

**THE STATE OF NEUROPEPTIDE-CYTOKINE STATUS IN ISCHEMIC HEART DISEASE**

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ABSTRACT

The spread of metabolic syndrome (MS) in developed countries, which, according to WHO experts, assumed the nature of a pandemic in the XXI century, contributes to the increase in the incidence of coronary heart disease (CHD). MS is currently considered a kind of cluster of risk factors for atherosclerosis, coronary heart disease and type 2 diabetes mellitus. Since the main diagnostic sign of MS is abdominal type of obesity, it is natural to assume that if it is present, certain clinical and pathogenetic features should be revealed in patients with coronary heart disease. By a well-known analogy with phenotypes Currently, chronic obstructive pulmonary disease can be considered a special phenotype of coronary heart disease against the background of abdominal obesity. A decrease in the production of endorphins is accompanied by an increase in the activity of the sympathetic system, an increase in the production of cortisol by the adrenal glands, stimulation of gluconeogenesis, increased synthesis of triacylglycerols and lipogenesis, which creates conditions for the potentiation of atherogenesis.

Keywords: ischemic disease, atherosclerosis, anxiety, depression, beta-endorphin, cytokines.

INTRODUCTION

The occurrence of coronary heart disease in combination with anxiety-depressive disorders is widespread in clinical practice. In such patients, affective spectrum disorders significantly aggravate the course of cardiological pathology in the form of progression of the atherosclerotic process and aggravate the prognosis. In modern literature, much attention is paid to the role of cytokines in the pathogenesis of various diseases. The cytokine network is a self-regulating system, the violation of which leads to excessive or insufficient synthesis of detectable cytokines, which, in turn, can cause the development of various pathological processes that form the basis of a wide range of human diseases. Proinflammatory cytokines have an effect on almost all organs and systems of the body involved in the regulation of the homeostasis system. At the same time, the role of cytokine status changes in the formation and progressive course of occupational neurointoxications is unexplored.

Markers of immune inflammation, and above all cytokines, are of particular importance in the proatherogenic effect in the foci of atherosclerosis. The main regulators of such processes at the neuroimmune level are endogenous opiate peptides. Their role in stabilizing the cytokine



content during the development of inflammation in the atherosclerotic plaque and in the process of adaptation of the heart muscle to stressful influences is noted. Despite the availability of reliable data on the role of markers of immune inflammation in atherogenesis, the validity of the regulatory value of opiate peptides in this process is still open questions about the influence of affective spectrum disorders on the neuropeptide-cytokine status of the immune system in patients with chronic coronary artery disease, as well as in what range these changes will be traced in pain and pain-free myocardial ischemia. In this connection, the purpose of this study was to assess the effect of the severity of anxiety-depressive disorders on the neuropeptide-cytokine status of the immune system in patients with chronic coronary artery disease in various clinical variants of its course, as well as a comparative characteristic of the degree of these changes in pain and pain-free myocardial ischemia.

Groups were formed, which, in turn, were divided into subgroups according to the percentage of painful and pain-free episodes of angina pectoris: 1st (n = 36) – patients with chronic coronary heart disease occurring against the background of moderate anxiety-depressive disorders; 2nd (n = 34) - subjects with chronic coronary heart disease and mild anxiety-depressive disorders; 3rd (n = 20) - patients with chronic coronary heart disease without anxiety-depressive disorders; 4th (n = 22) – control (healthy individuals). By the presence of painful and pain-free episodes of angina pectoris the authors highlighted: in the 1st group of patients, the painful form of coronary heart disease was detected in 44% of the examined (n = 17), the painless form of coronary heart disease was found in 56% of patients (n = 19); in the 2nd group of patients, the painful form of coronary heart disease - in 52% of the examined (n = 18), the painless form of coronary heart disease – in 48% (n = 16); in the 3rd group, the painful form CHD was confirmed in 37% of patients (n = 8), the painless form of CHD – in 63% of patients (n = 12). In all groups, the state of the psychophysiological status (psychological testing), the level of autonomic regulation (β -endorphin), the function of the cardiovascular system (SMECG) and peripheral blood levels of TNF α , IL-1 β , IL-6 and IL-4, IL-10 were evaluated. In the course of a clinical and laboratory examination, the authors found that in patients with chronic IHD, anxiety-depressive disorders have a direct pathological effect on the neuropeptide-cytokine status of the immune system in the form of suppression beta-endorphin, increasing the level of pro-inflammatory and reducing anti-inflammatory cytokines. At the same time, the most significant changes occur in subjects with pain-free myocardial ischemia.

INTRODUCTION

Anxiety-depressive disorders in comorbidity with diseases of the cardiovascular system are widespread in the clinic of internal diseases. At the same time, the presence of anxiety-depressive disorders in patients with coronary heart disease (CHD) has acquired the greatest relevance in clinical practice. In such patients, affective spectrum disorders significantly aggravate the course of cardiological pathology, contribute to the progression of atherosclerotic processes and lead to earlier complications in the form of myocardial infarction and strokes. Among the main pathophysiological mechanisms of the effect of anxiety-depressive disorders on the atherosclerotic process in patients with coronary heart disease, such



as disruption of interactions between the autonomic nervous and immune systems, activation of immune inflammation in the atherosclerotic plaque, the formation of an imbalance between the action of pro-inflammatory and anti-inflammatory cytokines should be considered.

The special importance of markers of the immune system, and above all cytokines, to have a proatherogenic effect in the foci of atherosclerosis is noted. Thus, TNF α enhances the expression of adhesion molecules on the endothelium, activates macrophages, neutrophils, promotes the secretion of prostaglandins and causes the synthesis of proteins of the acute phase of inflammation. IL-1 β triggers a cascade of inflammatory processes after damage to the endothelial wall, and IL - 6 promotes activation of the endothelium, enhances its adhesive ability to platelets and leukocytes, which leads to proliferation of smooth muscle elements of the vascular bed.

Regulators of pro-inflammatory and anti-inflammatory cytokines in the atherosclerotic process are endogenous opiate peptides of the autonomic nervous system (ANS). A special role here belongs to opioid peptides from the propiomelanocortin group, and first of all β -endorphin. Marked the ability of beta-endorphin to regulate cytokine production during the development of inflammatory processes during stress and depressive disorders. In addition, β -endorphin participates in the formation of stable anti-inflammatory activity during the progression of immune inflammation and thereby supports compensatory and adaptive nature of the immune system against the background of unfavorable external and internal conditions. High activity of β -endorphin increases the resistance of the myocardium to ischemic damage against the background of emotional stress, as well as in the process of adaptation of the heart muscle to stressful influences.

Thus, it follows from the above that atherosclerotic changes in the myocardium are the result of complex processes of neuroimmune interactions, in which the main role is assigned to cytokine links of the immune system and endogenous opiate peptides. Their participation in the atherosclerotic process, as a rule, strictly correlates with the presence of chronic stress in the anamnesis and, as a result, will be an unfavorable prognostic factor not only in the formation of anxiety-depressive disorders, but also in terms of the progression of cardiological pathology.

Nevertheless, to date, questions remain open about the effect of affective spectrum disorders on the neuropeptide-cytokine status of the immune system in patients with chronic coronary heart disease, as well as in what range these changes will be traced in painful and pain-free myocardial ischemia. The obtained data will contribute to the disclosure of additional links of pathogenesis in the atherosclerotic process at the level of neuroimmune interactions, which will allow objectifying the expediency of the use of in the therapy of patients with coronary heart disease and anxiety-depressive disorders, not only standard cardiotropic drugs, but also psychotropic drugs in combination with psychotherapeutic treatment.

In this regard, the purpose of this study was to assess the effect of the severity of anxiety-depressive disorders on the neuropeptide-cytokine status of the immune system in patients with chronic coronary artery disease in various clinical variants of its course, as well as a comparative characteristic of the degree of these changes in pain and pain-free myocardial ischemia.



MATERIALS AND METHODS

A clinical examination was conducted of 90 patients (men) aged 45 to 58 years, the average age was (51.0 ± 6.4) years. All subjects were represented by patients with a chronic form of coronary artery disease, occurring with painful and pain-free episodes of angina pectoris (I25 according to ICD-10) in comorbidity with anxiety-depressive disorders (41.2 according to ICD-10) of varying severity. The duration of observation of patients was 22 ± 7.3 days.

To solve the tasks set out in this work, groups of comorbid patients with anxiety-depressive disorders were formed:

1st ($n = 36$) – patients with chronic coronary artery disease occurring against the background of moderate anxiety and depressive disorders; 2nd ($n = 34$) - subjects with chronic coronary artery disease and mild anxiety and depressive disorders; 3rd ($n = 20$) – patients with chronic coronary heart disease without anxiety-depressive disorders; 4th ($n = 22$) - control (healthy individuals).

The exclusion criteria were patients with an active inflammatory process, oncological diseases and diseases of the immune system. In order to study the degree of influence of the severity of anxiety-depressive disorders on the state of the neuropeptide-cytokine status of the immune system in various variants of the course of chronic coronary heart disease, a clinical and laboratory study was conducted. In the examination groups, the state of the psychophysiological status, the level of autonomic regulation were studied, the function of the cardiovascular system and the indicators of the content of pro-inflammatory and anti-inflammatory cytokines in the peripheral blood were evaluated.

Psychological and psychophysiological processes were investigated using a standardized multifactorial personality study (SMIL), which is an adaptive version of the Minnesota Multidisciplinary Personality Questionnaire (MMPI), the 8-color Lusher test, the Spielberger–Hanin self-assessment scales of reactive and personal anxiety.

The indicators of the following SMIL test scales were analyzed: HS (hypochondriac fixation), D (propensity to depressive reactions), HY (propensity to hysteroid reactions), PD (psychopathic deviations), PA (propensity to paranoid reactions), RT (propensity to psychoasthenic reactions). The indicators of the following SMIL test scales were analyzed: HS (hypochondriac fixation), D (propensity to depressive reactions), HY (propensity to hysteroid reactions), PD (psychopathic deviations), PA (propensity to paranoid reactions), RT (propensity to psychoasthenic reactions).

The Lusher test parameters were used: LrSTR (presence of a stressful state), LrTR ((anxiety), Lr85 (concentricity/eccentricity), Lr NO-1 (deviation from the autogenic norm), Rp-1 (deviation from the general norm), LRLICH (balance of personal properties), LrVNS (vegetative index characterizing the balance of the autonomic nervous system). The presence of chronic coronary heart disease was verified in stationary conditions by examining the cardiovascular system using objective data (complaints, anamnesis) and instrumental research methods (ECG, daily monitoring of ECG with load tests, EchoCG). To assess the function of the cardiovascular system in coronary heart disease in this work, the indicators of daily ECG monitoring were evaluated.



A standard arrangement of electrodes on the chest was used in order to obtain modified chest leads V1 and V5. Subsequent analysis of the results made it possible to identify the nature of rhythm and conduction disturbances, transient decrease in the S-T segment, daily circadian heart rate variability. The following indicators were evaluated: the number, duration of painful and pain-free angina attacks, the depth of ST-segment depression, heart rate at the beginning of ischemic episodes. Horizontal or descending depression was considered ischemic ECG changes of the ST segment by 1.0-1.5 mm or more, the rise of the ST segment by 2 mm, as well as the transient inversion of the T-wave.

In all groups of inpatient examination, the presence of painful and pain-free episodes of angina pectoris was found, among which were: in the 1st group of patients, the painful form of coronary artery disease in 44% of the examined ($n = 17$), the pain-free form of coronary artery disease was established in 56% of patients ($n = 19$); in the 2nd group of patients, the painful form of coronary heart disease was detected in 52% of the examined ($n = 18$), the painless form of coronary heart disease – in 48% ($n = 16$); in the 3rd group, the painful form of coronary heart disease was confirmed in 37% of the examined ($n = 8$), the painless form CHD – in 63% of patients ($n = 12$). In all groups, painful and pain-free episodes of myocardial ischemia according to their equivalent, according to the accepted classification of the Canadian Society of Cardiology, they corresponded to the I-II functional class of angina pectoris.

The state of the suprasedgmental apparatus of the ANS was assessed by determining the level of the opioid peptide from the proopiomelanocortin group in the peripheral blood – beta-endorphin with the use of foreign BioSource International test systems (USA, California). The sensitivity of the method was 0.04-0.06 pg/ml. The cytokine status of the immune system was studied using test systems of domestic and foreign production to determine pro-inflammatory (TNF α , IL-1 β , IL-6) and anti-inflammatory (IL-4, IL-10) cytokines in the blood serum of patients by enzyme immunoassay. We used BioSource test systems International (USA, California) for the determination of IL-1 β , IL-4 and firms in blood serum ProCon (Saint Petersburg) – TNF α , IL-6, IL-10. The sensitivity of test systems for the determination of cytokines is 2 pg/ml, β -endorphin is 0.04-0.06 pg/ml.

Mathematical data processing was carried out on an IBM-compatible personal computer. The electronic database was created in the Microsoft Excel 2007 software environment, statistical analysis was performed using the Statistica for Windows application software package 6.0 (StatSoft, USA). The compliance of the studied samples with the law of normal distribution was preliminarily evaluated. The arithmetic mean and its standard deviation were determined ($M \pm SD$), 95% is the confidence interval for the mean ($M \pm m$).

RESULTS

Mental and psychophysiological status The individual personality characteristics studied by us with the help of the SMIL test showed that the subjects of the 1st group had a more significant increase in the values on the scales of the neurotic triad D, NS, HY, as well as the scales PD, RA and Rt, which indicates a higher depressive state in these patients compared to patients in group 2 ($p < 0.05$). According to the 8-color Lusher test in group 1, in relation to patients in group 2, the most significant differences were observed in terms of stress, anxiety,



concentricity/eccentricity, vegetative index and deviation from the general norm ($p < 0,05$). When analyzing the scales of the Spielberger–Hanin test, it was found that in patients Group 1 has increased reactive anxiety, which manifested itself in the form of persistent tension, anxiety, attention disorders and anxiety ($p < 0.05$). Personal anxiety in these patients was characterized by a tendency to perceive a large range of situations as threatening, dangerous and directly correlated with the presence of neurotic conflict, emotional and neurotic breakdowns ($p < 0,05$).

In group 2, reactive and personal anxiety was manifested by mild anxiety, tension, less tendency to worry and greater resistance to the effects of stressful social factors.

In the 3rd group, there are no significant deviations from the main indicators on the test scales SMIL, 8-color Lusher test, reactive and personal anxiety according to the Spielberger–Khanin test were not detected, which significantly differed from similar indicators of the 1st and 2nd groups of subjects ($p < 0.05$).

Thus, the revealed changes in the mental and psychophysiological status in the 1st group of subjects indicate the presence of persistent (moderate) depressive reactions, stress, psychopathic and psychasthenic manifestations of personality, as well as instability of vegetative regulation in the form of sympathicotonic type (ergotropic tone) of vegetative influences. In addition, the Spielberger–Khanin test showed that in the group of these subjects there are reactive and personal anxiety, which we regarded as moderate.

Assessment of the function of the cardiovascular system

After daily ECG monitoring in the groups of subjects, the following results were obtained:

– in patients with chronic coronary heart disease and moderate anxiety-depressive disorders, the number of painful and pain-free episodes of myocardial ischemia per day when walking, as well as against the background of low physical exertion (ladder test) significantly exceeded similar indicators in the 2nd and 3rd groups of subjects ($p < 0.05$). The duration of painful and pain-free episodes of myocardial ischemia in such patients also significantly exceeded similar indicators of patients groups 2 and 3 ($p < 0.05$);

– in patients with chronic coronary heart disease and mild anxiety-depressive disorders, the number of painful and pain-free episodes of myocardial ischemia per day, as well as their duration, were significantly higher than the existing changes than in the group of subjects without anxiety-depressive disorders ($p < 0.05$).

From the above, it should be concluded that patients with chronic coronary heart disease and moderate anxiety-depressive disorders have a greater number of pain and pain-free episodes of myocardial ischemia, which became longer in duration and were provoked by less physical exertion than in groups of other patients.

The state of the suprasedgmental area of the VNS

When analyzing the level of β -endorphin in peripheral blood in the examination groups, we revealed a significantly significant decrease in this indicator in the 1st group of patients in relation to the 2nd ($p < 0.05$) and 3rd ($p < 0.05$) groups. A significant decrease in β -endorphin was also found in patients in group 2 in relation to the subjects of group 3 ($p < 0.05$).



In addition, there was an increase in the level of β -endorphin b in the groups of patients with chronic coronary artery disease, occurring with pain-free episodes of angina pectoris, in relation to the subjects with chronic coronary artery disease and pain syndrome ($p < 0.05$).

Thus, a direct pathological effect of the severity of anxiety-depressive disorders on the level of β -endorphin in the form of suppression of its activity on the periphery. Increasing the level of content β -endorphin in subjects with pain-free myocardial ischemia indicates, most likely, about a compensatory reaction in the form of activation of the suprasedgmental region of the ANS, due to a more unfavorable prognostic course of this pathology.

The state of immune regulation

All indicators of cytokines of the pro-inflammatory and anti-inflammatory spectrum in the examination groups varied widely. Thus, it was found that in patients with chronic coronary heart disease, occurring with moderate anxiety-depressive disorders, there is an increase in indicators reflecting the activity of inflammation – TNF α , IL-1 β , IL-6 ($p < 0.05$), suppression of IL-4, IL-10 ($p < 0.05$) in relation to the examined others groups.

In addition, the authors found that in patients with chronic coronary artery disease and pain-free episodes of myocardial ischemia, there is a more significant increase in the activity of TNF α , IL-1 β , IL-6 and suppression of IL-4 and IL-10 than in the painful form of angina pectoris ($p < 0.05$).

The results of the clinical and laboratory examination allow us to summarize that in patients with chronic IHD, anxiety-depressive disorders have a direct pathological effect on the cytokine status of the immune system, and these changes directly correlate with the severity of affective spectrum disorders.

The revealed changes at the level of the cytokine pool of the immune system in pain-free myocardial ischemia in this case indicate a more unfavorable course in the atherosclerotic process in such patients.

CONCLUSIONS

1. The influence of the severity of anxiety-depressive disorders on the clinical course of the chronic form of coronary heart disease was noted. Thus, in patients with coronary heart disease and anxiety-depressive disorders of a moderate nature, a greater number of painful and pain-free episodes of angina pectoris were found, which became longer in duration and were provoked by less physical exertion.
2. The direct pathological effect of anxiety-depressive spectrum disorders on neuroimmune processes was revealed: decrease in the level of β -endorphin; increase proinflammatory cytokines (TNF α , IL-1 β , IL-6) and inhibition of anti-inflammatory cytokines (IL-4, IL-10) spectrum.
3. There was a regulatory imbalance at the level of the neuropeptide-cytokine link of the immune system in pain-free myocardial ischemia, which indicates a more unfavorable prognostic course of this pathology.

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