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ROUTES OF IMPLEMENTATION AND FACTORS OF ESCALATION OF SYSTEMIC INFLAMMATORY RESPONSE IN COMORBIDITY OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND CHRONIC PANCREATITIS

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Abstract

The study aimed to determine mechanisms of implementation of systemic inflammatory syndrome in patients with comorbidity of chronic obstructive pulmonary disease and chronic pancreatitis.

A total of 238 patients have been examined: 131 patients with chronic obstructive pulmonary disease in combination with chronic pancreatitis (main group) and 107 patients with an isolated chronic obstructive pulmonary disease (comparison group). Standard values were obtained while examining 20 almost healthy patients of the same age and gender, who made up the control group. Concentrations of cytokines: interleukin-1β, -2, -4, -6, -8 and tumor necrosis factor-α, quantification of C-reactive protein and ceruloplasmin activity in the blood serum has been determined. Statistical analysis has been performed on workstation by means of "Microsoft Excel" and "STATISTICA 6.0" software.

The study showed that chronic obstructive pulmonary disease exacerbation was accompanied with a significant increase in the activity of systemic inflammation mediators – the cytokine cascade and acute phase reactants, in both groups of patients with chronic obstructive pulmonary disease. However, the comparative analysis of the examined groups has proved the significant difference in cytokine status of patients with comorbidity of chronic obstructive pulmonary disease and chronic pancreatitis and in patients with isolated chronic obstructive pulmonary disease. Significant differences were found out in all investigated indices – IL-1β, IL-2, IL-4, IL-6 and TNF-α, except IL-8. Similar trends were observed in the concentrations of acute phase proteins – C-reactive protein and ceruloplasmin, whose levels in patients with comorbid disorders were significantly higher than those figures of persons with isolated chronic obstructive pulmonary disease.

Thus, it can be concluded that the presence of concomitant chronic pancreatitis in patients with chronic obstructive pulmonary disease potentiates activation of systemic inflammatory response that can be caused by formation of autoimmune reactions in an organism thereby contributing to a rapid progression of the pathological process and earlier formation of complications.

Keywords: *chronic obstructive pulmonary disease, chronic pancreatitis, systemic inflammation.*

Introduction

According to the latest edition of the Global Initiative for Chronic Obstructive Lung Disease [*GOLD, 2016*], chronic obstructive pulmonary disease is defined as "a common preventable and treatable disease, characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients" [*GOLD, 2016*]. In other words, an inherent characteristic of chronic obstructive pulmonary disease is a persistent progression of the pathological process, which invariably leads to the irreversible deterioration of lung function, and the presence of comorbid conditions can exacerbate pathological changes in these patients, thereby adversely affecting the course of chronic obstructive pulmo-

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nary disease [*Fabbri L, Rabe K, 2007; Chatila W et al., 2008; GOLD, 2016*].

Nowadays, chronic obstructive pulmonary disease is considered as a systemic pathology, which is not limited by involvement in the pathological process of the respiratory tract. Systemic inflammation leads to development of complications and affection of other vital organs and systems, and is a leading factor determining nature of the flow and progression, treatment and prognosis of the disease [*Fabbri L, Rabe K, 2007; Chatila W et al., 2008; Barnes P, Celli B, 2009*]. This problem becomes especially significant in case of presence of concomitant chronic diseases in patients with chronic obstructive pulmonary disease [*Rabe K et al., 2013*], which are also characterized by steady progressive course and formation of systemic inflammatory reactions, one of the representatives of which is chronic pancreatitis.

It is well known that inflammation mediators – the pro-inflammatory cytokines, leading positions among which are the interleukins – IL-1β, IL-6, IL-8 and tumor necrosis factor-α play a leading role in the pathogenesis of exacerbation of chronic diseases [*Cosio M et al., 2009; Drannik G, 2010*]. Results of their impact are an increase of vascular permeability, leukocyte migration, local tissue damage, generalization of the inflammatory response, damage of organs, which provide a natural detoxification processes with subsequent development of multiple organ failure [*Male D et al., 2007; Drannik G, 2010; Shishido S et al., 2012*].

At the same time, except cytokine cascade, the system of immunoregulation in these patients is provided by increasing content of acute phase reactants – C-reactive protein, orosomucoid, ceruloplasmin, ferritin, haptoglobin, fibrinogen and others [*Dahl M et al., 2007; Karadag F et al., 2008; Daha N et al., 2011*]. Sharp increase in concentration of these proteins in blood as a result of activation of the pathological process inherent in both chronic obstructive pulmonary disease exacerbation and chronic pancreatitis causes damage to tissues and organs.

Present study aimed to determine mechanisms of implementation of systemic inflammatory syndrome in patients with comorbidity of chronic obstructive pulmonary disease and chronic pancreatitis.

MATERIAL AND METHODS

A total of 238 patients with chronic obstructive pulmonary disease have been examined: 131 patients with chronic obstructive pulmonary disease in combination with chronic pancreatitis (main group) and 107 patients with an isolated chronic obstructive pulmonary disease (comparison group). The study involved patients with I and II degree of bronchial obstruction – spirometric classes GOLD 1 and GOLD 2. The age of the main group patients ranged from 28 to 65 years on average – 46.9±5.8 years, in patients with isolated chronic obstructive pulmonary disease – from 30 to 68 years, mean age – 48.1±7.9 years. Duration of chronic obstructive pulmonary disease anamnesis in the main group was 13.1±4.2 years, mean duration of chronic pancreatitis – 11.9±4.7 years. In the comparison group, history of chronic obstructive pulmonary disease averaged 12.8±4.9 years. Standard values were obtained while examining 20 almost healthy patients of the same age and gender, who made up the control group.

To assess the state of non-specific immunity the content of these parameters in blood was investigated by ELISA – concentration of cytokine IL-1β, IL-2, IL-4, IL-6, IL-8 and TNF-α using standard reagent kits (ProCon, Russia). The study was conducted by the immunoassay analyzer PR 1200 Sanofi Diagnostics Pasteur (France), in accordance with the manufacturer's recommendations. Determining the number of C-reactive protein was performed by ELISA using antibodies to the C-reactive protein, which were isolated from the antiserum to C-reactive protein by salting out with ammonium sulfate. Determination of serum ceruloplasmin was done by modified method of Revin [*Kamyshnikov V, 2000*].

Statistical analysis has been performed on workstation by means of "Microsoft Excel" and "STATISTICA 6.0" software.

The research was approved by Institutional Bioethics Committee and conforms to the principles provided in the Declaration of Helsinki (Br Med J, 1964; p. 177) with subsequent additions.

RESULTS AND DISCUSSION

The study showed that the phase of chronic obstructive pulmonary disease exacerbation is accompanied by formation of deviations in the cyto-

kine cascade of immunity as compared with the relatively healthy individuals, which confirms the presence of active inflammatory process (Table 1).

Table 1

The content of individual cytokines in the blood serum of patients with isolated chronic obstructive pulmonary disease (M±σ)

Indicators *(ng/l)*	Comparison group (n=107)	Control group (n=20)	Statistical significance*
TNF-α	39.4±2.1	24.2±1.5	t=2.533, p=0.013
IL-1β	44.3±2.7	26.0±1.6	t=2.262, p=0.026
IL-2	17.6±0.9	12.0±0.5	t=2.151, p=0.034
IL-4	27.1±1.6	32.7±0.4	t=2.456, p=0.017
IL-6	41.8±1.9	42.5±2.5	p>0.05
IL-8	52.9±2.9	68.3±1.2	t=2.601, p=0.011

Note: ** – significance of differences between the comparison group and healthy individuals.*

It should be noted that the most significant changes were observed in the content of IL-1 and TNF-α – these figures were 1.7 and 1.6 times higher than the values of healthy individuals, which is natural both with respect to the formation of inflammatory reactions and the immune system involvement in this process. Simultaneously, there was a moderate increase of IL-2, which is primary regulator of cytokine and provides stimulation of specific cellular immunity, and therefore, the inclusion of an immune response to infection mechanism of disease exacerbation.

The content of IL-8, which belongs to the pro-inflammatory cytokine link, and therefore, must be increased in these patients, not only did not exceed control indices, but also it was reduced. This circumstance may be explained by the fact that in addition to pro-inflammatory activity, at chronic obstructive pulmonary disease IL-8 provides neutrophil infiltration of bronchial wall and forming of peribronchial fibrosis. Therefore, absence of increase in levels of this cytokine can be considered as the result of the excess of its use in the processes of fibrosis, or insufficiency of its production, given the depletion of sources at a chronic relapsing course of disease.

With regard to IL-6, which is considered as the interleukin of double, pro- and anti-inflammatory action, in isolated chronic obstructive pulmonary disease it did not exceed the level of control indicators; probably it was a result of absence of the final phase of inflammation in these patients and, in the future, may lead to persistence of the process. At the same time, there was a decrease of IL-4, which plays a significant role in the anti-inflammatory response. This fact can be interpreted as the incompleteness of the inflammatory process and the lack of formation of a complete remission phase at this stage.

While studying the content of the pro- and anti-inflammatory cytokine link of immunity in patients with comorbidity of chronic obstructive pulmonary disease and chronic pancreatitis significant fluctuations of the content of these cytokines were installed when compared to the control group (Table 2).

Table 2

The content of individual cytokines in the blood serum of patients with comorbidity of chronic obstructive pulmonary disease and chronic pancreatitis (M±σ)

Indicators *(ng/l)*	Main group (n=131)	Control group (n=20)	Statistical significance*
TNF-α	92.3±2.2	24.2±1.5	t=5.687, p<0.001
IL-1β	72.4±2.5	26.0±1.6	t=5.238, p<0.001
IL-2	89.9±2.3	12.0±0.5	t=8.763, p<0.001
IL-4	77.6±3.5	32.7±0.4	t=4.524, p<0.001
IL-6	86.8±4.1	42.5±2.5	t=4.321, p<0.001
IL-8	53.9±2.3	68.3±1.2	t=4.104, p<0.001

Note: ** – significance of differences between the main group and healthy individuals.*

While comparing the cytokine status of patients with comorbidity of chronic obstructive pulmonary disease and chronic pancreatitis and in patients with isolated chronic obstructive pulmonary disease, significant differences were found in all investigated parameters, except of IL-8, the fluctuations of which were not reliable (Table 3).

Table 3

The content of individual cytokines in the blood serum of examined patients (M±σ)

Indicators *(ng/l)*	Main group (n=131)	Comparison group (n=107)	Statistical significance*
TNF-α	92.3±2.2	39.4±2.1	t=5.127, p<0.001
IL-1β	72.4±2.5	44.3±2.7	t=4.918, p<0.001
IL-2	89.9±2.3	17.6±0.9	t=5.751, p<0.001
IL-4	77.6±3.5	27.1±1.6	t=4.856, p<0.001
IL-6	86.8±4.1	41.8±1.9	t=4.211, p<0.001
IL-8	53.9±2.3	52.9±2.9	p>0.05

Note: ** – significance of differences between the groups.*

Thus, the level of IL-1β was 2.8 times higher than in control group and 1.6 times – in comparison group. The content of TNF-α in patients with comorbidity of chronic obstructive pulmonary disease and chronic pancreatitis exceeded the control value 3.8 times and indicators of patients with isolated chronic obstructive pulmonary disease – 2.3 times. At the same time, there was a significant increase in IL-2, which was 5.1 times higher than in comparison group and 7.5 – than in control group. IL-4 level was 2.4 times higher than the reference values and 2.9 times – the comparison group indicators (Figure).

IL-1β and TNF-α are known to be the major pro-inflammatory cytokines with systemic action and are considered as markers of active inflammation in the body. A significant increase of their levels in main group patients possibly is a consequence of the lack of complete immunological remission and latent course of chronic pancreatitis, or additional stimulation of an autoimmune component of inflammation in such pathological "tandem".

The study showed a significant increase of IL-2 level, the main action of which is stimulation, first of all, T-helpers of I type. Increasing of its concentration may be due to the action of the viral or bacterial agent, which led to an exacerbation of chronic obstructive pulmonary disease against the backdrop of the frequent recurrence of the process. It can promote the development of secondary immunodeficiency and autoimmune organ injury, thus ensuring the continuity of the process and the formation of pathological "vicious circle".

In turn, the reduction of IL-8 in patients with chronic obstructive pulmonary disease and chronic pancreatitis apparently was not only a result of its excessive use in process of fibrosis, but also the reduction of its synthesis due to increase of atrophic changes in bronchial mucosa in comorbid pathology. This fact can be interpreted as the dominance of lesions of bronchopulmonary system in conditions of stage remission formation of chronic pancreatitis.

Unlike isolated course of chronic obstructive pulmonary disease, a significant increase of IL-4 level is noted in patients with combined course of chronic obstructive pulmonary disease and chronic pancreatitis. Such changes in patients with comorbid pathology can be explained by a significant expression of an autoimmune component: constant circulation of antigens and immune complexes in blood that provide "stress" of immunity.

At the same time, an exacerbation of the patho-

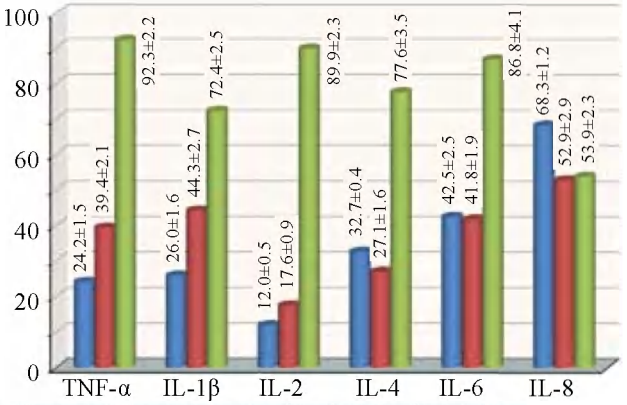

Figure. *The content of individual cytokines in examined individuals (ng/l)*

Notes: Control group (■), Chronic obstructive pulmonary disease (■), Chronic obstructive pulmonary disease and chronic pancreatitis (■)

logical process, in response to a massive release of cytokines, hepatocytes naturally increase production of acute-phase reactants, which was confirmed by the determination of the content of C-reactive protein and ceruloplasmin in examined individuals.

The study showed that the active phase of chronic obstructive pulmonary disease was accompanied by an increase in the concentrations of acute phase proteins in relation to that of healthy subjects in both groups. So the level of C-reactive protein in the comparison group exceeded indices of control 2.6 times, which may be due to its ability to provide an antibacterial effect (Table 4).

TABLE 4

Indicators of ceruloplasmin activity and C-reactive protein in blood serum of patients with chronic obstructive pulmonary disease (M±σ)

Indicators	Comparison group (n=107)	Control group (n=20)	Statistical significance*
Ceruloplasmin activity *(mg/l)*	311.0±28.0	276.0±33.0	p>0.05
C-reactive protein *(mg/l)*	3.65±0,22	1.43±0.06	t=4.085, p<0.001

Note: ** – significance of differences between the comparison group and healthy individuals.*

Meanwhile, change of ceruloplasmin activity in patients with isolated course of chronic obstructive pulmonary disease exceeded parameters of healthy individuals 1.1 times, but had only a character of trend, since the difference was not significant.

In patients with chronic obstructive pulmonary disease and chronic a significant increase of the maintenance of ceruloplasmin was found in the blood in relation to the values of healthy individuals 1.5 times (Table 5). The concentration of C-reactive protein in patients with combined course of chronic obstructive pulmonary disease and chronic pancreatitis exceeded the reference value 4.3 times. Comparative analysis of indicators in groups revealed that ceruloplasmin and C-reactive protein levels were higher in patients with comorbidity of chronic obstructive pulmonary disease and chronic pancreatitis than in comparison group 1.3 and 1.5 times, respectively (p<0.05).

Such differences in the quantitative composition of the acute phase proteins response in patients with such pathological "tandem" by activation of the complement system in the presence of chronic foci of infection may contribute to secondary tissue injury. In this case, we can expect not only the target organ damage, but also involvement of "relatively intact" organs and systems in the pathological process.

Thus, as a result of studies, it has been found out that there is an exacerbation of chronic obstructive pulmonary disease both in the isolated course of disease and in its combination with chronic pancreatitis, there is an observed increase in the concentration of proinflammatory cytokines and some acute phase proteins. The findings testify to the development of a systemic inflammatory response with significantly deeper deviations in patients with comorbid pathology.

Table 5

Indicators of ceruloplasmin activity and C-reactive protein in blood serum of patients with comorbidity of chronic obstructive pulmonary disease and chronic pancreatitis (M±σ)

Indicators	Ceruloplasmin activity *(mg/l)*	C-reactive protein *(mg/l)**
Main group (n=131)	415.7±31.0	6.1±0.23
Control group (n=20)	276.0±33.0	1.43±0.06
Statistical significance*	t=4.029, p<0.001	t=5.148, p<0.001

Note: ** – significance of differences between the main group and healthy individuals.*

While in comparison group patients overproduction of proinflammatory cytokines in the absence of adequate inhibition suggest a possible chronicity of inflammation, in main group patients a significant activation of pro- and anti-inflammatory immunity is a reflection of the generalization of the inflammatory response. Hyperexpression of the cytokine cascade in these patients leads to more active synthesis of acute phase proteins, activating the complement system, which may contribute to secondary organ damage, especially in conditions of comorbidity.

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