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Parameters of the Immune System in Children with Atopic Dermatitis

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Abstract: Atopic dermatitis is a chronic, relapsing inflammatory skin disease with pathogenesis involving genetic predisposition, immunological and epidermal barrier dysfunction, and environmental factors. The main symptom is attention; Skin rashes range from mild erythema to mild lichenification and erythroderma. Diagnosis includes taking a history and causes. Treatment includes recommendations for proper skin care, avoidance of triggers, and topical use of corticosteroids and immunosuppressants. Treatment of itching and superinfections is also important. In severe cases, systemic immunosuppressive therapy may be required. Atopic dermatitis that develops in childhood often regresses or its symptoms become significantly less severe in adulthood.

Keywords: Atopic dermatitis, immune system, IgE, IL-5, IL-13, TGF- β, eotaxin.

Introduction

More and more places are appearing where the permanent residence of a person poses a threat to his health [6]. The problem of chemical safety of human life has grown from a purely academic issue into a socially significant problem that is relevant for the population of entire regions [4]. This problem becomes especially important when practically no attention is paid to issues of ecology and ecotoxicology.

H. Höfling [5] calls the environmental situation in the world a “ time bomb,” and it is difficult to disagree with this definition. It is no coincidence that in cities with the chemical industry there is a steady trend towards an increase in a number of different diseases, such as cancer, allergy, infectious, metabolic and immune diseases [9].

The consequence of acute, and more often chronic, exposure to various chemical products of inorganic nature is a steady increase in the incidence of various diseases [7].

The Karaulbazar district of the Bukhara region, created in 1993 , is considered one of the young territorial entities of the republic. On its lands there are three village gatherings and the city of Karaulbazar, where the district administration and its authorities are located. On the territory of the regional center there is a cotton gin plant and a railway station serving passenger and freight lines. The economy of the region is based on agricultural and industrial enterprises. The oil refinery operates efficiently, bringing the main profit to the area. There is a residential complex located near the oil refinery site. There are medical institutions for adults and children. Attention was drawn to the fact that the frequency of visits to children's clinics with various allergic diseases, including atopic dermatitis, has increased.

The role of immunological disorders in the development of atopic dermatitis

In connection with the above, we conducted a study to study the parameters of humoral immunity in 55 school-age children (7-12 years old) with atopic dermatitis (AD) - group 1. The comparison group consisted of 20 children with AD of the same age, living in an environmentally more favorable region - group 2. 20 practically healthy children formed the control group.

The development of the skin inflammatory process in patients with atopic dermatitis is caused by a complex interaction of genetic mechanisms, environmental factors, infectious agents, defects

skin barrier, and immune mechanisms [1]. As you know, atopic dermatitis is a chronic disease based on IgE-dependent inflammation of the skin and its hyperreactivity, disrupting the natural reaction of the

skin to external and internal irritants. As can be seen from the data presented in Table 1, the level of IgE in sick children was significantly increased with a maximum value in children of group 1,

Table 1. The level of the studied parameters of the immune system in the examined children, (M ± m)

Indicators	Control group, n=20	Children with AD	
		Group 1, n=55	2nd group , n=20
IgE , ME /ml	37.82 ± 1.33	278.24 ± 44.53*	150.25 ± 26.48* ^
IL-5 , pg /ml	11.86 ± 0.81	73.65 ± 3.84*	41.58 ± 1.73* ^
IL-13 , pg /ml	6.53 ± 0.54	43.68 ± 1.43*	29.24 ± 1.22* ^
TGF β , pg /ml	10.91 ± 0.89	46.06 ± 4.02*	43.08 ± 3.28*
Eotaxin, pg /ml	53.84 ± 2.76	235.36 ± 7.53*	169.72± 4.68* ^

Note: *Values are reliable in relation to the control group

^Values are reliable in relation to group 1

($P < 0.05 – 0.001$)

which was more than 7 times higher than control values, averaging 278.24 ± 44.53 IU /ml ($P < 0.001$) and 1.85 times higher than in children with AD living in a more favorable region (150.25 ± 26.48 IU /ml, $P < 0.01$). It is generally accepted that the condition for the development of atopic disease is a hereditarily transmitted predisposition to increased production of IgE, which binds to tissue basophils and Fc receptors on other “inflammatory cells.” As a result of the interaction of IgE fixed on the surface of these cells with a specific antigen, they degranulate with the release of biologically active substances into the extracellular space, causing clinical manifestations of allergic inflammation. IgE is produced by plasma cells of the spleen, tonsils, adenoids, and mucous membranes of the respiratory tract, stomach and intestines. Infectious agents or foreign substances that have broken through the “first line of defense,” which is usually carried out by IgA, are bound by specific IgE on the surface of tissue basophils. The result of this interaction is the next stage of protection - the release of vasoactive amines and substances that have chemotactic activity from tissue basophils, eosinophils and blood basophils. This increases the influx of other protective factors, cellular and humoral, into the site of inflammation: IgG , complement, migration of neutrophils, eosinophils, etc. [2,3].

As the results of our research have shown, one of the main pathogenetic mechanisms of atopic dermatitis is dysregulation of IgE synthesis at the level of production of anti-inflammatory cytokines, which was the basis for the concept of an imbalance in the production of Th 1 and Th 2 cytokines in the pathogenesis of atopy, during which an increase in gene expression occurs IL-5, -13 and increased activity of B lymphocytes. Moreover, IL-5 is a chemoattractant for eosinophils, causes their degranulation, and plays a role in the pathogenesis of atopy. As can be seen from the data in Fig. 1, the level of IL -5 in sick children was significantly higher than the values in the control group. In particular. In children of group 1, the level of IL -5 averaged 73.65 ± 3.84 pg /ml, which is 6.2 times higher than the values in the control group (11.86 ± 0.81 pg /ml, ($P < 0.001$ In children of the comparison group, the level of IL -5 was 3.5 times higher than control values (41.58 ± 1.73 pg /ml, $P > 0.001$), but was significantly lower than in children of group 1 ($P < 0.05$).

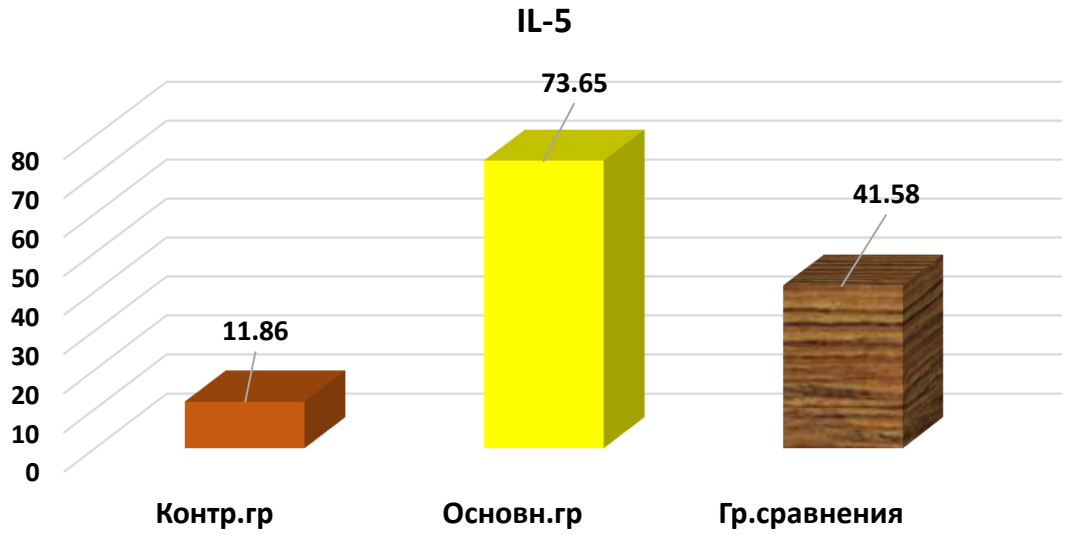


Fig.1. IL -5 level in examined children, pg /ml

IL-5 has a special place in the pathogenesis of allergic diseases due to its eosinophilotropic effect. IL-5 induces the production and release of eosinophils from the bone marrow and their maturation. The action of this cytokine is mainly associated with the late stages of eosinophil maturation and their activation. IL -5 prolongs eosinophil survival by blocking apoptosis. IL -5 appears to be the main cytokine responsible for eosinophilia in vivo . IL-5 is the main growth and differentiation factor of eosinophils, regulating their growth, differentiation, activation and survival, ensuring the mobilization of eosinophils from the bone marrow after exposure to an allergen. Eosinophils act as activators of the development and maintenance of allergic inflammation. Of all the cytokines involved in leukocyte differentiation, only IL-5, together with eotaxins, selectively controls the transport of eosinophils, causing the induction of tissue eosinophilia. However, the number of cells expressing IL-5 does not always correlate with the number of eosinophils in the skin. IL-5 increases the pool of eotaxin-sensitive cells [7]. The eosinophil-specific cytokine IL-5 can be present in the blood serum in all diseases based on both Th1 (interferon- γ) and Th2 (IL-13) immune responses [8].

IL -13 is tropic to the same receptors as IL-4, and accordingly has a similar effect. The level of IL -13 mRNA expression in the skin positively correlates with the severity of atopic dermatitis. As can be seen from the data presented in Fig. 2, the level of IL -13 was significantly higher than the values of the control group in children living in an environmentally unfavorable region, averaging 43.68 ± 1.43 pg /ml ($P < 0.001$). U

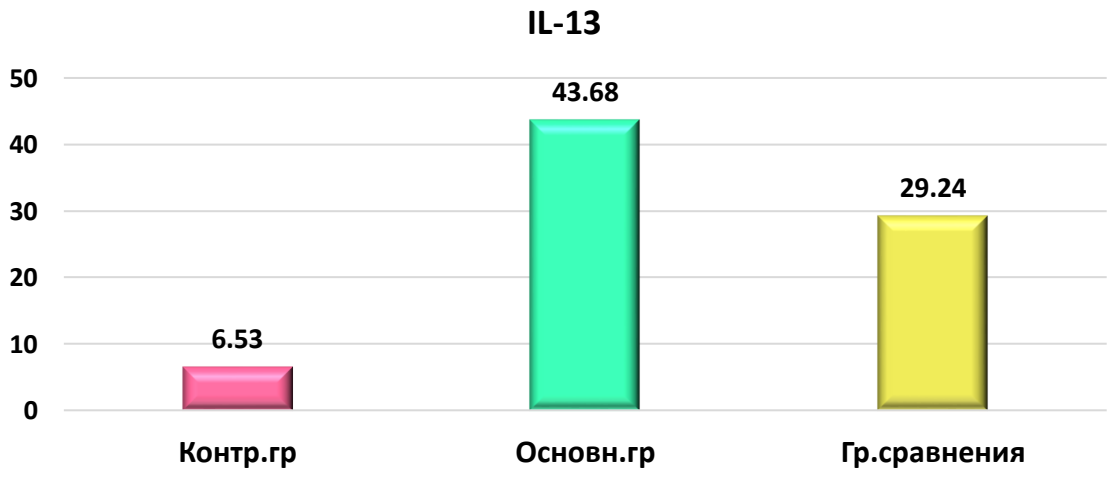


Fig.2. IL -13 level in examined children, pg /ml

children living in a more favorable region, the level of IL -13 was also higher than the values of the control group - 29.24 ± 1.22 pg/ml, (P <0.01), but however significantly lower than in children of the 1st group, (Fig. 2).

IL-13 affects the synthesis of desmosomal proteins, increases skin infiltration by inflammatory cells, promotes skin desquamation, and increases transepidermal water loss [8]. In the chronic course of atopic dermatitis, IL -13 is responsible for the appearance of skin itching. It is believed that the development of skin itching is associated with increased growth of dermal neuropeptide-secreting afferent nerve fibers. In experiments on animal models, increased expression of IL -13 in the skin induced the appearance of itching, increased IgE levels, and eosinophil infiltration [8]. There is evidence to suggest that IL-13 contributes to the development of cutaneous fibrosis [5]. The widespread involvement of IL-13 in the pathogenesis of atopic dermatitis justifies the use of monoclonal antibodies to IL-13 in therapy.

One of the elements that influence cell differentiation during immunopathological reactions is T-regulatory cells. The most important cytokine of T-regulatory cells is TGF- β. In our studies, the level of transforming growth factor -β was increased relative to data from healthy children. So, in children the main

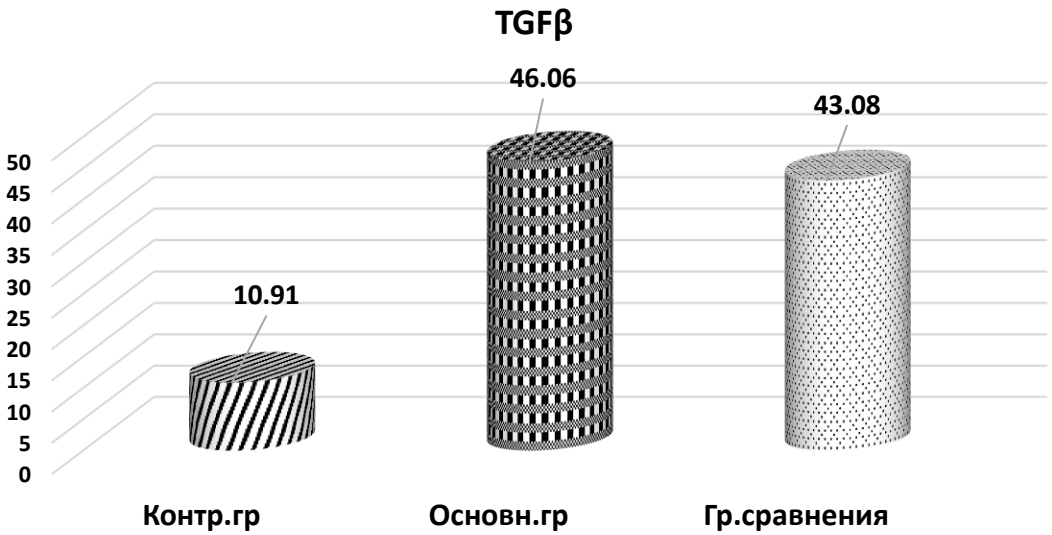


Fig.3. TGF β level in examined children, pg /ml

groups and comparison groups TGF β level was significantly increased compared to data from healthy children, and the level of this cytokine did not depend on place of residence (P <0.001) (Fig. 3). Thus, the level of TGF β in children with AD living in a more unfavorable region averaged 46.06 ± 4.02 pg /ml, and in children living in a more favorable region the level of TGF β averaged 43.08 ± 3.28 pg /ml.

Transforming growth factor -β is produced by a large number of cells, including stromal and epithelial cells, macrophages, and regulatory T lymphocytes. In turn, TGF- β is a regulator of cell differentiation: B lymphocytes, NK cells, dendritic cells, macrophages, mast cells, and granulocytes, but has the greatest effect on T cells. It has been established that increased concentrations of TGF- β are observed mainly in children with atopic dermatitis. TGF- β has an antiproliferative effect on T cells and also stimulates the differentiation of Th1 helper cells, thus preventing the development of allergic inflammation. This may indicate that low TGF- β expression contributes to the persistence of dermatitis and its persistence into adulthood. However, the literature describes the pro-inflammatory properties of TGF- β . In a study by A. Li et al . It has been shown that increased expression of TGF- β leads to infiltration of the skin by mast cells, which in turn contributes to the development of the skin inflammatory process. In addition, increased levels of TGF- β have been demonstrated in children with severe atopic dermatitis in combination with multiple food protein intolerance. Consequently, the concentration of TGF- β as a prognostic marker of the course of dermatitis can only be considered

taking into account a number of other factors: features of clinical manifestations, the state of the epidermal barrier, and the values of other immunological parameters.

Eotaxin-1 (CC motif-containing chemokine 11 (CCL11), also known as eosinophil chemotactic protein) is a non-glycated polypeptide with a m.m. 8.3 kDa of 73 amino acid residues, which in humans is encoded by the CCL11 gene. This gene is encoded by three exons and is located on chromosome 17. Eotaxin and related MCPs proteins play an important role in regulating the inflammatory characteristics of allergic diseases. Several studies have demonstrated the involvement of chemokines in the process of eosinophil accumulation in vitro and in vivo . Eotaxin plays an important role in stimulating the local recruitment of eosinophils from blood microvessels to sites of allergic tissue inflammation. Eotaxin is believed to regulate chemoattraction and activation of leukocytes. In our studies, eotaxin levels were sharply increased in children with atopic dermatitis (Fig. 3).

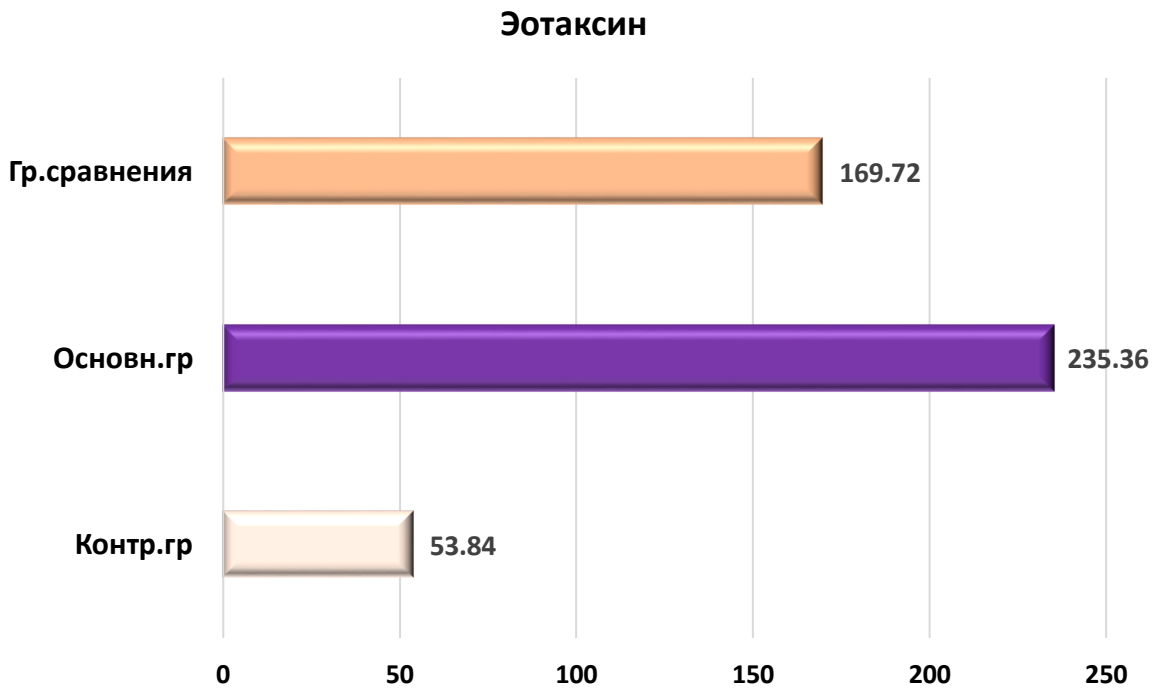


Fig.3. Eotaxin level of examined children, pg /ml

Thus, in children with this pathology, the level of eotaxin averaged 169.72 ± 4.68 pg /ml, which was 3.15 times higher than the values in the control group (P <0.001). In children of the main group living in an ecologically unfavorable region, the level of eotaxin was even higher, averaging 235.36 ± 7.53 pg /ml (P <0.001), which is 4.37 times higher than the control values.

The main functions of specific chemoattractants (chemokines) are to attract various types of cells (eosinophils, mast cells, basophils) to the tissue site of inflammation and their activation. Under the influence of chemokines, cell adhesion to the vascular endothelium occurs, followed by migration through the vascular wall into the tissue, where, as a result,

degranulation releases mediators. Chemokines serve as the most important (after IgE) activators of degranulation of these cells during an allergic reaction. The greatest selective chemoattractive effect is exerted by eotaxin and eotaxin-2, which belong to the class of CC chemokines and interact with CR3 receptors, which are expressed on all of the above cells [9], but are most pronounced on eosinophils. Eotaxins are responsible for increasing the number and activation of eosinophils

for various diseases. Cutaneous eosinophilia is characteristic of allergic diseases, in particular atopic dermatitis. The number of eosinophils in the skin has been shown to correlate with the number of cells expressing eotaxin.

The results we obtained from studying the level of cytokines in children with atopic dermatitis allowed us to calculate the shift coefficient from normative indicators, i.e. indicators of children without allergic manifestations according to the formula we developed:

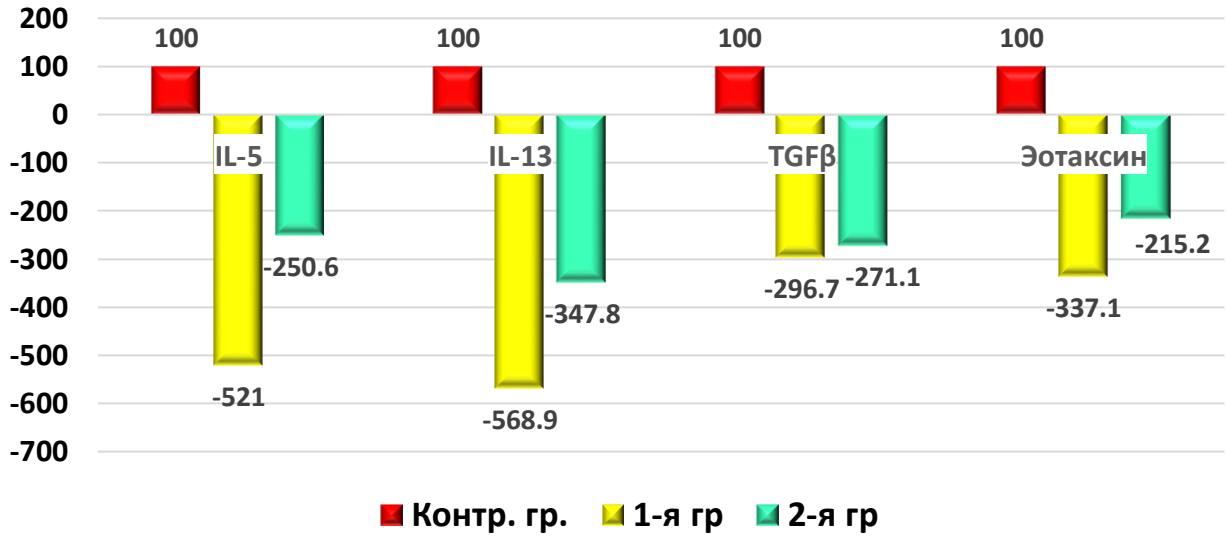
$$K(shift) = \frac{M(k) - M(p)}{M(k)} \times 100\%$$

K(shift) - shift coefficient

M (k) – value of the control group

M (p) – value in patients

The derived shift coefficient (K-shift) revealed interesting



Rice. 4. Coefficient of cytokine shift in the examined children, %

patterns (Fig. 4). In children with atopic dermatitis living in conditions of environmental distress, there was a high level of tension in the content of anti-inflammatory cytokines IL -5 and IL -13 and eotaxin compared to the control, i.e. children without allergic diseases. While the content of transforming growth factor -β did not differ significantly in sick children. Therefore, the level of TGF β does not depend on the allergen load but depends on the inflammatory process caused by suppression of the immune response.

Due to the fact that the levels of anti-inflammatory cytokines IL -5 and IL -13, as well as the level of eotaxin, react sharply to the allergen, we considered it appropriate to calculate an index that combines indicators using the following formula:

$$\textbf{IPTZ} = \frac{\text{Eotaxin}}{\text{IL 5 + IL 13}}$$

Where **IPTZ is** the disease prognosis index

Calculations showed that in practically healthy children who made up the control group, **IPTZ** was at the level 2.9 U **,** and in children living in

Table 2. Contents of IL -5, IL -13 and eotaxin in the blood serum of examined children

Indicators	Control group	Children with AD	
		Main group	Comparison group
IL-5 , pg /ml	11.86	73.65	41.58
IL-13 , pg /ml	6.53	43.68	29.24
Eotaxin , pg /ml	53.84	235.36	169.72
Eotaxin / (IL-5+IL13), Units	2.9	2	2.5

unfavorable zone, **the IPTZ level** was 2 U, while in children with AD living in a more favorable zone, **the IPTZ level** was 2.5 U (Table 2). As can be seen from the table, the more severe AD is the lower the index. The lower **the IPTZ,** the higher the content of eosinophils in the peripheral blood, and the lower the level of microelements - zinc, calcium, and vitamin D.

The results of the studies showed that the development of AD in children under the influence of allergens in the region of the oil refinery is based on immunological disorders. Consequently, immunological parameters such as IL -5, IL -13, and eotaxin, starting from the early period of atopic dermatitis, can serve as a reliable prognostic and diagnostic criterion for its course.

Thus, studying the features of the pathogenesis of atopic dermatitis based on the assessment of the cytokine profile and identifying markers of the severity of the disease is an extremely relevant area of clinical allergology and immunology to determine not only the prognosis of the disease but also therapeutic targets in the future. New treatments for atopic dermatitis using biological agents such as cytokines, antibodies, and fusion proteins are currently being developed. Careful identification of significant specific immunological and inflammatory markers of atopic dermatitis can be extremely promising for the development of new targeted drugs, and will also allow for advanced selection of patients who need treatment with certain drugs. This will significantly increase the effectiveness of therapy and make it possible to develop personalized approaches to the diagnosis and treatment of this chronic disease.

Conclusions and prospects

It has been established that children with AD living in an environmentally unfavorable area have increased production of IgE, anti-inflammatory cytokines (IL -5 and IL -13), as well as eotaxin, compared with the indicators of children living in a more favorable area, which indicates the importance spectrum of sensitization. The level of TGF β in all children with AD was elevated, regardless of the area of residence.

The cytokine shift coefficient has been established in children with AD. A high intensity of cytokine status indicators was revealed in children living in the area of the oil refinery. A prognosis index for the course of AD was derived, based on determining the ratio of anti-inflammatory cytokines and eotaxin. It has been established that IPTZ < 2.5 is a diagnostic criterion for the unfavorable course of AD.

The effectiveness of differentiated and complex treatment of children with AD, depending on the clinical condition of the child, was reflected in an increase in the adaptive capabilities of the body, in an increase in the period of remission with restoration of normal levels of IgE, anti-inflammatory cytokines, eotaxin and transforming growth factor -β in the blood serum, achieving control of disease symptoms and increasing quality of life of children.

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