The Peerian Journal
Open Access | Peer Reviewed
Volume 11, October, 2022.
ISSN (E): 2788-0303
Website: www.peerianjournal.com
Email: editor@peerianjournal.com

Characteristics Of Neuropeptides-Cytokines in Patients with Cardiovascular Pathology Occurring Against the Background of Anxiety and Depressive Disorders

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Abstract
To date, the pathogenetic process of coronary heart disease and hypertension should be based on complex reactions of neuroimmune interactions characterized by activation of proinflammatory cytokines, opiate receptors and endogenous opioid peptides. These changes are mediated by high activity at the the main regulatory systems that increase the resistance of the myocardium to acute and chronic ischemic damage. Nevertheless, there is insufficient data on the severity of these changes in the polymorbid course of coronary heart disease and hypertension, occurring against the background of anxiety and depressive disorders. In this connection, the purpose of this work was to study regulatory disorders at the level of the neuropeptide-cytokine pool of the immune system in patients with polymorbid cardiovascular pathology occurring against the background of anxiety and depressive disorders. A clinical examination of 85 patients (men) aged 35 to 45 years, with polymorbid cardiovascular pathology (ischemic heart disease in combination with hypertension of the second stage), occurring against the background of anxiety and depressive disorders, was conducted. To solve the tasks set out in this work, groups of comorbid patients with anxiety-depressive disorders were formed: 1st (n = 40) - patients with polymorbid pathology; 2nd (n = 20) – patients with ischemic heart disease; 3rd (n = 25) - patients with hypertension of the second stage; 4th (n = 30) – control (healthy persons). In order to study regulatory dysfunctions at the level of the neuropeptide-cytokine link of immunity, the state of the suprasegmental apparatus of the autonomic nervous system and the cytokine pool of the immune system were studied in the examination groups. Test systems were used to determine beta-endorphin, pro-inflammatory cytokines (TNFa, IL-1β, IL-6) and anti-inflammatory (IL-4, IL-10) spectrum in the blood serum of patients.

Key words: ischemic disease, hypertension, anxiety, depression, beta-endorphin, cytokines

Introduction
Currently, systemic inflammatory activity, manifested by the interaction of pro-inflammatory (TNFα, IL-1β, IL-6) and anti-inflammatory (IL-4, IL-10) cytokines, is considered as an integral

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part of the pathogenesis of coronary heart disease (CHD) and hypertension (AH). Changes in the cytokine spectrum in CHD and AH are mediated by high activity of the sympathetic-adrenal and renin-angiotensin-aldosterone systems due to chronic hypoxia and increased catabolic processes. Multiple regulatory effects of cytokines are systematized in a multidirectional way action in the atherosclerotic process. Thus, pro–inflammatory cytokines - TNFα, IL-1β and IL-6 – are considered as atherogenic, and anti–inflammatory factors - IL-4 and IL-10 – as atheroprotective mediators.

According to modern research, cytokines of the pro-inflammatory and anti-inflammatory spectrum are directly involved in the pathogenesis of cardiovascular diseases. At the same time, IL-1ß 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. Against the background of ischemic injuries in organs and tissues, as well as the course of arterial hypertension, the level of atherogenic cytokines in the blood serum increases several times

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The role of regulators of pro-inflammatory and anti-inflammatory cytokines in atherosclerotic processes belongs to endogenous opiate peptides (endorphins and enkephalins) of the autonomic nervous system (ANS). The main effect of opioid neuropeptides, primarily beta-endorphin, is to regulate the synthesis of markers of immune inflammation, primarily cytokines. According to recent studies, it has been found that with coronary heart disease, against the background of psychoemotional stress, there is an increase in the level of beta-endorphin in peripheral blood. Activation of β-endorphin against the background of a stress reaction in patients with coronary artery disease increases the resistance of the myocardium to ischemic damage. The level of beta-endorphin increases significantly during emotional stress, in the process of adaptation of the heart muscle to stressful influences, including immobilization stress, hemorrhagic shock and myocardial hypertrophy.

Acute myocardial ischemia caused by coronary thrombosis, cardiac surgery or coronary artery ligation also leads to an increase in concentration β-endorphin in blood plasma.In addition, in patients with acute myocardial infarction, the level of β-endorphin in blood plasma is 10 times higher than normal, and in people in a state of cardiogenic shock, the concentration of β-endorphin is 20 times higher than in healthy individuals.

It should be summarized that CHD and AH proceed as a complex process of neuroimmune interactions characterized by activation of proinflammatory cytokines, opiate receptors and endogenous opioid peptides, which reduce inflammatory processes at the systemic level, in local foci of atherosclerosis and increase myocardial resistance to ischemic damage. The processes of adaptation of the cardiovascular system to ischemic damage, occurring against the background of prolonged psychoemotional stress, chronic stress, anxiety-depressive and somatovegetative

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disorders, are disrupted. This is primarily due to suppression beta-endorphin at the level of the hypothalamic-pituitary zone, its insufficient anti-ischemic and anti-inflammatory activity. Despite the availability of research results proving that the rapid progression of atherosclerosis in CHD and AH is facilitated by regulatory disorders in the functioning of the autonomic nervous, immune nevertheless, questions remain open about the severity of these dysfunctions at the level of the neuropeptide-cytokine link of immunity with polymorbid cardiovascular pathology occurring against the background of anxiety and depressive disorders.

The aim of the study was to study regulatory disorders at the level of the neuropeptide–cytokine link of the immune system in polymorbid cardiovascular pathology occurring against the background of anxiety and depressive disorders.

MATERIALS AND METHODS

A clinical examination was conducted of 85 patients (men) aged 35 to 45 years, the average age was 38.0 ± 4.6 years. The subjects had coronary heart disease (I20 according to ICD-10) and stage II GB (I10 according to ICD-10) in comorbidity with anxiety-depressive disorders (F 41.2 according to ICD-10). The duration of observation of patients was 24±8.4 days.

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

1st (n = 40) – patients with coronary heart disease and stage II AH; 2nd (n = 20) – patients with coronary heart disease; 3rd (n = 25) – patients with stage II AH; 4th (n = 30) – 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 regulatory dysfunctions at the level of neuropeptides-the cytokine link of the immune system, a clinical and laboratory study was conducted in the examination groups. The state of vegetative regulation and indicators of the cytokine pool of the immune system were studied using test systems of domestic and foreign production to determine beta-endorphin, pro-inflammatory cytokines (TNF α, IL-1β, IL-6) and anti-inflammatory (IL-4, IL-10) spectrum in the blood serum of patients by enzyme immunoassay. We used BioSource test systems International (USA, California) for the determination of IL-1ß, IL-4 and the company in blood serum ProCon (Saint Petersburg, Russia) – TNF α, IL-6, IL-10. The beta-endorphin production parameters were determined using BioSource International test systems (USA, California). The sensitivity of test systems for the determination of cytokines is 2 pg/ml, β-endorphin is 0.04- 0.06 pg/ml.

In addition, qualitative and quantitative paired correlations were evaluated between the main indicators characterizing the state of the suprasegmental apparatus of the ANS (β – endorphin), pro-inflammatory (TNF α, IL-1β, IL-6) and anti-inflammatory (IL-4, IL-10) cytokines. The relationships were evaluated with a correlation coefficient $r < 0.3$ as weak, $0.3 < r < 0.4$ as medium, $0.4 < r < 0.7$ as moderate and $r > 0.7$ as strong.

Mathematical data processing was carried out on an IBM-compatible personal computer. The electronic database was created in the Microsoft Excel 2003-2007 software environment, statistical analysis was performed using the Statistica for application software package Windows. 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 (M±SD) were determined, and the 95% confidence interval for the mean (M±m) was determined.

RESULTS

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The state of vegetative regulation

Clinical and laboratory studies revealed a significantly significant decrease in the level of β-endorphin in the 1st group of patients in relation to the 2nd ($p < 0.05$) and 3rd ($p < 0.05$) groups of patients with monopathology . In addition, the level of β-endorphin in the peripheral blood of group 3 patients was also significantly higher than that of group 2 patients ($p < 0.05$).

The state of the immune system

All indicators of cytokines of the pro-inflammatory and anti-inflammatory spectrum in the examination groups varied widely. A statistically significant increase in TNF α was found in the 1st group of patients ($p < 0.05$), a subsequent decrease in TNF α was noted in the 2nd ($p < 0.05$) and 3rd groups ($p < 0.05$) of the examination. At the same time, the level of TNF α in the blood serum of group 3 patients differed from those of group 2 patients ($p < 0.05$). The indicators of IL-1ß of the 1st and 2nd groups differed unreliably. In group 3, the level of IL-1ß was lower than in patients in groups 1 and 2 of the examination ($p < 0.05$).

Changes in the level of IL-6 were also detected in patients with polymorbid cardiovascular pathology. There was a statistically significant decrease in IL-6 in the 2nd group of patients ($p < 0.05$), a further decrease in IL-6 was noted in the 3rd group ($p < 0.05$) of the examination in relation to patients of group 1. At the same time, the concentrations of IL-6 in the blood serum of patients of group 3 significantly differed from the indicators of group 2 patients ($p < 0.05$). When assessing the level of IL-4 and IL-10 in vivo, an increase in anti-inflammatory cytokines was observed in group 2 patients ($p < 0.05$), in the future their level increased in the 3rd group of patients ($p < 0.05$) compared with patients of the 1st group of examination. Concentrations of IL-4 and IL-10 in the blood serum of patients Group 3 significantly differed from group 2 ($p < 0,05$).

Interrelations of indicators of the functioning of the suprasegmental apparatus of the ANS and the cytokine link of immunity

The following was revealed:

– in patients with polymorbid cardiovascular pathology, direct weak correlations were established between the beta-endorphin content index and the TNF α and IL-10 levels in blood serum; moderate correlations were established between the beta-endorphin content index and the IL-1ß, IL-6 and IL-4;

–in patients with coronary heart disease and anxiety-depressive disorders, direct correlations of moderate strength between the level of β-endorphin and IL-1β, IL-6, IL-4, IL-10; weak direct correlations between the values of the level of β-endorphin and TNF α;

– in patients with AH and anxiety-depressive disorders, direct correlations of moderate strength between the level of β-endorphin and TNF α, IL-1β, IL-6 and IL-10; weak direct correlations between the values of the level of β-endorphin, as well as IL-4;

– in the healthy group, direct strong correlations between the level of β-endorphin and TNF α, IL-1β, IL-6, IL-4 and IL-10.

The strength of correlations between the level of β-endorphin and the cytokine link of the immune system in patients with polymorbid cardiovascular pathology significantly differed from the correlations of patients with isolated course of AH, Coronary heart disease and control groups ($p < 0.05$). In patients with an isolated course of coronary heart disease, the strength of correlations between the level of content beta-endorphin and indicators of the cytokine link of the immune system also differed from the indicators of correlational relationships of patients with AH and

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control groups ($p < 0.05$). The strength of correlations between the level of β-endorphin, cytokines of the proinflammatory and anti-inflammatory spectrum of patients with isolated course of AH also significantly differed from the indicators of correlations of the control group ($p < 0.05$).

DISCUSSION

Analysis of indicators reflecting the state of vegetative regulation in patients with polymorbid cardiovascular pathology allowed us to determine a decrease in the level of beta-endorphin in peripheral blood is approximately 1.5-2 times, compared with patients with monopathology, which reliably objectifies violations in regulatory processes at the level of the suprasegmental region of the ANS in the group of these patients. In the course of the clinical and laboratory study, the results were obtained that allow us to characterize the degree of dysfunction at the level of the cytokine pool of the immune system in groups of patients with polymorbid and monopathology. Thus, in the group of patients with polymorbid cardiovascular pathology, a significant increase in the level of peripheral blood cytokines reflecting the activity of inflammation (TNF α, IL-1β, IL-6) and a decrease in anti-inflammatory cytokines (IL-4, IL-10) spectrum was found, compared with patients with isolated coronary artery disease and AH. These data indicate an increase in the immuno-inflammatory process in the polymorbid course of coronary heart disease and AH against the background of anxiety-depressive disorders. When comparing paired correlations in patients with polymorbid cardiovascular pathology, direct moderate correlations were established between the content of β-endorphin and IL-1ß, IL-6 and IL-4, as well as weak correlations between the level of β-endorphin, TNF α and IL-10, which indicates violations in the control of the ANS over their functions at the level of the cytokine pool of the immune system.

In addition, a clear relationship is determined between the level of production of beta-endorphin, pro-inflammatory and anti-inflammatory cytokines in patients with polymorbid and monocardial vascular pathology occurring against the background of anxiety and depressive disorders. At the same time, the activity of indicators of the cytokine link of immunity directly correlates with the level of beta-endorphin and the clinical course of cardiological pathology.

Thus, differences in the regulatory portrait marked by correlations of indicators characterizing the state of the suprasegmental region of the ANS and the cytokine pool of the immune system in patients with polymorbid pathology. Differences in the regulatory portrait in patients with polymorbid cardiovascular pathology are due to the restructuring of regulatory interactions at the level of the neuropeptide-cytokine link of immunity, which will contribute to the progression of atherosclerotic processes in the heart and blood vessels in the group of these patients.

Conclusion

In patients with polymorbid cardiovascular pathology occurring against the background of anxiety-depressive disorders, desynchronization in the functioning of the autonomic nervous and immune systems was revealed, manifested by the restructuring of regulatory interactions at the level of the neuropeptide-cytokine link of immunity in the form of a 1.5-2-fold decrease in the level of peripheral blood beta-endorphin, an increase in proinflammatory (TNF α, IL-1ß, IL-6) and a decrease in anti-inflammatory (IL-4, IL-10) cytokines.

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