profile revealed reliable values of the studied mediators of immune response.

Pro-inflammatory cytokines have many functions. Their main role is to "organise" the inflammatory response. One of the most important and early effects of proinflammatory cytokines is the increased expression of adhesion molecules on endothelial cells, as well as on

leukocytes themselves, which leads to the migration of leukocytes from the bloodstream into the focus of inflammation. Proinflammatory cytokines have predominantly local action. The entry of excessively secreted proinflammatory cytokines into the circulation contributes to the manifestation of systemic effects of inflammation, and also stimulates the production of cytokines by cells distant from the focus of inflammation. At the systemic level, proinflammatory cytokines stimulate the production of acute phase proteins, cause an increase in body temperature, affect the endocrine and nervous systems, and in high doses lead to the development of pathological effects (up to septic shock) [14]. Interleukin-2 (IL2/IL-2) is one of a family of polypeptides that mediate the interaction between leukocytes. It was originally called T-cell growth factor. It stimulates proliferation and enhances the function of other T cells, natural killer (NK) cells and B cells. IL-2-activated B-cells generate secretory rather than membrane-bound IgM, and macrophages reach maturity and produce transforming growth factor-β (TGF-β) upon IL-2 stimulation. As can be seen in Fig.2, the analysis of serum IL-2 content in patients with AP of different course established significantly significant indices. Thus, IL-2 synthesis in the 1st group of AP patients was increased 6,1 times (P<0,001), in the 2nd group of AP patients 7,7 times (P<0,001) in comparison with control values (1st group - 56,90±2,32 pg/ml, 2nd group - 72,29±3,11 pg/ml against 9,34±0,26 pg/ml). Median (Me) serum IL-2 of examined patients in group 1 with AP abortive course was 51.9 pg/ml, interquartile range (IQR) 25-75% (Q1 - Q3) 45.9 - 86.5 pg/ml, whereas in the 2nd group of patients with OP with progressive course Me was 73,5 pg/ml, IQR Q1 - Q3 65,9 - 85,3 pg/ml, in comparison with the control group Me 9,4 pg/ml, IQR Q1 - Q3 8,10 - 10,35 pg/ml. The obtained results in patients with AP of non-alcoholic origin, especially with abortive course, probably can be elevated due to the inclusion of the immune system and cytokine response in response to inflammatory processes in the body. We suggest that there are several possible explanations for this, such as activation of the immune system as a response to inflammation in the pancreas; inflammation characteristic of AP, which stimulates the production of various cytokines, including IL-2, as part of the body's immune and inflammatory response to damaged tissue; systemic changes in the body, including dysfunction of the immune system; and it is not excluded that cytokine levels may vary between patients depending on their individual characteristics, including gene. We also suggest that an increased level of IL-2 in patients with non-alcoholic AP with a progressive course may be associated with activation of the immune system and inflammatory processes in the body that characterize this severe and complicated variant of the disease, probably due to the presence of a strong systemic inflammatory reaction, and inflammation activates the immune system, and in response to this activation of IL-2 can be produced in large quantities; by the immune response to infection, due to the weakening of the immune system; progressive AP can cause oxidative stress, which leads to tissue damage and activation of immune cells; progressive AP can cause systemic complications such as organ failure and sepsis, which further activates the immune system and increases the level of cytokines, including IL-2; as well as individual factors.

Interleukin-6 (IL6/IL6) is a pleiotropic mediator of the immune response, synthesized by mononuclear phagocytes, fibroblasts, lymphocytes, hepatocytes, endothelial, mesangial and other cells. IL-6 is a strong pro-inflammatory cytokine, like IL-1 and TNF, but is produced later than the latter, inhibits their formation, and belongs to cytokines that complete the development of an inflammatory reaction. It is known that IL-6 has a great influence on the regulation of the immune response: it provides stimulation and proliferation, as well as differentiation of B cells, enhances antibody formation, and also participates in the production of multipotent colony-forming factors and megakaryocytes, can suppress apoptosis of neutrophils, which have high cytotoxic activity against tumor cells, stimulates hepatocytes to synthesis various plasma proteins.

Determination of IL-6 concentration in the blood can be used as a marker of activation of the immune system. Normally, IL-6 is present in small amounts in the blood or is not detected at all.

The analysis of the results of the conducted studies showed that the level of IL-6 in the groups of patients with OP significantly exceeded the values of the control group many times. Thus, the

IL-6 content in the 1st group of patients with OP was increased by 7.7 times, with an average value of 62.50±2.21pg/ml (P<0.001), and in the 2nd group by 8 times, with an average value of 64.84±2.35 pg/ml (P<0.001), then as a control group, this indicator averaged 8.12±0.42 pg/ml.

The Me of serum IL-6 of the examined patients of the 1st group with OP with abortive course was 63,1 pg/ml, IRR Q1 - Q3 52,7 - 71,7 pg/ml, and in the 2nd group of patients with AP with progressive course Me was 65,1 pg/ml, IRR Q1 - Q3 54,5 - 77,1 pg/ml, in comparison with the control group Me 7,8 pg/ml, IRR Q1 - Q3 6,4 - 9,4 pg/ml. The obtained results allow us to assume that in patients of both groups the increased level of serum IL-6 indicates the presence of the strongest inflammatory response, reaction to tissue damage of pancreas and adjacent organs, cytokines induction in response to toxins and tissue necrosis, systemic effects and complications, concomitant conditions and individual factors.

Transforming growth factor-beta (TGF-β/TGF-β) is a type of cytokine that controls proliferation, cell differentiation, and other functions in most cells.

TGF-β has a variety of functions in the body. Inhibitory effects are predominant when acting on the immune system. TGF-β also influences the formation of cytotoxic NK- and T-cells. Overall, TGF-β plays an important role in the regulation of various processes in the body, including immune response, tissue remodelling, wound healing and anabolic processes.

According to the conducted immunological studies, all obtained indices of the examined patients with AP were significantly different from the serum level of TGF-β, which was many times higher than the control values. So TGF-β expression in the 1st group of patients with AP was increased 3,6 times, with the average value 202,68±3,04 pg/ml (P<0,001), and in the 2nd group 3,2 times with the average value 181,74±7,84 pg/ml (P<0,001), while in the control group the average value was 55,92±2,77 pg/ml.

The median serum TGF-β in the examined patients of the 1st group with an abortive course was 202.4 pg/ml, IQR Q1 - Q3 197.2 - 216.3 pg/ml, and in the 2nd group of patients with progressive course Iu was 187.5 pg/ml, IQR Q1 - Q3 142.3 - 214.3 pg/ml, compared with the indicators of the control group Iu 56.8 pg/ml, IQ Q1 - Q3 43.35 - 69.10 pg/ml.

The results indicate a likely complex and multifaceted relationship between elevated serum levels of TGF-β and AP of non-alcoholic origin with abortive and progressive course. Such relationships require additional research and analysis, and they may depend on many factors, including the individual characteristics of patients, the stage of the disease and the dynamics of its course. Here are some possible aspects of this relationship: TGF-β plays an important role in the regulation of inflammatory and reparative processes.In the case of AP, even with abortive course, inflammation and damage to pancreatic tissues may occur. An increased level of TGF-β may be part of the body's attempts to activate repair and healing mechanisms, as well as it may indicate a more intense inflammatory response in AP. With a progressive course, it is associated with a more severe and prolonged inflammation of the pancreas and surrounding tissues. Tissue damage during AP can lead to the formation of fibrous tissues. TGF-β is involved in the regulation of fibrosis processes that may occur during tissue healing. Progressive AP is accompanied by a more pronounced formation of fibrous tissues, which can lead to an increase in the level of TGF-β.Also, TGF-β can affect immune responses in the body, immune changes may be associated with the course of AP, even if it is abortive.

Thus, research in the field of acute pancreatitis, including analysis of clinical, laboratory and immunological parameters, is key to a deeper understanding of this disease and its mechanisms. Such an integrated approach makes it possible to develop more effective strategies for the diagnosis, treatment and prevention of acute pancreatitis. It is important to emphasize that data collection and analysis should be conducted in strict accordance with ethical standards and regulations in the field of human research. Acute pancreatitis research requires the cooperation of medical institutions, scientists and specialists in various fields in order to achieve the best results and improve the health of patients.

The results obtained proved the effectiveness of the proposed new method for determining clinical and immunological disorders in acute pancreatitis, which was expressed in improving treatment results, reducing the frequency or absence of relapses of the disease, improving quality of life and reducing the level of unsatisfactory outcome with a significant increase in the number of good outcomes.

Conclusions :

1. A clinical, instrumental and laboratory study of patients with an established diagnosis of acute pancreatitis of non-alcoholic origin with abortive and progressive course was conducted.
2. There was a significant increase in some parameters in the general and biochemical blood analysis in the examined patients with AP.
3. A study of the cytokine profile of patients with an established diagnosis of acute pancreatitis of non-alcoholic origin with abortive and progressive course was conducted.
4. A significantly high serum IL-2 content was found in the 1st group of patients with AP by 6.1 times, in the 2nd group of patients with AP by 7.7 times compared with the control values.
5. A significantly significant increase in serum IL-6 was revealed in the 1st group of patients with AP by 7.7 times, in the 2nd group by 8 times compared with the control values.
6. Measuring serum IL-6 levels can be useful both in the diagnosis and monitoring of acute pancreatitis, not only with progressive, but including its abortive course.

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