Review / Обзор

Role of nonspecific risk factors in atopic dermatitis

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Annotation
The increasing prevalence of atopic dermatitis (AD) over recent decades suggests that environmental factors play an important role in the etiology and pathogenesis of the disease. Nonspecific factors refer to external (or exposomal) factors and include human and natural factors that influence the health of a population: for example, the socioeconomic status of the patient; climate, including air temperature, exposure to ultraviolet radiation, air pollution; and living in a city or rural area. Although studies have shown the influence of these factors on the course of AD, in general, none of them significantly increases or decreases the risk of developing the disease. This review briefly discusses studies on the role of nonspecific environmental risk factors and their impact on the course of AD in children and adults.
Keywords: atopic dermatitis, nonspecific risk factors, climate, socio-economic conditions, urban/rural environment.

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Аннотация
Увеличение распространенности атопического дерматита (АтД) за последние десятилетия свидетельствует о том, что факторы окружающей среды играют важную роль в этиологии и патогенезе заболевания. Неспецифические факторы относятся к внешним (или экспосомным) факторам и включают человеческие и природные факторы, влияющие на здоровье популяции: например, социально-экономический статус больного; климат, в том числе температуру воздуха, воздействие ультрафиолетового излучения, загрязнение воздуха; а также проживание в городе или сельской местности. Несмотря на то, что в исследованиях показано влияние этих факторов на течение АтД, в целом ни один из них достоверно не увеличивает или не снижает риск развития заболевания. В этом обзоре кратко обсуждаются исследования, посвященные роли неспецифических внешних факторов риска и их влиянию на развитие и течение АтД у детей и взрослых.
Ключевые слова: атопический дерматит, неспецифические факторы риска, климат, социально-экономические условия, городская/сельская среда.

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The pathogenesis of atopic dermatitis (AtD) is affected by a number of environmental factors in different ways (i.e. exposomes) [1–3]. External (exposome) factors are divided into *nonspecific*, or *a general external environment*, (human and natural factors, affecting the health of the population, — climate, urban environment, social and economic conditions); *specific* (air humidity, ultraviolet (UV) radiation, allergens, microbes, diet, tobacco and other pollutants) and *internal environment*, *dependent on the host* (interaction between body cells, for example, cutaneous and intestinal microbiota; inflammation and oxidative stress) [2, 3].

According to the latest data, mechanisms, responsible for the onset and exacerbation of AtD, involve interactions between genes and epithelial barrier, immune disorders, skin dysbiosis as well as the effect of various environmental factors [4, 5]. Due to impaired skin barrier function, in particular due to a genetic defect (including filaggrin mutations), penetration of allergens and infectious agents into the skin becomes easier [6].

According to the new concept — *"hypothesis of epithelial barrier"* — inflammation in the epithelial layer, which covers the skin surface as well as respiratory, urogenital and gastrointestinal tract, develops, first of all, when patients live in the urban environment [1]. Epithelial cell activation and release of such cytokines as IL-33, IL-25, thymic stromal lymphopoietin(TSLP), etc., upon allergen exposure, infectious agents or tissue damage due to skin itching, cause immune responses of Th2-type [7, 8]. Although Th2 axis is considered major in AtD pathogenesis, recent studies confirm the involvement of additional immune pathways, in particular Th1, Th17 and Th22-lymphosites [7, 8].As a result of impaired epi-

thelial barrier function, due to external factors, there is also change in the microbiome structure; in conjunction with disorders of immune regulation, it affects the maintenance of chronic inflammation in the skin [2,4–6].

Any of exposome factors might cause exacerbation and trigger AtD. The most significant role of external factors (e.g., air pollution and climate) in children with variants of filaggrin mutation, having lesions on exposed skin (face, arms,neck) [6]. The famous American scientist Leung

D. believes that other equally important triggers with AtD are *S. aureus*, herpes simplex virus, stress and allergens [4].

Although the impact of various risk factors on AtD development has been shown in numerous studies and confirmed under experimental conditions, their role in the start of the atopic march has not been determined yet [7].

Meanwhile, a wide variety of risk factors with AtD has been studied mainly in children: starting from nutrition and ending with certain external and internal, in particular, in different periods (pre- and postnatal) child development [8].

In many cases patients use exposure to the specific triggers to control their disease activity. Among the many environmental factors that affect the course of AtD, some can even play a protective role (e.g., consumption of unpasteurized milk) [2, 3].

NONSPECIFIC FACTORS

Urbanization, air pollution and climate change are the global factors, which affect public health worldwide,in contrast to the local ones, one of which is, in particular, the healthcare system in in specific regions.

HEALTHCARE

Availability and quality of healthcare differ, depending on economic development of the country of residence, social status, race and ethnicity, including AtD patients [9]. It is clear that obstacles to obtaining highly qualified medical help are a lack of expert physicians and even medical institutions with a modern infrastructure [2]. Also, if a patient belongs to an economically poor family or lives in conditions with limited access to education, this directly affects the effectiveness of treatment, including the opportunity to purchase necessary medicine. Particularly, in patients with bronchial asthma the above-mentioned socio-economic conditions lead to an increase in exposure to allergens and the development of more frequent and severe attacks of the disease [10]. Also, dilapidated and old housing as well as living in ecologically unfavourable areas were associated with increased prevalence and a more severe course of AtD in children [9, 11]. On the other hand, a reduction in the risk of AtD in the children, living in rural areas was revealed in the population (black population of South Africa), homogeneous by ethnicity and geographical origin [12]. It has long been known that colonization of the skin *S. aureus* is as risk factor, with which researches associate severity of AtD, allergic sensitization and impaired barrier function of the epidermis [4–6].

It is interesting to note that even among children with bronchial asthma the highest indicators of positive skin culture on *S. aureus* were more common in those who lived in the city or families with a low income [13]. The level of air pollution, especially inside the premises is also associated with a patient's low socioeconomic status [14]. In turn, impediments to access to quality health care due to socioeconomic problems can contribute to the development of stress in patients [8].

URBAN/RURAL LIFESTYLE

Hygiene hypothesis has long been debated as a possible explanation for growing allergic diseases: in particular, it has been observed that the youngest child among brothers and sisters has the lowest risk of developing AtD; or this risk decreases in infants, visiting kindergarten in the first year of life [15].

Other evidence, supporting the importance of environmental factors with AtD,include ecological differences between a city and a village.

It is believed that AtD is more common among patients, living in the city, compared to rural and suburban areas [3]. However, according to meta-analysis, conducted in 2010 by Schram M. et al, out of 26 studies, included in the analysis, 11 show a significantly higher prevalence of AtD in patients, living in the city; 14 — no such association is found, and only 1 study identifies a lower incidence of AtD in patients, living in the city [16]. Thereby, this comparative analysis underlines the potential role of various environmental factors in developing AtD.

Although exact factors are not quite clear, one explanation is related to the effect of farm animals on human health. Moreover, a link is shown between certain elements of a rural way of life (especially, the consumption of unpasteurized milk) and a reduction in prevalence of AtD [17, 18]. There was an interesting study, conducted jointly by Finnish and Russian scientists in a population of children, living in a genetically homogenous, but economically different region of Karelia at the Russian-Finnish border [19]. The comparative analysis showed 3–10 times higher prevalence of allergic diseases (bronchial asthma, hay fever, AtD, rhinitis as well as atopic sensitization) in Finland than in Russian Karelia, and, moreover, these patterns persisted for 10 years of observation [19]. Skin microbiome and bacterial and fungal content in the nasal mucus are also contrastingly different with a predominance of the genus *Acinetobacter* in children, living in Russia.

In addition, the disruption of the gut microbiome, especially at an early age, might affect human immunity and atopy pathogenesis (development of tolerance or sensitization). The change of microbiocenosis in urban environments, taking antibiotics, reducing exposure to farm animals and(or) their absence lead to a low effect of endotoxins and increased Th2-cells in epithelial and mucous membranes in patients with allergic diseases [20].

The urban way of living is also associated with progression of AtD and atopic multimorbidity in children with atopy in their parents, filaggrin mutations and allergic polysensitization in the anamnesis [21].

CLIMATE

One of the reasons for rising prevalence of AtD in industrialized countries is considered global climate change: in particular, rise in air temperature and increased greenhouse gas emissions that cause changes in atmospheric UV radiation and air humidity [22]. Furthermore, climate changes (droughts; mass displacement of people from new uninhabitable areas, etc.) pose the greatest threat to health of people, living in low- and middle-income countries.

Climate factors (temperature and air humidity, precipitation, UV radiation, etc.) are characterized by severe seasonality, and all of them certainly affect the skin. Particularly, both local and global changes in the outside temperature might be associated with the severity of skin manifestations in patients with AtD (although we cannot exclude simultaneous relationship between these factor and others).

Meanwhile, evidence of the association between air temperature and prevalence of AtD contradicts each other, perhaps because of various analytical methods or criteria for determining cold or hot weather. Several studies showed that both high and low air temperature is associated with exacerbation of AtD in observed patients [23–28]. Thus, in the USA, where there is one of the most diverse climates in the world, the frequency of out-patient visits was the highest in adults and children with AtD, living in the east of the country, where there is the lowest temperature, which reached its peak in winter [23]. According to other data, only cold or, on the contrary, hot weather is associated with exacerbation of AtD [24, 25].

It is more logical to expect a decrease in the prevalence of AtD in areas with high air temperature [22, 24]. Usually people, living in warmer climates, spend more time outdoors, and, therefore, exposure to UV rays might have a protective effect on the skin [23]. On the other hand, patients with an established diagnosis of AtD do not tolerate high air temperature as heat can cause sweating. As a rule, with sweat, which may develop the irritation action on the skin and contribute to Th2-type inflammation, itching of the skin becomes worse. Children with AtD reacts most to changes in temperature, who have more severe symptoms in spring, autumn and winter [25].

Despite the fact that sun exposure has a positive effect on the skin (UV rays contribute to raising the level of antimicrobial peptides in the skin, modulate the composition of the microbiota, etc.), some studies have found an association between poorly con-

trolled AtD and higher air temperature, including children [26–28].

Patients with Atd do not also tolerate extreme cold weather that might cause dry and itchy skin. Low air temperature may contribute to production of Th2-cytokines and affect the activity of mast cells in the skin that is strongly correlated with inflammation and impaired epidermal barrier of the skin [29].

Two studies show a very significant impact of climate on the course of AtD. Thus, displacement of children aged 4–13 with severe AtD, living in Norway (subarctic/moderate climate), to the subtropical climate of Gran Canaria for 4 weeks led to a significant improvement in skin symptoms on SCORAD scale and quality of life as well as reduced need for local steroids in 1 and 3 months [30]. A rapid decline in the intensity of itching is also noted in adult patients with AtD, who underwent sanatorium treatment in the high mountain region of Davos, Switzerland [24].

It is important to consider the influence of other effects of climate change on AtD (cold and dry weather conditions, flood, etc.) [31, 32]. Scientists believe that global warming will be accompanied by flood due to melting polar ice, sea level rise and longer rains. Thus, during flood events, occurred in Thailand, there was a significant increase in emergency department visits of children aged 0–12, suffering from AtD [25].

Climate changes and global warming will probably contribute to an increase in the concentration of such aeroallergens as pollen and fungi in the air, and also in the duration of pollination of plants and allergenicity of pollen itself [30–33]. It is shown that higher air temperature is associated with the extension of flowering season, and higher levels of CO_2 contribute to an increase in biomass of pollen produced and its allergens. In particular, raising level of pollutants in the air causes changes in allergenicity of ambrosia pollen [33]. This, ultimately, exacerbates allergenic load in patients with seasonal rhinoconjunctivitis. The study by Krämer U. et al confirms deterioration of skin symptoms in children with AtD and sensitization to grass pollen in summer [30].

CONCLUSION

The impact of different exposome factors on the development and course of Atd has been found in many studies. However, according to the literature, there are the most studied issues related to specific exposome factors, including their exposure in the prenatal and early period of a child's life (type of feeding, exposure to air pollutants, in particular tobacco smoke, vitamin D level, contact with pets, etc.). Although studies show the effect of nonspecific exposome factors on clinical manifestations of AtD, generally, none of them reliably increase or, on the contrary, decrease the risk of disease in children.

Undoubtedly, other factors have a modulating effect on above-mentioned nonspecific ones. Particularly, viruses, allergens, antioxidants, different pollutants, etc., which are closely associated with environment. These and other questions require further study.

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Dali Sh. Macharadze — article design development, text writing, text editing.

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