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SCIENTIFIC REVIEWS AND LECTURES

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CYTOKINOVY MECHANISMS OF FORMATION OF BRONCHIAL ASTHMA AND OBESITY

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ABSTRACT

Considering high prevalence of BA incidence and the progressing growth of number of persons with an excess weight of different degree of expressiveness, today the combination BA and obesity is a current problem of practical health care around the world.

The article examines the results of scientific research on the analysis of clinical and laboratory indicators of bronchial asthma (BA) in obese patients. The analysis of literary data concerning pathophysiological mechanisms of influence of excess amount of fatty tissue on character of a course of bronchial asthma is carried out. It has been established that significant volumes of adipose tissue are a source of pro-inflammatory cytokines, aggravating the course of asthma.

Researches have shown that fatty tissue is metabolically highly active and participates not only in deposition of fats and their mobilization, but also in regulation of a number of exchange processes in scales of the whole organism. Researches of biochemical processes in adipocytes (cells of fatty tissue) have shown that their activity isn't limited to influence on metabolic processes. In researches it is revealed that the high level of an expression of a number of regulatory factors (cytokine) which are taking part in formation and maintenance of inflammatory processes in an organism is characteristic of cells of fatty tissue. This fact allows considering obesity as a disease, one of components of which is the condition of the chronic inflammation covering the whole organism in general. In researches it has been shown that in the presence of obesity such signs as are specific to inflammatory process: inclusion of the intracellular alarm ways which are responsible for inflammatory activation of cells; an expression of the superficial membrane structures and receptors participating in intercellular interactions when forming inflammation; development of the cytokine stimulating further development and maintenance of the inflammatory answer; formation of the markers of a sharp phase characterizing prevalence and clinical value of inflammatory process.

Thus, the understanding of the general mechanisms which are the cornerstone of formation of obesity and BA will promote development of new methods of diagnostics and treatment.

Keywords: bronchial asthma, obesity, cytokine, systemic inflammation.

Despite achievements of modern medicine, introduction of new medical technologies in daily work of the practicing doctor there are still a lot of questions demanding studying. A current and complex problem is the choice of tactics of treatment of patients with a syntropy of diseases when diseases are interconnected, have joint or close etiological or / and pathogenetic

factors. Relevant and poorly studied are interfering syntropies, at which the disease developed against the background of previous one, makes heavier its course. A striking example of such syntropy is the bronchial asthma (BA) and obesity.

Both pathologies have gained now character of global epidemics in which various age populations in different

geographical zones are involved. About 10% of resources of public health care, according to some information, are spent for treatment of patients with BA and the states associated with it [7]. By rough estimates, its prevalence in the different countries is from 3 to 15% of the population today, and for the last three decades the number of patients with the diagnosis BA has increased in

economically developed states more than three times. At the same time researches show that in the same regions of the world where there is an increase in BA incidence, also the progressing growth of number of persons with an excess weight of different degree of expressiveness is observed.

Today rather large volume of scientific data which confirm existence of a certain interrelation between BA and obesity is saved up. It is shown that existence of obesity is combined with higher frequency of developing of asthma and also with more expressed weight of its course [6]. It has been revealed that it, as a rule, persons of more advanced age, with existence of various accompanying pathology. There are data that the association BA and obesity is more characteristic of female persons. At the same time this problem is present also at pediatric practice, especially because the combined epidemic of asthma and obesity in the developed countries is shown most visually at children's age [8].

The bronchial asthma at children associated with obesity differs from atopic BA and is characterized by Th1-polarization [15]. Influence of obesity at children on manifestations is BA presented in the table [1].

According to results of immunological mechanisms it is established that the expression of receptors of congenital immunity (Toll-like receptors (TLR)) at the children who are ill BA with obesity and normal body weight was characterized by higher TLR2 and TLR9 level in group of corpulent patients. Besides at the same patients decrease in production Th1-cytokine and a tendency to increase in a profile of the Th2-answer were defined [9].

Clinically the most essential and most significant feature of a current BA both among adults, and among children with obesity the smaller efficiency of basic therapy with use of inhalation glucocorticosteroids (I-GCS)

is considered that quite often demands increase in a daily dose of the applied medicines and interferes with the expected decrease in disease severity in the course of treatment [5]. Moreover, on some observations, existence of obesity, depending on degree of its expressiveness, influences the frequency of hospitalization of patients concerning exacerbation of asthma within a year in comparison with the patients with normal body weight at equal severity of a disease, raising it on average twice. At the same time at such patients not only the lowered response to basic therapy of I-GCS, but also a certain tolerance to effect of the bronchodilator medicines which are intensively used during aggravation is noted [10].

Thus, considering the growing indicators of prevalence of asthma and obesity now there was a need of more profound analysis of pathogenetic mechanisms of leaders to development of this pathology.

Today there are no doubts that fatty tissue is metabolically highly active and participates not only in deposition of fats and their mobilization, but also in regulation of a number of exchange processes in scales of the whole organism. The most known example in this regard is participation of fatty tissue in carbohydrate exchange, namely, in formation of resistance to insulin at patients with an excess weight and diabetes of the 2nd type [16, 18].

Researches of biochemical processes in adipocytes have shown that their activity isn't limited to influence on metabolic processes. In G. Hotamisligil researches with coauthors it is revealed that the high level of an expression of a number of regulatory factors (cytokin) which are taking part in formation and maintenance of inflammatory processes in an organism [4] it is characteristic of cells of fatty tissue allows to consider obesity as a disease, one of components of which is the condition of the chronic

inflammation covering all organism in general.

In numerous researches it has been shown that in the presence of obesity such signs as are specific to inflammatory process: inclusion of the intracellular alarm ways which are responsible for inflammatory activation of cells; an expression of the superficial membrane structures and receptors participating in intercellular interactions when forming inflammation; development of the cytokine stimulating further development and maintenance of the inflammatory answer; formation of the markers of a sharp phase characterizing prevalence and clinical value of inflammatory process [12].

Above-mentioned properties are shown in cells of various types, but generally it concerns cells of fatty tissue and immune system [2, 3]. In particular, it has been shown that at obesity in fatty tissue there is an essential proliferation of cells of macrophages. At the same time in her levels of production of such pro-inflammatory cytokine as a tumor necrosis factor alpha (TNF- α) and one of factors of a chemotaxis of monocytes increase.

It is supposed that in the conditions of obesity structural elements of fatty tissue are in a condition of the accruing hypertrophy and the constant oxidative stress caused, in particular, by toxic influence of intermediate products of metabolism of fatty acids. It leads to activation of intracellular alarm systems in the adipocytes and an expression of the factors stated above which are carrying out chemotaxis macrophages and promoting their migration in fatty tissue. The last, in turn, activate and further strengthen inflammatory processes in all fatty tissue of an organism [14].

Thus, large volumes of fatty tissue become a constant source of significant amounts of the pro-inflammatory cytokines synthesized by both adipocytes, and the macrophages migrating in fatty tissue that

Features of a phenotype of the childhood BA with obesity

Characteristics	usual allergic phenotype BA	phenotype of BA with obesity
The beginning of a disease	Early beginning (aged up to 5 years)	Variable beginning
Atopy	Often	Rare
Nature of inflammatory process	High level of eosinophils, increase in fraction of NO ₂ in the exhaled air	Mixed, with prevalence of neutrophils, decrease in NO ₂ fraction in the exhaled air
Function of lungs	Incidental bronchial obstruction, variable remodeling	Normal indicators of FVCL, variable decrease in the Tiffno index
Severity	Variable	Variable or more expressed symptoms, decline in quality of life
Answer to the test on a bronchoprovocation	Typical for the majority	It can be reduced
Answer to the test on a bronchodilatation	Mainly fast	It is more often lowered
Response to therapy	Resistance to steroids - seldom	Resistance to steroids - often, the good answer on antagonists receptors of leukotriens
Secondary diseases	Allergic rhinitis, eczema, sinusitis, uneasiness, GER	High level of insulin, increase TG-, LDL, GER

Note. FVCL – the forced vital capacity of lungs, TG-triglycerides, LDL – lipoproteids of low density, GER –reflux of gastroesophagitis.

leads to formation and maintenance in an organism of chronic slow inflammatory process. The feature of this inflammation is that it not quite corresponds to the standard pathophysiological idea of this process. For its description special terms, such as meta-inflammation or para-inflammation have been offered. Its characteristic feature can be considered the low intensity which isn't giving direct clinical symptoms, but, at the same time, the expressed system city, that is the impact on a wide range of bodies and fabrics leading to change of their metabolism, violation of their function and parallel activation of reactions of immune system in them.

Pro-inflammatory cytokines, being products of synthesis of the activated macrophages, have, in turn, ability to stimulate activity of other cellular elements of immune system that leads to the subsequent further strengthening of the inflammatory answer. In this regard one of the most important targets of the pro-inflammatory cytokine synthesized by macrophages and adipocytes is T-helper, the regulatory subpopulations of T-lymphocytes exercising control of character, orientation and intensity of the immune answer.

The inflammation generated by the activated macrophages at obesity isn't connected with penetration into an organism of the alien agent and, therefore, has no specific anti-gene focus and isn't connected with synthesis of specific antibodies. However, one of the cytokine produced by the activated macrophages in fatty tissue, namely SILT-6 has ability to stimulate reactions, controllable T-helper the Th-2 [11] type, thereby influencing pathogenesis of bronchial asthma as the initiator of the chronic inflammation and a factor switching the regulatory T-helper profile in the direction of reactions like Th-2, i.e. the humoral immune answer that leads to disproportionately high synthesis of immunoglobulins of a class E (IgE) - one of the leading factors of development of atopic bronchial asthma.

TNF- α which level is considerably increased at obesity also plays a role in separate links of pathogenesis of bronchial asthma, strengthening the inflammatory phenomenon in a wall of bronchial tubes. This pro-inflammatory cytokine participates as in development of an acute inflammation due to stimulation of a chemotaxis of neutrophils in the inflammation center, and in synchronization of process due to activation of platelets and induction of synthesis (NO₂) [13] nitrogen oxide.

Interesting was a fact that the level of the interleukin-10 suppressing production above the listed pro-inflammatory

cytokine of SILT-6 and FNO- α at obesity is considerably reduced that can be also considered as one of the factors increasing extent of inflammatory reaction in an organism and contributing to heavier course of asthma at corpulent persons [17].

Thus, as show results of researches, both asthma, and obesity represent the diseases forming steady inflammatory process in an organism. In the first case more local, concentrated mainly in walls of airways, in the second case — much more widespread, influencing many bodies and systems. The combination and mutual strengthening of these factors lead to a change in severity of a clinical course of asthma and difficulty of control of a disease. From the practical point of view, the data on interrelation of bronchial asthma and obesity which are available today demand development of new schemes of diagnostics and treatment of these conditions.

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