

ASSESSMENT OF THE IMPACT OF ENDOTOXICOSIS IN CHRONIC PANCREATITIS ON THE PSYCHO-EMOTIONAL STATE AND AUTONOMIC STATUS OF PATIENTS

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Abstract

We examined 69 patients with a diagnosis of CP who were treated on an outpatient basis. The following hematological indices were determined: leukocyte intoxication index (LII), adaptation index (IA) with subsequent determination of the type of non-specific adaptive response, lymphocyte-granulocyte index (ILG).

The correlations of LII with the parameters of psycho-emotional state (neuroticism, reactive (RA) and personal (PA) anxiety according to the Eysenck, Spielberger-Khanin questionnaires), AD according to the Wayne questionnaire, the duration of the disease and condition of the pancreas were studied.

The obtained results proved the presence of significant interactions between the parameters of inflammation and endotoxycosis with indicators of autonomic status and the state of the pancreas. All of this makes it necessary to prescribe anti-inflammatory and vegetotropic drugs to the patients with CP in order to enhance protocol treatment.

Keywords: *chronic pancreatitis, endogenous intoxication syndrome, autonomic status, leukocyte intoxication index, adaptation index, lymphocyte-granulocyte index.*

Introduction

The Syndromes of endogenous intoxication (SEI) and autonomic dysfunction (AD) belong to the typical and defining clinical and pathogenetic mechanisms of formation and severity of chronic pancreatitis (CP). According to modern views, SEI is a non-specific process of clinical and biochemical manifestations, which is the result of disorders of microcirculation, gas exchange, lipid peroxidation processes. SEI is accompanied by a discrepancy between the formation and excretion of both products of normal metabolism and the accumulation of substances of pathological metabolism, tissue destruction and cellular stress mediators [1, 2]. The components of SEI during exacerbation of CP are an increase in the level of pancreatic enzymes in the blood, activation of the kallikrein-kinin system, proteinase-inhibitory imbalance in combination with coagulation disorders, accumulation of medium molecular peptides, oxidative stress [3, 4, 5, 6]. Oxidative stress is not only one of the pathogenetic mechanisms of CP development, but also its complications: diabetes and pancreatic cancer [7, 8, 9].

SEI can be identified by the content of medium weight molecules, cytokines, immunoglobulins and other markers, as well as hematological indices. Currently, the following classification of hematological indices is used (Ovsyannikova, 2007): 1) indices of intoxication (leukocyte intoxication index of J. Kalf-Kalif (LII), hematological index of intoxication, index of nuclear shift; 2) indices of non-specific reactivity (index of the ratio of neutrophils and lymphocytes, adaptation index (IA)); 3) indices of inflammatory activity (lymphocyte-granulocyte index (ILG), index of the ratio of leukocytes and ESR). LII is one of the most important indicators for assessing the course, treatment effectiveness and prognosis of diseases [10]. It makes it possible to assess the state of the inflammatory and intoxication component in the clinical course of the disease.

An important parameter is the state of the autonomic nervous system, because it is through it that the connection between the body and the psyche is established as well as the body's readiness for effective adaptation to the disease. The disease

is perceived by the body as stress. According to the theory of Hans Selye, who was the first to propose the term "stress" in 1936, there are successive stages of eustress and distress. Eustress is also called "good" stress, because during this stage the body's defenses are mobilized, which makes it possible to maintain homeostasis. Distress is characterized by disruption of adaptive reserves and, as a consequence, the emergence of manager's syndrome, psychosomatic diseases and others [11, 12, 13]. Thus, stress is essentially an adaptation, a non-specific protective reaction that occurs in response to various stressors. These include environmental pollution, difficulties at work or in family life, non-compliance with work and rest, and so on.

There are favorable non-specific adaptive reactions of eustress, which include calm activation and increased activation and adverse distress reactions – defective adaptation, stress, reactivation. Orientation reactions occupy an intermediate place between favorable reactions and unfavorable ones. The type of reaction is determined by the adaptation index (IA) and the proportion of lymphocytes (%) in the peripheral blood. Eustress reactions are characterized by significant proliferation of lymphoid tissue, increased levels of mineralocorticoids with constant levels of glucocorticoids, balanced functioning of the nervous, endocrine and immune systems. Distress reactions are characterized by increased secretion of cortisol and adrenaline, suppression of the immune system (stress response); excessive proliferation of lymphoid tissue with lymphocytosis (reactivation); adrenal depletion and absolute leukopenia (defective adaptation) [14, 15]. The assessment of IA makes it possible to improve the comprehensive treatment of the patient, which motivated the study of this indicator in patients with CP.

The value of ILG in CP was also evaluated, because with the help of this index it is possible to differentiate the nature of intoxication (autoimmune or infectious). The growth of ILG is possible in autointoxication due to the formation of endotoxins and is associated with relative lymphocytosis [16].

The article also analyzes the peculiarities of the state of the autonomic nervous system in patients

with CP, as the presence of AD complicates the course of CP. All organs and systems of our body are under the constant control of the autonomic nervous system. The problem of chronic pancreatitis remains one of the most topical problems in modern gastroenterology. Despite the introduction of new methods, there is a low effectiveness of treatment of CP, which is probably due to lack of knowledge about certain mechanisms of pathogenesis, in particular the role of AD in the development and progression of CP. Thus, the peculiarities of the state of the autonomic nervous system in CP are of considerable scientific interest. We did not find any studies of hematological indices of inflammation and intoxication, and especially in comparison with parameters of autonomic status of patients with CP, which motivated us to conduct this research work.

Methods

We examined 69 patients diagnosed with CP, who were treated on an outpatient and day patient basis, as well as in the Department of Internal Medicine of the Ternopil Municipal City Hospital №2. The proportion of men among the examined was 48 % (n = 33), women – 52 % (n = 36). Patients of working age predominated. The average duration of the disease was (9.1 ± 3.8) years. The diagnosis of CP was established on the basis of a clinical protocol adopted in accordance with the order № 638 of the Ministry of Health of Ukraine dated 10.09.2014. Patients with CP in the phase of exacerbation and unstable remission (10-14 days of treatment) underwent general clinical and biochemical examinations. Accompanying diseases among the examined patients with CP were gastroduodenitis, secondary enterocolitis, noncalculous cholecystitis in remission, cryptogenic and reactive hepatitis in remission, inactive viral hepatitis C, type II diabetes mellitus, mild form in the phase of compensation, stage 1 hypertension, osteochondrosis and ascariasis.

The following hematological indices were determined: leukocyte intoxication index (LII), adaptation index (IA) with subsequent determination of the type of non-specific adaptive response, lymphocyte-granulocyte index (ILG).

The leukocyte index of intoxication of J. Kalf-Kalif (LII) was calculated by formula 1:

$$\text{LII} = (4 \times \text{myelocytes} + 3 \times \text{juveniles (metamyelocytes)} + 2 \times \text{band neutrophils} + \text{segmented neutrophils}) \times (\text{plasma cells} + 1) / (\text{lymphocytes} + \text{monocytes}) \times (\text{eosinophils} + 1) \text{ (formula 1).}$$

Normative values of LII vary depending on age – from 0.62 ± 0.09 to 1.6 ± 0.5. LII values in the range of 1.0-2.0 indicate mild, 2.1-7.0 – moderate, 7.1-12.0 – severe, more than 12.1 – terminal degree of SEI [10].

Non-specific reactivity was determined by the adaptation index (IA) according to formula 2:

$$\text{IA} = \text{lymphocytes} / \text{band neutrophils} \text{ (formula 2).}$$

The stress response is characterized by IA up to 0.30, and the proportion of lymphocytes up to 20 %, the orientation reaction – respectively 0.31-0.50 and 20-28 %, the reaction of mild activation – 0.51-0.70 and 29-33 %, the reaction of increased activation – 0.71-0.9 and 34-45 %, the reaction of re-activation – more than 0.90 IA and more than 45 % of lymphocytes, respectively. At defective adaptation absolute leukopenia (<4.1×10⁹/L) is observed.

Lymphocyte-granulocyte index (ILG) was determined by formula 3:

$$\text{ILG} = (\text{lymphocytes} \times 10) / (\text{myelocytes} + \text{metamyelocytes} + \text{band neutrophils} + \text{segmented neutrophils} + \text{eosinophils} + \text{basophils}) \text{ (formula 3).}$$

Regulatory values range from 4.19 to 4.93.

The correlations of LII with the parameters of psycho-emotional state (neuroticism, reactive (RA) and personal (PA) anxiety according to the Eysenck, Spielberger-Khanin questionnaires), AD according to the Wayne questionnaire, the duration of the disease and condition of the pancreas were studied. The indicators of RA and PA were evaluated according to the generally accepted method: low indicators were considered up to 30 points, medium – 31-45 points, high – more than 45 points.

Neuroticism was considered to be mild when receiving 3-7 points, moderate – 8-11 points, pronounced – 12-15 points, quite pronounced – 16-18 points, extremely pronounced – 19-24 points. Less than 12 points were considered to be emotional stability.

The Wayne Questionnaire, which consists of 11 questions, was used to identify signs of autonomic disorders. The sum of points above 15 indicates a high probability of autonomic dysfunction.

The condition of the pancreas was assessed by the content of pancreatic α-amylase in the blood

and ultrasound data in points. The following signs indicate a chronic process in the pancreas: the decrease or increase of the organ or its part in size; fibro-sclerotic changes in the parenchyma; blurred contours; heterogeneity of structure; calcifications; dilation of the ducts of the pancreas; presence of pseudocysts, calcification.

Statistical processing of the study results was performed using the program Statistica 6.0. The average values (M) as well as their standard errors (m) were calculated and analyzed. The probability of discrepancies in the average values was assessed by Student's t-test. Wilcoxon (W)-test was used for the populations whose distribution differed from the normal. Correlation analysis (r) was performed with the calculation of the Pearson correlation coefficient in the presence of a normal distribution and Spearman rank correlation coefficient – in the case of distribution other than normal. The results were considered reliable at the level of their statistical significance $p < 0.05$.

Results

According to the Eysenck questionnaire, 71 % of patients with CP showed an increased level of neuroticism (mean 14.9 ± 2.2). Patients with CP according to the level of neuroticism were distributed as follows: in 25.0 % (n = 17) – pronounced, in 31.0 % (n = 22) – quite pronounced, in 15 % (n = 10) – extremely pronounced neuroticism. Normal values were observed in only 29 % of patients: in 7 % of patients (n = 5) found little expressed, and in 22 % (n = 15) – moderate neuroticism. According to the Wayne questionnaire, 87 % (n = 60) of patients with CP showed signs of autonomic dysfunction.

We also found an increase in both reactive and personal anxiety (the distribution of all patients by the level of reactive and personal anxiety is shown in Fig. 1.). The average value of reactive anxiety is 44.8 ± 3.3 , personal – 43.1 ± 3.6 .

The depth of endotoxemia according to LII was analyzed. Kalf-Kalif LII values in 63 % (n = 43) of patients with CP showed the presence of signs of SEI of mild and moderate degree of severity (the data are shown in Fig. 2).

An analysis of the structural condition of the pancreas of patients with CP was performed, which was evaluated according to the visualization criteria

of the Marseille-Cambridge classification. Changes in the pancreas in the examined patients corresponded to mild and moderate severity of CP: 21.5 % of patients (n = 15) according to ultrasound 0-1 points, 26.0 % (n = 18) – 2 points, 38.0 % (n = 26) – 3 points, 14.5 % (n = 10) – 4-5 points.

A correlation analysis of the parameters of autonomic dysfunction, LII and the structural state of the gland by ultrasound manifestations in points was performed. Significant correlations were established between LII and personal anxiety (direct weak $r = 0.23$, $p < 0.05$), neuroticism (direct moderate $r = 0.41$, $p < 0.05$), autonomic dysfunction (direct weak, $r = 0.1$, $p < 0.05$), duration of the disease (direct weak $r = 0.15$, $p < 0.05$), structural condition of the pancreas by ultrasound manifestations in points (direct weak) $r = 0.29$, $p < 0.05$), the level of pancreatic α -amylase (direct medium strength $r = 0.30$, $p < 0.05$). Thus, the correlation analysis revealed a statistically significant relationship between the parameters of endotoxemia and autonomic status, as well as the duration of CP and the structural state of the pancreas.

The values of IA in patients with CP were also analyzed (data in Table 1).

Among the examined patients by the level of IA the most common reaction was orientation – in 39 % of patients (n = 27). Favorable non-specific adaptive reactions (mild activation and increased activation) were observed in 36 % (n = 25), distress reactions (stress, reactivation, defective adaptation) – in 25 % (n = 17). The average value of IA was 0.48 ± 0.18 , which corresponds to the upper limit of the orientation reaction. In our opinion, special attention should be paid to patients with an orientation reaction according to the level of IA, since orientation reactions may be insufficient and become a background for the progression of chronic pancreatitis under stressors, which for patients with CP can be psycho-emotional stress due to the long duration of the disease, the presence of pain, the need to follow a diet etc.

Inflammatory activity in our study was determined by ILG. The average value of the ILG index was 4.7 ± 1.7 . An increase in the index, indicating the predominance of the autoimmune component of intoxication, was observed in 42.0 % (n = 29) of the examined, the average value of the

index in this group was 6.4 ± 1.2 . This change is associated with relative lymphocytosis. The main function of granulocytic neutrophils is to protect against pathogenic microorganisms, whereas lymphocytes are involved in immunological reactions, including autoimmune. The value of the index within the norm was set in 10.0 % of patients ($n = 7$) – 4.4 ± 0.19 , the overall immune response in this group had no significant deviations from the adequate immune response. In 48 % ($n = 33$) of patients with CP, the value of ILG was below its lower limit – 3.3 ± 0.5 , which indicates the predominance of granulocytes in the dynamics of the immune response. The lag in the response of monocytes and lymphocytes reflects a decrease in their activity and a delay in the phase of complete phagocytosis. This imbalance reflects the protracted process of the disease with the inability of the immune system to complete the inflammation. The identified features need to be taken into account in the formation of treatment tactics of these patients.

Discussion

According to the Eysenck questionnaire, 71 % of patients with CP showed an increased level of neuroticism (mean 14.9 ± 2.2). We also found an increase in both reactive and personal anxiety. In our opinion, a large proportion of patients with moderate and high levels of anxiety can be explained by a rather long course of CP – (9.1 ± 3.8) years.

In 63 % of patients with chronic pancreatitis, the presence of endogenous intoxication of mild and moderate severity according to the Kalf-Kalif index has been established, which makes it necessary to use medications aimed at its correction.

Significant correlations were established between LII and personal anxiety (direct weak $r = 0.23$, $p < 0.05$), neuroticism (direct moderate $r = 0.41$, $p < 0.05$), autonomic dysfunction (direct weak, $r = 0.1$, $p < 0.05$), duration of the disease (direct weak $r = 0.15$, $p < 0.05$), structural condition of the pancreas by ultrasound manifestations in points (direct weak) $r = 0.29$, $p < 0.05$), the level of pancreatic α -amylase (direct medium strength $r = 0.30$, $p < 0.05$). This proved the presence of significant interactions between the parameters of inflammation and endotoxemia with indicators of autonomic status and the state of the pancreas. Therefore, it is

necessary to prescribe anti-inflammatory and vegetotropic drugs to patients with CP to enhance protocol treatment.

Among patients with CP, favorable adaptive reactions were observed in only 36 % of the examined, adverse – in 25 %, intermediate – in 39 %, and the average value of the adaptation index was – 0.48 ± 0.18 , which corresponds to the upper limit of the orientation reaction. This motivates additional prescription of vegetotropic and adaptogenic drugs to such patients with CP.

Only in 10 % of patients with chronic pancreatitis the general immune response has no deviations from the adequate immune response, in 48 % of the examined there is an inability of the immune system to complete inflammation, in 42 % – the predominance of autoimmune intoxication, which requires to enhance the anti-inflammatory therapy with bioregulatory drugs in order to harmoniously complete the inflammation.

Acknowledgments

The authors declare no conflict of interest. The authors declare, that all the procedures and experiments of this research respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008, as well as the national law.

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Table 1. Distribution of patients with CP by IA

	Type of reaction	Proportion of patients % / abs.value	Average value
Favorable non-specific adaptive reactions	Mild activation	19 % (n=13)	0.25±0.028
	Increased activation	17.4 % (n=12)	0.36±0.036
Neutral reactions	Orientation reaction	39 % (n=27)	0.56±0.043
Adverse distress reactions	Stress	11.6 % (n=8)	0.73±0.020
	Reactivation	3 % (n=2)	0.98±0.065
	Defective adaptation	10 % (n=7)	0.56±0.196

Figure 1. Distribution of patients by the level of RA and PA

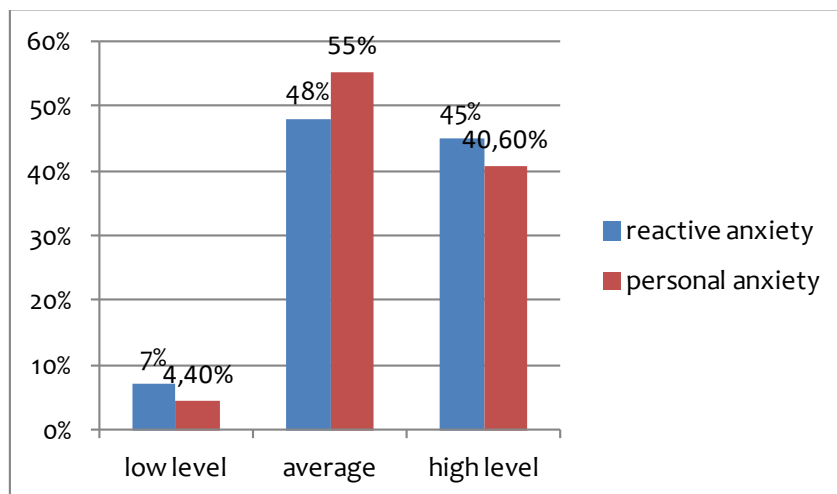


Figure 2. Distribution of patients with CP according to the degree of endogenous intoxication according to LII values

