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ROLE OF TRIGGER FACTORS AND EFFECT OF DIAMINE OXIDASE DEFICIENCY ON CLINICAL MANIFESTATIONS OF ATOPIC DERMATITIS

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When examining 87 patients with moderate and severe forms of atopic dermatitis aged 16 to 49 years, trigger factors in various clinical forms of atopic dermatitis were analysed. It was revealed that diamine oxidase deficiency and trigger factors aggravate the course of atopic dermatitis. Diamine oxidase deficiency in atopic dermatitis was combined with insignificant dynamics in relation to IgE and slow regression of the SCORAD index. It was revealed that the degree of influence of diamine oxidase on the course of atopic dermatitis (especially at SCORAD≥25) makes it possible to identify a group of patients who need additional regulation of tissue histamine conversion and active blocking of exogenous histamine liberators. A low level of diamine oxidase activity correlated with a slow regression of clinical symptoms of dermatosis, including more persistent pruritus, deterioration of the general condition, insomnia, irritability, and psycho-emotional asthenia.

Key words: aetiology of atopic dermatitis, diamine oxidase, clinical forms of atopic dermatitis, SCORAD index

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РОЛЬ ТРИГЕРНИХ ФАКТОРІВ ТА ВПЛИВ НЕДОСТАТНОСТІ ДІАМІНОКСИДАЗИ НА КЛІНІЧНІ ПРОЯВИ АТОПІЧНОГО ДЕРМАТИТУ

При обстеженні 87 пацієнтів з середніми та важкими формами атопічного дерматиту віком від 16 до 49 років проаналізовані провокуючі фактори при різних клінічних формах атопічного дерматиту. Виявлено, що дефіцит діаміноксидази та тригерні фактори посилюють перебіг атопічного дерматиту. Дефіцит діаміноксидази при атопічному дерматиті поєднувався з незначною динамікою по відношенню до IgE та повільним регресом індексу SCORAD. Виявлено, що ступінь впливу діаміноксидази на перебіг атопічного дерматиту (особливо при SCORAD≥25) дозволяє виділити групу пацієнтів, яким необхідна додаткова регуляція конверсії тканинного гістаміну й активне блокування гістаміноліберaторів, що надходять екзогенно. Низький рівень активності діаміноксидази корелював з повільним регресом клінічних симптомів дерматозу, включаючи більш стійкий свербіж, погіршення загального стану, безсоння, дратівливість та психоемоційну астенізацію.

Ключові слова: етіологія атопічного дерматиту, діаміноксидаза, клінічні форми атопічного дерматиту, індекс SCORAD

The study is a fragment of the research project "Improvement of algorithms of diagnosis, treatment, and prevention of chronic dermatoses, benign and malignant skin neoplasms", state registration no. 0121U113996.

Atopic dermatitis (AD) is a chronic allergic disease characterized by genetic determinism, hyperimmunoglobulinemia E, a recurrent course, and age-related skin manifestations.

In the last decade, there has been an increase in the incidence of atopic dermatitis and associated processes, which include bronchial asthma, allergic rhinitis, and allergic conjunctivitis. According to official statistics, about 20 % of the population of Ukraine suffer from atopic diseases that significantly affect the patient's quality of life [3].

The implementation of the pathological process in AD is associated with genetic determinism. Polymorphisms were found in the genes COL6A5 (3q22.1), COL8A1 (3q12.1), and COL10A1 (6q22.1), responsible for the synthesis of various types of collagen with a predominance of type 10. It is known that a change in the structure of collagen contributes to structural disorders in the dermis with the subsequent development of chronic inflammation [7, 12, 13].

There is evidence of a negative effect of house dust allergens and, in particular, dust mites (Dermatophagoides Pteronyssinus and D. Farinae) on the course of AD. The important provoking allergens also include plant pollen, which is most actively released in the spring and summer period [10, 12].

The main food allergens that influence AD exacerbation include such histamine liberators as: cow's milk, egg white, soy, peanuts, wheat, hazelnuts. At an older age, food allergens include products containing plant pollen (honey, floral fragrance, confectionery, etc.) [1, 2, 8, 12].

Taking into account the variety of etiological factors of AD, it is important to choose rational methods of treatment of this dermatosis with a high safety profile.

Antihistamines are included in the therapeutic protocols for the treatment of AD only as adjuvants providing mainly “antipruritic and sedative effects” [14]. In many patients, the blocking of histamine can interrupt the chain of pathological reactions and reduce the activity of the skinning process. At the same time, there are people with complete tolerance to antihistamines caused by a disturbance in the conversion of tissue histamine and the inclusion of additional inflammatory mediators (serotonin, bradykinin, cadaverine, etc.) in the pathological process [4, 12].

An indirect criterion for assessing the activity of histamine-induced processes in AD is the level of total IgE. The role of immunoglobulin E in the activation of AD and its effect on the severity of dermatoses is not fully understood. The European Association of Dermatology and Venereology suggests the use of the terms: IgE-associated and non-IgE-associated atopic dermatitis. It is proposed to highlight the true and pseudoallergic processes associated with atopic dermatitis [5, 11].

The analysis of histamine metabolism in atopic dermatitis makes it possible to identify the groups of patients with a histamine-dependent course of dermatosis, and to select the optimal therapeutic regimen in the presence of histamine intolerance. One of the most significant markers for assessing the histamine profile in chronic dermatoses is the level of diamine oxidase (DAO).

DAO is an enzyme that is involved in the process of histamine breakdown and, in many allergic diseases, allows to reveal of latent pathological conditions caused by histamine intolerance or impairment of its conversion in tissues [5]. Histamine intolerance is known to be accompanied by symptoms similar to AD, urticaria and allergic rhinitis.

The purpose of the study was to analyse the triggering factors in various clinical forms of atopic dermatitis, to determine the level of diamine oxidase, total IgE and the Scoring atopic dermatitis index in a group of patients suffering from moderate to severe atopic dermatitis, to study the dynamics of these indicators during treatment, to determine the degree of influence of diamine oxidase deficiency on the course of atopic dermatitis.

Materials and methods. We observed 87 patients aged 16 to 49 years suffering from moderate and severe atopic dermatitis who were referred for allergological assessment and follow-up to the Regional Dermatovenerologic Dispensary in Odessa for the period 2019–2021. Among them were 33 men and 54 women. The mean duration of AD was 9.5 years; the mean age was 24.3 years.

Informed consent was obtained from all the patients included in the study. The authors declare that all the procedures and experiments of this study respect the ethical standards in the Declaration of Helsinki of 1975, as revised in 2008, as well as the national law.

The study group included patients with the duration of the disease over 3 years. The study did not include patients with mild forms of atopic dermatitis.

The clinical diagnosis of atopic dermatitis was made according to the diagnostic standard of Hanifin and Rajka [6]. The diagnostic standard of Hanifin and Rajika includes the following:

1. Must have three or more basic features: pruritus, typical morphology and distribution (flexural lichenification in adults, facial and extensor eruptions in infants and children), chronic or chronically relapsing dermatitis, personal or family history of atopy (asthma, allergic rhinitis, atopic dermatitis.
2. Must have three or more following minor features: xerosis, ichthyosis/palmar hyperlinearity, keratosis pilaris, immediate (type I) skin test reaction, elevated serum IgE, early age of onset, tendency toward cutaneous infections (especially staph. aureus and herpes simplex), tendency toward non-specific hand or foot dermatitis, nipple eczema, cheilitis, recurrent conjunctivitis, Dennie-Morgan infraorbital fold, keratoconus, anterior subcapsular cataracts, orbital darkening, facial pallor, facial erythema, pityriasis alba, anterior neck folds, itch when sweating, intolerance to wool ad lipid solvents, perifollicular accentuation,

food intolerance, course influenced by environmental and emotional factors, white dermographism, delayed blanch.

SCORAD (SCORing Atopic Dermatitis) index was used to assess AD severity. When the index is below 25 (out of a maximum score of 103), AD severity is considered to be "mild", between 25 and 50 to be "moderate" and over 50 to be "severe". The index is based on information about the area of the body affected by dermatitis, the intensity of the dermatitis plaques regarding erythema, oedema, oozing, lichenification, dryness and excoriation (graduated 0–4) as well as subjective symptoms including the disturbance of sleep and degree of pruritus (graduated on a visual analog scale from 0–10).

The patients were asked to fill out a questionnaire about the main trigger factors in various clinical forms of the disease.

We carried out standard laboratory examinations, including general blood analysis, the determination of the level of IgE, and diamine oxidase (twice). Sampling was carried out in the morning in a fasting state, with the administration of antihistamines and contact with histamine liberators limited beforehand. The first study coincided with the period of exacerbation of dermatoses, the second one – with the subsiding of acute symptoms of the disease.

To relieve acute symptoms of the disease, all patients under our supervision were offered therapy that meets the standards of the European Association of Dermatology and Venereology [15]. Basic therapy was used at all stages of treatment, regardless of the severity of the disease, and included emollients twice a day for 2–3 weeks ("Physiogel" (Stiefel Laboratories, Ireland), "Lipikar baum AP+M" (La Roshe-Posay, France)) and bath oils twice a week for 1 month ("Oilatum" (Stiefel Laboratories, Ireland)). With the stability of the process and an increase in the SCORAD index ≥25, topical steroids twice a day for 10–14 days ("Locoid" 0.1 % cream, "Astellas", Ireland), calcineurin inhibitors twice a day for 10-14 days ("Protopic" 0.1% ointment, "Astellas", Ireland) and UVB therapy (311nm) twice a week for 2 month were used.

Results of the study were statistically processed by using the Microsoft Excel package and Statistica 6.0. package (StatSoft Inc., USA). The data were processed by calculating the arithmetic mean and its statistical error using the Student's t-test method, the results obtained are presented as the mean and the arithmetic mean error, with a confidence level of $p<0.05$.

Results of the study and their discussion. The main clinical forms of atopic dermatitis among the patients under our supervision included:

– Widespread AD with a tendency to Hill's erythroderma (SCORAD ≥50) – in 8 (9 %) patients;

– Widespread AD with no topographic association (SCORAD ≥50) – in 18 (21 %) patients (fig. 1);

– AD with topographic association (flexor surfaces, including the neck) (SCORAD≥25), – in 52 (60 %) patients (fig. 2);

– Widespread AD, with eczematization (SCORAD ≥25) – in 9 (10 %) patients

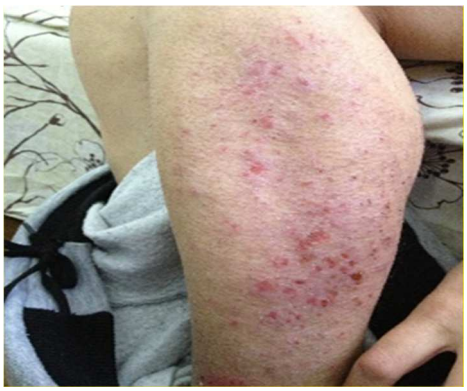
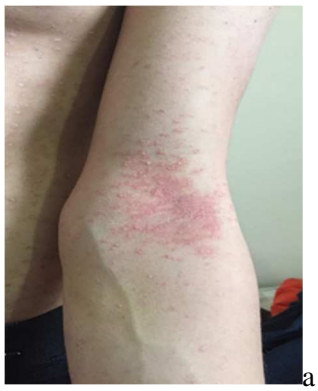


Fig 1. Widespread AD without topographic association (SCORAD≥50)



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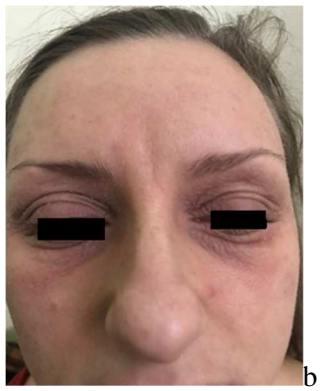

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Fig: 2. Atopic dermatitis affects the flexor surfaces of the limbs, including the neck, face (SCORAD≥25–50)

Before conducting clinical and laboratory studies and carrying out therapeutic measures, all patients under our supervision were asked to fill out a questionnaire that allowed to identify the main trigger factors in various clinical forms of the disease. The most frequently mentioned trigger factors for atopic dermatitis were: food and non-food allergens, stress, seasonality, infectious diseases, inappropriate therapy. Food (40 %) and non-food allergens (24 %) were the main causes of exacerbation of atopic dermatitis in the group of patients under our supervision. Among food allergens, the following histamine liberators were most common: cow's milk, eggs, seafood, citrus fruits, honey, tomatoes, chocolate.

The highest incidence of food trigger factors was observed among patients with topographic constancy of AD – 19 (22 %) patients, and slightly less in the group of persons suffering from atopic

dermatitis without topographic association – 9 (10 %). In atopic eczema (AD with pronounced exudation), food triggers were the cause of exacerbation of dermatoses in 5 (5 %) patients (table 1).

Table 1

Main trigger factors in various clinical forms of atopic dermatitis

Clinical forms of AD	Stress	Food allergens	Non-food allergens	Seasonality	Inappropriate therapy	Infectious diseases	Other
with a tendency to Hill's erythroderma 8 (9 %)	3 (3 %)	3 (3 %)	1 (1 %)			1 (1 %)	
widespread without topographic association 18 (21 %)	3 (3 %)	9 (10 %)	4 (4 %)	1 (1 %)	1 (1 %)		
widespread with topographic association 52 (60 %)	9 (10 %)	19 (22 %)	14 (16 %)	5 (6 %)	2 (2 %)	1 (1 %)	2 (2 %)
atopic eczema 9 (10 %)	2 (2 %)	5 (5 %)	1 (1 %)		1 (1 %)		
Total 87	17 (20 %)	36 (40 %)	20 (24 %)	6 (7 %)	4 (5 %)	2 (2 %)	2 (2 %)

Stress factors triggered an aggravation of AD in 3 (3 %) patients with Hill's erythroderma, in 3 (3 %) patients with disseminated dermatosis and in 9 (10 %) patients with a topographic constancy of rashes.

According to the questionnaire, the main non-food triggers of AD included antiseptics, detergents, cosmetics, hair dyes, as well as aerogenic fragrances. The highest incidence of non-food exacerbation factors was found in atopic dermatitis with the topographic association of rashes – 14 (16 %), the lowest – 1 (1 %) in AD with a tendency to Hill's erythroderma. Relatively rare causes of the activation of atopic dermatitis include infectious diseases – only 2 cases (2 %).

When examining patients, the most significant deviations in laboratory parameters included hyperimmunoglobulinemia E more than 300 IU/ml in 54 (62 %) patients, eosinophilia (more than 6 %) in 37 (43 %), leukocytosis (more than 9.5 g/l) – in 25 (29 %) patients.

Before the initiation of treatment, the level of diamine oxidase was below normal (less than 10 IU / ml) in 23 (26 %) patients, while its value decreased below 6 IU / ml in 5 (6 %) of them. In the group of patients with DAO deficiency, the mean total IgE was 309.7 IU / ml, and in the group of patients with normal levels of the studied enzyme, the mean total IgE was 278.4 IU / ml, with a difference of 13.8 %. There were no significant differences in the level of eosinophils in the patients of the general study group and the group with DAO deficiency (indicators were 5.4 % and 6.3 %, respectively). An increase in the mean value of the SCORAD index ≥25 before treatment was noted in 31 (36 %) patients of the general study group; in the group of patients with a reduced level of DAO, the SCORAD index exceeded 25 in all 23 respondents (26 %). A low level of DAO activity correlated with a slow regression of clinical symptoms of dermatoses, including more persistent pruritus, deterioration of the general condition, insomnia, irritability, and psycho-emotional asthenization.

The positive dynamics of the SCORAD index (decrease≤25) 30 days after the initiation of treatment was observed in 27 (31 %) patients of the general study group, the absolute values of the studied index were 21.7 ± 2.3 before treatment, and 13.3±1.5 after treatment (a 38 % decrease). At the same time, in patients with DAO deficiency, the decrease in SCORAD after 30 days of therapy was not as pronounced and amounted to 23.8±1.8 before treatment, and 19.7±1.5 after treatment (a 13 % decrease). The accumulation of histamine in peripheral tissues (including the skin) in case of impaired conversion promotes increased pruritus, erythema, exudation, inflammation, i.e., all the symptoms characteristic of atopic dermatitis. This explains the pronounced stability of the course of dermatosis with DAO deficiency and, accordingly, a slower regression of the SCORAD index (tables 2)

Table 2

Dynamics of the SCORAD index, total IgE, eosinophils in the group of AD patients with normal DAO levels and with with DAO deficiency

Indices	Dynamics of indices			
	Patients with normal DAO levels		Patients with DAO deficiency	
	1st day	30th day	1st day	30th day
DAO (IU/ml)	15.7±0.9	16.6±0.7	9.3±0.7	10.6±0.9
IgE (IU/ ml)	278.4±1.3	241±2.1	309.7±1.6	289±1.1
Eosinophils (%)	5.4±0.7	4.9±0.9	6.3±0.4	5.1±0.9
SCORAD Index (mean value)	21.7±2.3	13.3±1.5	23.8±1.8	19.7±1.5

Note: p≥0.3

In the group of patients with normal DAO levels, the level of total IgE decreased after 30 days by 13.3 % from 278.4±1.3 IU/ml to 241±2.1 IU/ml, while in the group of patients with DAO deficiency the level of total IgE decreased over the same period from 309.7±1.6 IU/ml to 289±1.1 IU/ml, i.e., only by 6.8 % (fig. 3, 4).

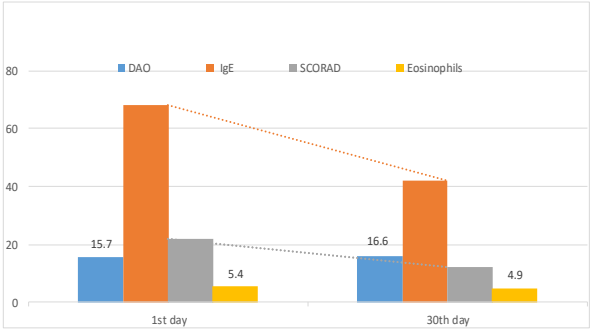

Fig. 3. Dynamics of the SCORAD index, IgE, eosinophils in the group of AD patients with normal DAO levels.

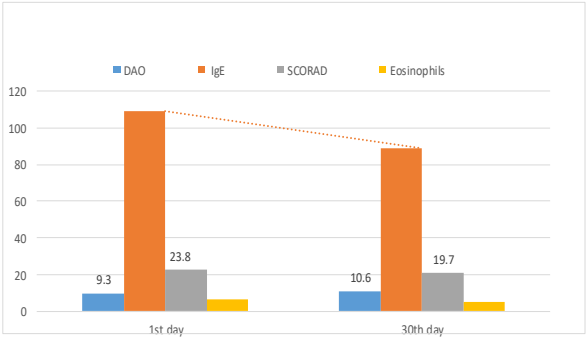

Fig. 4. Dynamics of the SCORAD index, IgE, eosinophils in the group of AD patients with DAO deficiency.

The slowdown in the regression of total IgE in the presence of DAO deficiency can be explained by the stimulating activity of histamine accumulating in peripheral tissues. The activity of this mediator contributes to an increase in vascular permeability and the accumulation of pro-inflammatory cytokines in affected areas, in particular IL-4, 6, TNF-α, that stimulate B-lymphocytes to excessive IgE production.

Thus, the effect of DAO on the course of AD is multifaceted and can be manifested not only by laboratory deviations, but also by the clinical features of the course of dermatoses. In order to exclude disturbances in the conversion of histamine (a possible reason for the aggravation of the course of dermatoses), it is advisable to determine the level of activity of the diamine oxidase enzyme in persons suffering from moderate and severe forms of atopic dermatitis.

In the majority of cases, DAO deficiency is combined with decreased susceptibility of AD to treatment, while standard methods of treatment do not provide a lasting positive effect. Further study of the degree of influence that DAO levels have on the course of AD will reveal additional causes of dermatosis resistance and expand its therapeutic algorithm.

Atopic dermatitis is considered a chronic allergic disease with multifactorial etiopathogenesis. In this study we have examined 87 patients with moderate and severe forms of atopic dermatitis and revealed that the most common mentioned trigger factor for AD was food (40 %), which included cow's milk, eggs, seafood, citrus fruits, honey, tomatoes, chocolate. These results are in line with the data of conducted similar studies about detection of allergic reactions to food in patients with AD [1, 2]. It should also be noted that the European Association of Dermatology and Venerology defines this group of food triggers (as well as: hazelnuts, peanuts, soybeans, cereals, floral fragrances) as the main group of histamine-liberating substances that increase the release of histamine into the intercellular space [14].

We also found that non-food allergens (24 %), stress (20 %), seasonality (7 %), infectious diseases (2 %) and inappropriate therapy (5 %) can play role in the exacerbation of the disease.

From the data obtained, it can be seen that the most significant trigger factors of AD are substances that actively stimulate histamine synthesis (food and non-food substances), which confirms the importance of studying causative histamine liberators and the activity of enzymes involved in the conversion of histamine in atopic dermatitis.

An analysis of the trigger factors of atopic dermatitis revealed their predisposition to exacerbation of various forms of dermatosis.

Thus, the activation of erythrodermic forms of AD was more often stimulated by stress and food allergens – in 6 (7 %) patients; the exacerbation of topographically associated forms of AD was more often due to the effect of food and non-food triggers in 9 (22 %) and 14 (16 %) of patients, respectively, seasonality also played a great role in this form of the disease – in 5 (6 %) patients.

We analysed the level of diamine oxidase and its effect on the course of atopic dermatitis. To date, little data is available on the prevalence of this enzymatic deficiency in patients with AD. We found that 26 % of our patients had deficiency of this enzyme. Maintz L. et al. (2006) have monitored plasma DAO activity in patients with atopic eczema and reported that among them DAO deficiency was 19 % [9]. We also revealed that low level of DAO may be associated with a more severe course of atopic dermatitis. Thus, in patients with AD measuring the serum diamine oxidase activity can help identify subjects who

can benefit from additional regulation of tissue histamine conversion and active blocking of exogenous histamine liberators.

Conclusions

1. In this study, the trigger factors (food and non-food allergens, stress and seasonal factors) involved in the exacerbation of AD exhibit different stimulating activity against various clinical forms of dermatosis.

2. The degree of influence that diamine oxidase has on the course of atopic dermatitis was determined. Thus, DAO deficiency aggravates the course of atopic dermatitis, which is manifested by the persistence of clinical symptoms and low efficiency of standard treatment methods. In addition, DAO deficiency in AD is combined with insignificant dynamics in relation to total IgE and a slow regression of the SCORAD index.

3. It has been established that the degree of influence that diamine oxidase has on the course of AD (especially at SCORAD≥25) makes it possible to identify a group of patients requiring additional regulation of tissue histamine conversion and active blocking of exogenous histamine liberators.

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