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STUDY OF SENSITISATION TO MOULD FUNGI IN PATIENTS WITH MICROBIAL ECZEMA

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There is no single concept of the etiology of eczema, and the complex links in of the pathogenesis of eczema, the formation of which reflects the dynamic and interrelated changes in the functions of various organs and systems of the body. One of the most important pathogenetic mechanisms of eczema, as well as allergy in general, is the development of immune reactions caused by exogenous allergens. Unlike pollen allergens, mold allergens are more complex in structure and cause not only IgE-mediated allergy, as each of their components (spores, mycelium, hyphae) to a certain extent has allergenic potential and can cause a multidirectional immune response. 78 (90.7 %) patients had an increased level of specific IgE to at least one of the investigated mold allergens. The highest concentration level of IgE (more than 17.5) was observed for the allergen of the fungus Penicillium notatum in 15.1 % of patients with chronic microbial eczema. The results of the study can be the basis for further study of mycogenic sensitisation.

Key words: sensitisation, moulds, microbial eczema, IgE.

І.Б. Попова, І.П. Кайдашев, Я.О. Ємченко, К.В. Васильєва, О.В. Безега ДОСЛІДЖЕННЯ СЕНСИБІЛІЗАЦІЇ ДО ПЛІСНЯВИХ ГРИБІВ У ХВОРИХ НА МІКРОБНУ ЕКЗЕМУ

Немає єдиної концепції етіології екземи, недостатньо вивчені складні ланки патогенезу екземи у формуванні яких відображена дінамічна і взаємопов'язана зміна функцій різних органів і систем організму. Одним з важливих патогенетичних механізмів екземи, як і взагалі алергії, є розвиток імунних реакцій, обумовлених екзогенними алергенами. На відміну від пилкових алергени пліснявих грибів є більш комплексними за своєю структурою та спричинюють не лише IgE-опосередковану алергію, оскільки кожен з їх компонентів (спори, міцелій, гіфи) певною мірою володіє алергенним потенціалом і здатний зумовити різноспрямовану імунну відповідь. У 78 (90,7%) хворих виявлено підвищений рівень специфічного IgE хоча б одного з досліджувальних алергенів до пліснявих грибів. Найвищий рівень концентрації IgE (більше 17,5) спостерігався до алергену гриба Penicillium notatum у 15,1% хворих на хронічну мікробну екзему. Отримані результати дослідження можуть бути основою для подальшого вивчення мікогенної сенсибілізації.

Ключові слова: сенсибілізація, плісняві гриби, мікробна екзема, IgE.

The study is a fragment of the research project "Development of advanced methods for diagnosing and comprehensive treatment of chronic dermatoses and infections primarily transmitted sexually, taking into account the identification of additional factors significant in the pathogenesis of these diseases", state registration No. 0117U000272.

Today, the focus of scientific medical research is not only on studying the causes of pathological processes but also on the mechanisms of resistance to their occurrence and development. A key aspect of assessing resistance to risk factors involves studying molecular and cellular protection mechanisms, as well as the body's immunological parameters [1, 4]. Chronic recurrent eczema, cosmetic defects, and itching are additional stress factors that contribute to psychovegetative disorders and exacerbate the severity of the disease. As a result, a "vicious circle" is formed: stress \rightarrow dermatosis \rightarrow stress [2, 3, 5]. It should be noted that the conditions leading to the persistence of eczema, regardless of disease remission, act as an additional

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factor in reducing the patient's adaptive capacity [2, 5]. This pathology accounts for more than 40 % of the total structure of dermatological morbidity, with a tendency for continuous growth [1, 9].

There is no unified concept of the etiology of eczema, and the complex links in its pathogenesis are not yet sufficiently studied, reflecting the dynamic and interconnected changes in the functions of various organs and systems of the body [10, 14, 15]. In recent years, the immunoallergic concept has taken a leading role in the etiopathogenesis of eczema, aligning with the empirically identified stages of microbial eczema: the development of non-allergic banal pyodermas at the site, progressing through eczematides and localized forms to generalization of the process [14, 15]. Immune system disorders in eczema are characterized by changes in the T-cell, humoral, and phagocytic immune responses, manifesting as a relative and absolute decrease in the levels of T- and B-lymphocytes, T-helper cell deficiency, suppression of T-suppressor functional activity, and a marked reduction in the number of spontaneous and complementmediated neutrophil granulocytes [2, 4, 9]. A positive association between histocompatibility system antigens B22 and CW1 has been identified in patients with true eczema. This combination of antigens has been found among representatives of the Slavic race, allowing us to consider these antigens as genetic markers of eczema in Slavs [13, 14, 15]. Taiwanese scientists have demonstrated the influence of serine protease inhibitors SPINK5 and IL13 on the development and manifestation of true eczema (specifically, the rs6892205 G and rs20541 alleles, respectively) [4, 14, 15]. Various immunological changes play a significant role in the manifestation of true eczema, imbalance in the system of cyclic nucleotides and prostaglandins, and positive association of dermatosis with histocompatibility antigens CW1 and B22, which are genetic markers of eczema. [13, 15] A hereditary component is believed to prevail in the onset of atopic eczema. Therefore, it is often found in families with members suffering from asthma. If one of the parents (mainly the mother) is ill, the child's chance of getting eczema is approximately 40 %. If both the father and mother are ill, it is 50 %–60 %. One of the most critical problems in modern dermatology is an individual approach to diagnostic, treatment, and prevention programs. The success of its solution depends mainly on how fully and systematically both the somatic and mental components of the patient's personality are described. Clinical, genetic, and immunological studies allow us to classify dermatosis as a disease of a hereditary-constitutional nature, and the proportion of genetic and environmental factors in different forms of eczema is different. According to modern concepts, the eczematous process on the skin develops due to the complex action of exogenous and endogenous factors that cause sensitisation of the body. Among these factors, diseases of the digestive and excretory systems, neuroendocrine and immune disorders, microcirculation, and haemostasis disorders are significant. In general, one of the essential pathogenetic mechanisms of eczema and allergies is the development of immune reactions caused by exogenous allergens [6, 7, 8]. In contrast to pollen allergens, mold allergens are more complex in structure and cause not only IgE-mediated allergy, as each of their components (spores, mycelium, hyphae) has a certain degree of allergenic potential and can cause a multidirectional immune response, which prompts the comparison of aeroallergens in the immunopathogenic aspect [7, 8, 11, 12].

The purpose of the study was to determine the level of specific IgE to mold allergens: Mucor Racemosus, Alternaria Tenuis, Candida albicans, Penicillium notatum, Cladosporium herbarum, and Aspergillus fumigatus in patients with chronic microbial eczema to assess the degree of mycogenic sensitization, with the goal of improving the diagnosis and treatment of this disease.

Materials and methods. A study was performed to measure the level of specific IgE in the blood serum of 86 patients with a confirmed diagnosis of microbial eczema, who had been suffering from the condition for at least one year and were undergoing inpatient treatment at the dermatology and venereology center of the M.V. Sklifosovsky Poltava Regional Clinical Hospital, under the Poltava Regional Council, from 2019 to 2024. The research was approved by the Bioethics and Ethical Issues Committee of the Poltava State Medical University. All patients signed an informed consent form to participate in the study. Clinical manifestations were widespread with an asymmetric polymorphic rash on the skin of the lower legs, dorsum of the hands, and lateral surfaces of the trunk; lesions had clear boundaries, which were represented by multiple microvesicles, pustules with purulent and yellowish crusts, peeling against the background of erythema and infiltration Patients complained of severe itching, significant pain, and frequent relapses of the disease, which were difficult to treat [1, 10]. The study included 86 patients aged 35 to 65 years diagnosed with chronic microbial eczema, which was established based on clinical presentation. Patients with severe microbial eczema or those receiving corticosteroid treatment were excluded from the study. The level of specific IgE in blood serum was determined using an enzyme-linked immunosorbent assay (ELISA) with test systems, including cellulose discs with applied allergens such as Mucor Racemosus, Alternaria Tenuis, Candida albicans, Penicillium notatum, Cladosporium herbarum, and Aspergillus fumigatus, produced by Dr. Fooke (Germany). The optical density of the tested samples

was measured using the "Stat Fax 303 plus" ELISA reader (USA). The standard curve and controls were required to meet the acceptable value range as indicated in the Quality Control Certificates provided with the kit. Based on the analysis of literature and statistical data, we selected the six most common types of fungal allergens for the study, namely Mucor Racemosus, Alternaria Tenuis, Candida albicans, Penicillium notatum, Cladosporium herbarum, and Aspergillus fumigatus.

Results of the study and their discussion. The study involved 86 patients aged 35 to 65 diagnosed with chronic microbial eczema, established based on clinical presentation. Of these, 53 (61.6 %) had microbial eczema for 1–3 years, 24 (27.9 %) for 4–7 years, and 9 (10.4 %) for more than ten years. In 78 (90.7 %) of patients, an increased level of specific IgE to at least one of the investigated allergens to moulds was detected (Table 1).

Table 1

Concentration of sIgE to allergens (%)						
sIgE level	Mucor racemosus	Alternaria tenuis	Candida albicans	Penicillium notatum	Cladosporium herbarum	Aspergillus fumigatus
0.35–0.7, low	59.3	47.7	52.3	24.4	44.2	39.5
0.7–3.5, moderate	19.3	30.2	27.9	37.2	37.2	27.9
3.5–17.5, high	16.3	17.4	19.8	23.3	16.3	30.2
<17.5, very high	5.8	4.7	-	15.1	2.3	2.3

Mean level of specific IgE in the examined group of patients

According to the results of the study, a low level of specific IgE (0.35–0.7 середнє тире без пробілів) was found in 51 (59.3 %) of the examined group of patients to allergens of the fungus Mucor racemosus, an average level (0.7–3.5) in 17 (19.8 %) of patients, high (3.5–17.5) in 14 (16.3 %) of patients and very high (<17.5) in 5 (5.8 %) of patients. The level of specific IgE to Alternaria tenuis allergens was found to be low in 41 (47.7 %) of patients, medium in 26 (30.2 %) of patients, high in 15 (17.4 %), and very high in 4 (4.7 %) of patients. The level of specific IgE to Candida albicans allergens was found to be low in 45 (52.3 %) of patients, medium in 24 (27.9 %) of patients, high in 17 (19.8 %) of patients, and no very high level of specific IgE to allergens of this fungus was detected. The level of specific IgE to 2(33.3 %), and very high – 13 (15.1 %) of the examined group of patients. The level of specific IgE to allergens of Cladosporium herbarum was determined as follows: low – 38 (44.2 %) of patients, medium – 32 (37.2 %), high – 14 (16.3 %) of patients, and very high – 2 (2.3 %) of patients, medium – 32 (37.2 %), of patients, medium – 32 (37.2 %), high – 14 (16.3 %) of patients, and very high – 2 (2.3 %) of patients. The level of specific IgE to allergens of Aspergillus fumigatus was determined as follows: low in 34 (39.5 %) of patients, medium in 24 (27.9 %) of patients, and very high in 2 (2.3 %) of patients, high in 26 (30.2 %) of patients, and very high in 2 (2.3 %) of patients.

Regarding individual types of mould allergens, the highest percentage of IgE antibodies was detected to Penicillium notatum allergens – 39.5 %, with the average level of indicators being increased by two times, to Aspergillus fumigatus – 32.6 %, to Mucor Racemosus – 22.1 %, to Alternaria tenuis – 20.1 %, to Cladosporium herbarum – 19.8 %, to Candida albicans – 19.8 % (Fig. 1).

At the same time, in 68.6 % of patients with an established increase in the level of specific IgE, allergy to two or more mould allergens was detected in general, of which 50 % reacted to two allergens. In another 50 % of cases, allergy was detected to three or more allergens.

The study's results revealed reliable data indicating that patients with microbial eczema who are allergic to Penicillium notatum will also be sensitised to other types of fungi. In turn, 64 % of patients had comorbidity of sensitisation to almost six species of fungi, of which 43 % were simultaneously allergic to Aspergillus fumigatus.

Thus, most of the patients who participated in the study had elevated IgE levels to the moulds Penicillium and Aspergillus allergens.

Aspergillus fumigatus has been studied most extensively, with 19 allergens characterised. Both Penicillium notatum and Aspergillus fumigatus contain common antigens, such as peroxisomal protein, heat shock protein, and alkaline serine protease. This suggests that this is why the comorbidity of sensitisation to Penicillium and Aspergillus allergens is most common (43 %).

Based on the results obtained, it can be assumed that mycogenic sensitisation in a patient complicates the pathological process and duration of the disease, its course, and the effectiveness of treatment. The data obtained also suggest that the hypersensitivity of individuals with microbial eczema to the allergens of opportunistic fungi is highly important. As can be seen from the results of our study, people who are allergic to moulds are often sensitive to several types of moulds. This indicates that the degree of mutual reactivity is high among different types of moulds, similar to the reactivity to plant pollen. As a result of the pathological effects of mycotic infection on the human body, toxic substances are formed - "biopolymers", which are characteristic only of the fungus's vital activity and are involved in the

biodegradation of macroorganism cells. The studied toxins of micromycetes include carbon-hydrogen arsenates, selenates, and telerates. Their toxic effect leads to inhibition of oxidative forsythylation, destruction of disulfide bonds in keratin fibres, and disruption of protein-membrane components, which in turn leads to inhibition of the transport of substances through the membrane. The role of fungi in forming several enzymatic substances has been proven: a-amylase, glucose oxidase, fibrolein dextrogenase, peptidohydrolase, and collagenase. The pathological effects of fungal enzymes contribute to the breakdown of collagen and amylopectin, the breakdown of proteins into peptides and amino acids, the destruction of bonds in the secondary structure of collagen fibres, and the disruption of blood clotting processes [15].



Fig. 1. Frequency of detection of increased levels of specific IgE to of individual fungi in patients with chronic microbial eczema (emphasis added), A – to Penicilliuim notatum, B – to Aspergillus fumigatus, C – to Mucor racemosus, D – to Alternaria tenuis, E – to Candida albicans, F – to Cladosporium herbarum.

A long-lasting mycotic process has a major systemic impact on the human body. More and more often, the literature contains evidence of the development of severe mycotoxicosis in humans. It is becoming clear that the consequences can be diverse, even to the development of systemic damage [9]. The variety of forms, courses, pathogenesis, and multiformity of the clinic depends on many criteria of the micro- and macroorganisms. The morphological state of the pathogen, significantly the persistence of the microorganism, plays an important role, which, along with the state of the immune, nervous, endocrine, and other systems, affects the dynamics of the pathological process. Immune system dysfunctions are characterised by changes in the T-cell humoral and phagocytic components of immunity, which is reflected in a relative and absolute decrease in T- and B-lymphocyte levels. It is characterised by a lack of T-helper cells, suppression of the functional activity of T-suppressors, and a sharp reduction in the number of spontaneous and complementary neutrophil granulocytes [7]. Dysimmunoglobulinaemia is accompanied by an increase in IgE and IgG4 levels and a decrease in IgA and IgM [12]. Since the increased induction of IgE reflects the activity of Th2 cells that suppress antifungal cellular immunity and promote the development of infection, detecting a high titer of specific IgE can serve as a diagnostic and prognostic sign [11]. It has been experimentally proven that increased activity of Th2(CD4+ cells of the 2nd subtype secreting IL-4, IL-5, IL-10) leads to suppression of Th1 lymphocyte activity. It stimulates antibody formation, including the production of IgA and IgE, and inhibits phagocytosis and fungicidal action of macrophages and neutrophils. It has been observed that the predominance of Th1 or Th2 types of immune response depends on the duration of the infection. Switching to the Th2 response can also occur at intermediate stages to control the excessive destructive activity of phagocytes [14].

It is also essential that some types of opportunistic fungi can contaminate the air of residential and public spaces with mycelium and spores. Various types of fungi of the genera Alternaria, Cladosporium, Penicillium, Aspergillus, and others can be etiological factors in bronchial asthma, allergic dermatoses, and rhinoconjunctivitis [15]. The species composition of fungi from different studies has a slight difference. In terms of the number of species isolated and the frequency of detection, the species of fungi found can be arranged in the following sequence: Alternaria, Cladosporium, Penicillium, Aspergillus, Trichoderma,

Botritis, Phoma, Tamnidium, Stemphillium, Acremonium, Acremoniella. In our study, Penicillium and Aspergillus came out on top, which may be due to the climatic conditions in our country and the living conditions of the study group of patients.

As you can see, all this creates favourable conditions for the development of mycogenic sensitisation because contact with fungal allergens and house dust allergens occurs almost constantly, and, in most cases, there are no distinct seasonal fluctuations. Determination of variations in the levels of specific IgE to fungal allergens in the homes of patients with mould allergy throughout the year revealed that specific IgE to Penicillium and Aspergillus are detected in patients throughout the year, as are clinical symptoms of mould allergy. Of the group of patients we examined, 37 % live in the private sector in rural areas, 8.7 % are urban residents but live in the private sector, and 54.3 % live in multi-storey buildings in the city. However, it should be noted that fungi are always present in the human environment, but not all people develop mycoses. One of the essential reasons for the development of mycogenic allergy is changes in the immunological reactivity of the human body. The immunoallergic concept plays a leading role in the pathogenesis of microbial eczema. Usually, the skin microflora is not only non-pathogenic but also participates in its protection by suppressing pathogenic strains with non-pathogenic ones. Bacterial and fungal microflora synergism in various pathological processes has been clinically and experimentally proven.

Conclusion

Thus, it can be assumed that fungal sensitization in chronic microbial eczema is a significant characteristic. Fungal colonization of the skin is one manifestation of secondary immunosuppression. In turn, fungal infection itself exacerbates immune deficiency. Therefore, we can hypothesize that this vicious cycle leads to an increase in disease severity.

These results demonstrate that the level of specific IgE reflects the degree of sensitization to mold allergens. In 90.7 % of patients, elevated levels of specific IgE to at least one of the studied mold allergens were detected. Sensitization to Penicillium notatum allergens was found in 39.5 % of patients, to Aspergillus fumigatus in 32.6 %, to Mucor racemosus in 22.1 %, to Alternaria tenuis in 22.1 %, to Cladosporium herbarum in 19.8 %, and to Candida albicans in 19.8 % of patients. Comorbid sensitization to nearly six fungal species was detected in 68.6 % of patients, with 43 % simultaneously allergic to Aspergillus fumigatus. Moreover, the highest IgE concentration (greater than 17.5) was observed for the Penicillium notatum allergen in 15.1 % of patients with chronic microbial eczema.

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