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THE ROLE OF IMMUNE RESPONSE MEDIATORS IN PATIENTS WITH ACNE

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ABSTRACT

Background: Despite the fact that there are a large number of studies devoted to the study of various aspects of the problem of acne, many of its aspects remain unexplored. As you know, acne develops against the background of certain changes in the immune system. **The aim** of the study is to study the clinical features and levels of pro- and anti-inflammatory cytokines in patients with acne. **Objective:** Were examined 68 patients with acne aged 14 to 35 years. The levels of serum cytokines (IL-4, IL-6, IL-10 and IL-17A) were studied by ELISA. **Result:** The results of the study showed that in patients with acne, hypersecretion of the studied cytokines is noted, depending on the severity of the disease. Thus, the level of IL-4 exceeded the value of the control group by 1.9 times, IL-6 - by 2.7 times and IL-17A - by 4.3 times. Elevated levels of cytokines cause the chronic course of the disease.

KEYWORDS: Acne, Acne immunopathogenesis, Pro- inflammatory cytokines, Interleukins.

INTRODUCTION

Acne is a chronic inflammatory disease that manifests itself as open or closed comedones and inflammatory skin lesions in the form of papules, pustules and nodules, which are localized mainly on the skin of the face, upper limbs, upper chest and back.[1-11]

In the occurrence of acne, the main role is played by an increase in the production of sebum; hyperandrogenism in women, in which the activity of androgenic hormones (male gender steroids) increases in the body; improper nutrition; decreased immunity; disease of internal organs; stressful conditions.[7-13]

In general, acne is one of the most common skin diseases in the practice of a dermatologist. Acne affects 85% of people aged 12 to 24, 8% of people aged 25 to 34, and 3% of people aged 35 to 44. In adolescence, boys and girls suffer from acne in almost equal proportions, while with late acne, women are in the lead. Acne ranks first in the structure of cosmetic pathology and third in terms of the frequency of patients visiting dermatovenereologists and cosmetologists; at the same time, the number of patients older than 30 years increases.[6,14,17,20] Acne is a multifactorial systemic chronic disease of the body with damage to the sebaceous glands and hair follicles.[13,14] According to various studies, the leading factors in the development of common acne are.[18] Violation of the composition and production of sebum; - changes in the hormonal and immune status of the body; - violation of keratinization of the follicular canal; - intensive colonization of the ducts of the sebaceous glands by pathogenic microflora; - the development of an inflammatory reaction in the perifollicular areas; - genetic predisposition.

Environmental factors, psychological stress, smoking, hormonal dysfunctions, uncontrolled use of drugs and cosmetics, hereditary predisposition affect the severity of acne.[16,18] The question of their participation as a trigger factor in various clinical forms of acne remains open.

Despite the fact that there are a large number of studies devoted to the study of various aspects of the problem of acne, many of its aspects remain unexplored.[6,7] As you know, acne develops against the background of certain changes in the immune system, and despite the presence of a bacterial factor in the pathogenesis of acne, there are a large number of studies showing that the nature of the patient's immune response to *P. acnes* more important than the infectious agent. From which it follows that the role of the immune system in the pathogenesis of acne deserves close study.[15,14] A number of authors noted that pro- inflammatory cytokines play an important role in initiating the appearance of acne.[5,8,11]

In connection with the above, **the aim** of this study was to study the clinical features and the level of pro- and anti-inflammatory cytokines in patients with acne.

MATERIALS AND RESEARCH METHODS

We examined 68 patients with acne aged 14 to 35 years. Among them were 42 female patients and 24 male patients. The duration of the disease was 3–12 years.

Patients were examined at the initial visit and monthly during the course of treatment. The control group consisted of 28 healthy men and women.

Laboratory studies were carried out by determining the complete blood count, biochemical studies and determining the level of serum cytokines (IL-4, IL-6, IL-10 and IL-17A). When determining the concentration of cytokines, test systems of JSC "Vector Best" (Novosibirsk, RF) were used. The determination of cytokines was carried out by ELISA, according to the attached instructions.

Statistical processing of the obtained data was carried out using the computer program Statistica 6.0. The significance of differences in the average values of the compared indicators was assessed by Student's t test (t).

RESULTS AND ITS DISCUSSION

The study of anamnestic data showed that the onset of morbidity in women was 13 years old, in men - 16 years old. Among persons of both genders, the age group of 21-30 years prevailed - 46.4%. The second place was occupied by the age group of 14-20 years. The third place in terms of occurrence was the age group of 21-35 years. The minimum occurrence of acne was in the age groups of 30-35 years. The distribution of patients according to the classification proposed by the American Academy of Dermatology, in accordance with clinical signs, showed that grade 1 - the presence of comedones and up to 10 papules was observed in 30 (52.4%) of the examined patients; 2nd degree - comedones , papules, up to 5 pustules were in 26 (38.2%) patients and grade 3 - comedones , papulo- pustular rash, up to 5 nodes was recorded in 17.8% (12) patients (Fig.1).

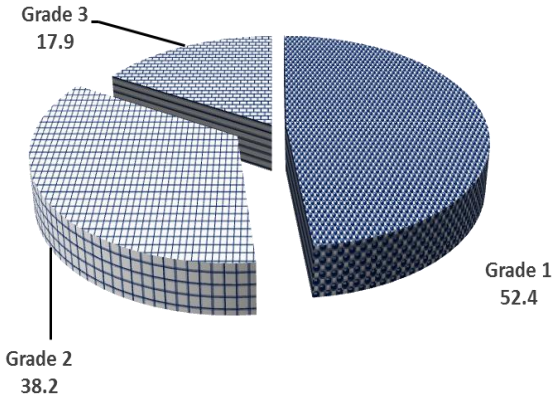

Fig. 1: Clinical forms of acne, %.

With a disease duration of up to a year, women consulted a doctor 2.8 times more often than men (73.5% vs. 35.3%) (Fig.2). There were no differences by gender with the duration of the disease from 5 to 10 years (48.6% and 51.4%) and over 10 years (45.6% and 54.4%).

In other words, the duration of the disease up to 5 years prevailed in women by 2.8 (up to a year) and 1.8 times (from a year to 5 years) ($p < 0.05$). There were no gender differences with the duration of the disease for more than 5 years ($p>0.05$).

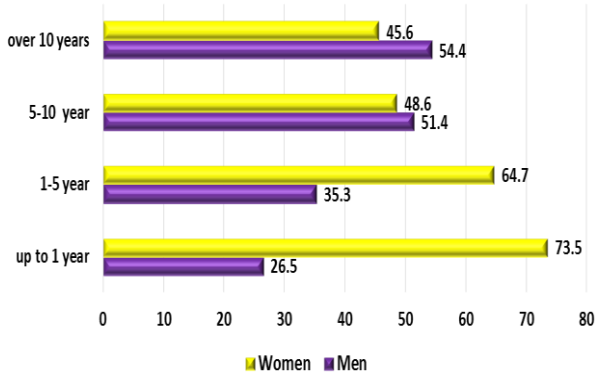

Fig. 2: Distribution of patients with acne, taking into account the duration of the disease and gender, %.

Acne belongs to the group of multifactorial dermatoses, hereditary predisposition to this disease in the whole sample was found in 25 (36.7%) patients. The frequency of hereditary predisposition to acne was studied taking into account gender. Registration of hereditary predisposition in men (52%) and women (48%) did not differ significantly ($p>0.05$). More than half of men and women (56.9%) noted the presence of dermatosis in first-

line relatives. which was manifested either by dysfunction of the gonads with hyperproduction of androgens, or by increased sensitivity of the cells of the sebaceous glands to the products of testosterone metabolism

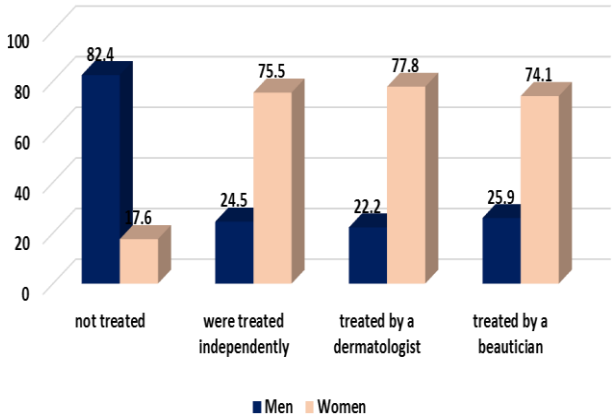

Fig. 3: Distribution of patients with acne, Taking into account various options for previous Therapy and Gender.

Of particular interest was a retrospective analysis of previous therapy in the presence of acne. 78.7% of patients received preliminary treatment using its various variants. An analysis of this factor, taking into account the gender of patients, is shown in Figure 3. Patients with acne turned to dermatologists, cosmetologists for the treatment of the disease and were treated on their own on the advice of friends, relatives, and pharmacy staff. Advertising in mass media played a significant role.

Interestingly, the number of previously untreated men was significantly 4.7 times higher than women (82.4% versus 17.6%). Treatment by a dermatologist (m - 22.2% and f - 77.8%), a cosmetologist (m - 25.9% and f - 74.1%), as well as self-treatment (m - 24.5% and f - 75 .5%) women practiced more often with a ratio of 3.5 - 2.9 - 3.1, respectively.

In this comprehensive study, we determined the quantitative indicators of one of the key cytokines - proteins involved in inflammation - IL-4, IL-6, IL-10 and IL-17A in patients with acne, depending on the severity of the course of the disease.

Table 1: The level of cytokines in the examined contingent, M± m.

Cytokines, pg /ml	Control gr. n=28	1st group, n=30	2nd group, n=26	3rd group, n=12
IL-4	6,3 ± 0,72	8,4 ± 0,79*	12.5 ± 0.79 *	15.2 ± 1.0 * _
IL-6	11,8 ± 0,95	24,3 ± 0.9*	28.4 ± 1.0*	31.7 ± 1.23*
IL-10	13,2 ± 0,97	18.3 ± 0.95*	26.3 ± 1.05*	38.5±0.91*
IL-17A	12,8 ± 0,93	23.7 ± 0.97*	32.6 ± 1.1*	46.3 ± 1.36*

Note: *Values are significant in relation to the control group ($P < 0.05 – 0.001$)

As can be seen from the data in Table 1, the level of IL-4 in acne was significantly increased relative to the control group, and the most elevated level was observed in patients with the 3rd degree of skin lesions ($P < 0.001$). IL-4 is a cytokine of the interleukin group that regulates the growth and differentiation of B-lymphocytes, as well as the processes of biosynthesis and secretion of antibodies. It is produced by activated CD 4+ T lymphocytes (Th2), mast cells and eosinophils. It interferes with the differentiation of Th1 cells and their production of characteristic cytokines. IL-4 suppresses the pro- inflammatory activity of macrophages and their secretion of IL-1, TNF- α and IL-6, that is, it has an anti-inflammatory effect [Yarilin A.A., 2008]. In addition, it stimulates the expression of vascular adhesion molecules-1, which ensure the migration of macrophages and other cells to the focus of inflammation, i.e., cell infiltration.[11,12]

IL-6 in patients with acne was increased in patients of the 1st group by 2 times ($P < 0.01$), in the 2nd group - by 2.4 times ($P < 0.01$) and in the 3rd group - in 2.68 times ($P < 0.001$). IL-6 refers to pro- inflammatory cytokines, i.e. to proteins that increase inflammation activity. The source of IL-6 in the body are various cells: T-lymphocytes, monocytes, endothelial cells, etc. IL-6 stimulates the formation of acute -phase proteins - haptoglobin, C-reactive protein, haptoglobulin, etc. - which in turn contribute to an increase in the inflammatory process . Also, IL-6 regulates the immune

response and is involved in the activation of lymphocytes, which trigger the formation of currently required immunoglobulins, or antibodies.

The main function of IL-10 is to protect tissue from damage during inflammation. This cytokine has immunoregulatory properties and is classified as an anti-inflammatory. IL-10 suppresses the secretion of cytokines by T-helper type 1, thus controlling the balance of Th1/Th2 and regulating the inflammatory response according to the negative feedback principle. IL-10 induces terminal differentiation of B cells into plasma cells.[10] In patients with acne, the level of IL-10 in the skin is increased and its excess leads to a weakening of anti- infective protection.[11]

Interleukin-17 belongs to pro- inflammatory cytokines and is involved in many stages of the immune response. It stimulates the production of chemokines and, as a result, stimulates the migration of neutrophils to the site of inflammation. One of the most important biological effects of IL-17 is its ability to produce many cytokines and chemokines that have a pleiotropic effect on different cells - IL-8, IL-6, TNF-α, IL-1, as well as prostaglandin E2 (PGE-2*).*[4] IL-17 triggers an extensive tissue reaction leading to the migration of neutrophils to the area of inflammation. It can be produced by many cells; however, T-helper type 17 (Th17) provides the most pronounced production.[7] IL-17 is synthesized by a wide range of immunocompetent cells, including mast cells, neutrophils, dendritic cells, macrophages, and natural killer cells. Targets for IL-17 are keratinocytes , synoviocytes , fibroblasts, epithelial cells. Activation of these cells induces the synthesis of cytokines that enhance the recruitment of Th17 cells (and neutrophils) to the inflammation zone.[11]

In acne, follicular hyperkeratosis and increased cohesion of corneocytes disrupt the processes of keratinization at the mouth of the hair follicles, where the lumen of the sebaceous gland opens. This leads to blockage of the follicular duct of the sebaceous gland by horny scales and the formation of a microcomedone. With hyperkeratosis of the outer (epidermal) part of the follicular canal, open comedones are formed, the black color of which is due to the products of sebum lipid oxidation, mainly squalene. With hyperkeratosis of the deep part, the outlet of the follicular canal does not expand, but is filled with fat and detritus, closed comedones.[15,20]

Follicular hyperkeratosis, obstruction of the duct of the sebaceous-hair follicle (SVF) and lipid-rich sebum lead to blockage of the follicle and difficulty in the penetration of air into the duct and the creation of anaerobic conditions for the development and reproduction of facultative anaerobes.

Attachment of microorganisms involves neutrophils and phagocytes of peripheral blood in the pathological process, producing pro- and anti-inflammatory cytokines that activate the enzyme cyclooxygenase, which promotes the formation of the main inflammatory mediator, leukotriene B4 (LTB4), from arachidonic acid.[5,8,11,12] LTV4 stimulates neutrophils, T-lymphocytes, monocytes and eosinophils with their subsequent release of hydrolytic enzymes and nitric monoxide (NO). This leads to the destruction of the wall of the sebaceous gland with the release of its contents into the dermis and the development of an inflammatory reaction, which is clinically manifested in the form of purulent-inflammatory elements of the rash - papules, pustules, nodes and cysts.

Thus, in the formation of acne, the leading role belongs to hypertrophy and increased functioning of the sebaceous glands, follicular hyperkeratosis, activation of microorganisms, followed by the development of inflammation with the participation of cytokines.

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