Review article

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ATOPIC DERMATITIS IN CHILDREN

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Atopic dermatitis represents a non-infectious, multifactorial inflammatory and chronic dermatosis. Pruritus is the main symptom. The pathophysiology of atopic dermatitis is very complex and includes genetic disorders, a defect in the epidermal barrier, an altered immune response and a disruption of the skin's microbial balance, all of which damage the epidermis, causing itchy skin lesions. The prevalence varies, but it is generally present in 30% of children, and 85% of cases manifest before the age of 5. The triad of atopic diseases consists of atopic dermatitis, allergic rhinitis and asthma. A retrospective analysis of the documentation of the children who were treated at the Pediatric Clinic of the University Clinical Center Niš from 2018 to 2019 focused on anamnestic data, clinical manifestations, and laboratory parameters obtained from the medical records of the subjects. The total number of examined children was 40, among them, 21 were male and 19 female. They were divided into 3 age groups, from 2 months to 7 years. Anamnestic data indicate a connection between AD and other disorders of atopic diseases, allergic rhinitis, asthma, respiratory infections, and milk allergies. *Acta Medica Medianae 2015;54(3):54-60.*

***Key words**: atopic dermatitis, asthma, allergic rhinitis*

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Introduction

Atopic dermatitis (AD) is a non-infectious, multifactorial chronic inflammatory dermatosis with pruritus as the main symptom. It includes erythema, xerosis, erosions and excoriations, oozing, and lichenification.

The chronic course of the disease, which shows a high degree of relapses and the involvement of the whole family in the treatment process, greatly affects the quality of life (1).

It involves genetic changes, a defect in the epidermal barrier resulting in an altered immune response and disruption of the skin's microbial balance, all of which damage the epidermis and cause itchy skin. Repeated scratching initiates a self-perpetuating cycle of scratching, which can have a significant impact on subsequent disruption of the skin barrier.

The basis for the manifestation of different phenotypes and endotypes of atopic dermatitis is provided by numerous changes at the genetic level (2).

Etiopathogenesis

The multifactorial etiopathogenesis of AD includes gene mutations, inadequate response of the immune system to the factors from the external environment, and defects in the epidermal barrier.

Prevalence varies, but AD is generally present in 30% of children, and in 85% of cases the disease manifests itself before 5 years of age. The triad of atopic diseases is represented by AD, allergic rhinitis and asthma (3).

AD is one of the main risk factors for developing asthma - more precisely, children with AD are more likely to develop it than children without AD.

Patients with specific IgE antibodies to common environmental allergens (extrinsic AD) present at the age of 2–4 years and diagnosed with eczema have a higher risk of progression to allergic rhinitis and asthma than those with eczema without IgE sensitization (intrinsic AD). IgE sensitization is the main risk factor for the progression and persistence of asthma, but it affects the early onset and severity of AD (4).

There are different forms of the disease that are manifested by different primary changes that are not in accordance with the classical concept of AD, which begins in childhood.

The most important factors that can contribute to the manifestation of the disease and its relapse are skin exposure to detergents, soaps, woolen and synthetic materials, aeroallergens such as dust mites from house dust, animal hair, and allergens in children in food (egg whites, milk, soy, peanuts, walnuts, almonds, wheat flour, fish, crustaceans) (5).

Atopic diseases show a genetic connection. In monozygotic twins, the concordance rate is 80% compared to 30% in dizygotic twins.

Genetic polymorphisms found in AD are responsible for mediators that trigger atopic inflammation.

This dermatosis can be caused by various external and internal factors that can act independently or together (6).

The stratum corneum with all its structural components and the stratum granulosum are two essential structures of the epidermal barrier (Figure 1).

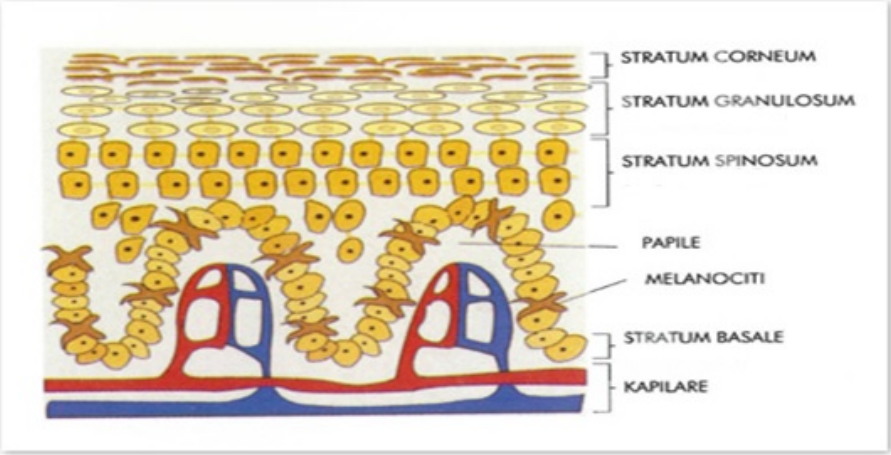

Figure 1. Review of skin layers

The histopathological image in acute dermatitis with vesicles is characterized by a change that includes spongiosis, acanthosis, parakeratosis that occurs in the epidermis and vasodilatation, edema, and lymphatic-histiocytic infiltration in the dermis.

IL-4 and IL-13 are two types of cytokines that play an important role in the production of chemokines, dysfunction of the skin barrier, suppression of antimicrobial peptides (AMP) and allergic inflammation, as confirmed by studies (7).

Evidence for the importance of DNA methylation has been shown by recent studies and an association between umbilical cord blood methylation at 5′-C-phosphate-G-3′ IL-4R sites and the development of eczema at 1 year of age of the baby.

Neurons that express the histamine-H1 receptor and histamine-H4 receptor result in histamine activation, which can cause itching as well as an allergic reaction. H1 antihistamines are prescribed as therapy in the treatment of itching after the appearance of urticaria, but their effect is limited in the treatment of chronic pruritus in patients with eczema.

The lipid matrix consists of lipids such as ceramides, long-chain free fatty acids (FFAs) and cholesterol. The matrix is organized in lamellar bodies and located between corneocytes. When epidermal differentiation occurs, precursor lipids are located in lamellar bodies within the upper cell layers of the epidermis and extruded into the extracellular domain. The enzymatic treatment that follows this process produces the main classes of lipids, which are necessary to maintain the integrity of the epidermal barrier.

Altered lipid composition was observed in skin with changes and skin without lesions. More precisely, long-chain EO ceramides are very important because they are covalently bound to keratin proteins and cover the surface of each corneocyte. Levels of long-chain ceramides are reduced in AD patients who are colonized with Staphylococcus aureus compared to those not colonized.

By examining AD, we came to the knowledge that S. aureus is frequently present in patients with a more severe form of the disease, while S. epidermidis presents in those with a milder form of the disease. S. aureus colonizes the skin of patients with AD and its role is crucial in the development and progression of the disease.

Colonization of S. aureus can result in the expansion of B-cells independently of T-cells, which also affects regulation of pro-inflammatory

cytokines, such as TSLP, IL-4, IL-12 and IL-22. This stimulates mast cell degranulation.

AD patients have a lower number of bifidobacteria in their intestines and a higher number of staphylococci compared to healthy individuals. Overgrowth of pathogenic bacteria, such as Escherichia coli and Clostridium difficile, is thought to be associated with lower concentrations of beneficial bacteria, reduced induction of regulatory T (Treg) cells, and increased intestinal permeability.

A specific or altered microbial composition in the intestines prevented the activation of Th2-immunity and stimulated regulatory immunity, producing regulatory dendritic cells and Treg cells. However, further studies are needed to reach a conclusion on how dysbiosis affects the function of the epidermal barrier and the development of AD (8).

In AD, epidermal lipids are altered both qualitatively and quantitatively.

It is known that affected individuals have a lack of natural moisturizing factors (urea and amino acids) and impaired epidermal lipid metabolism. This explains why their skin is more prone to dryness and has an impaired barrier function.

It has been proven by previous studies that sensitivity to allergens in early childhood and children with AD is more likely to later develop allergic rhinitis and asthma. The effect of aeroallergens on AD is great because there is no correlation between allergic rhinitis and AD (9).

At this time, there is very little information about the factors that influence the onset of asthma and allergic rhinitis in children with AD. However, based on several studies, it can be said that they are preceded by immunoglobulin E (IgE) sensitization.

The preclinical phase (phase 0) of AD begins already in childhood. Chronic inflammation of the skin occurs, but without any evidence of IgE sensitization.

In this phase, sensitization to allergens occurs. These allergens are most often from food and from the external environment, which leads to the classic IgE-related phenotype of AD. This results in chronic inflammation of the skin, suitable for *Staphylococcus* colonization (10).

Key elements in the pathophysiology of asthma development are infiltration of the bronchial mucosa with eosinophils and bronchial hyperreactivity. It has been proven that patients with AD can have hyperreactivity even without a diagnosis of asthma. The triggers for the development of bronchial hyperreactivity have not been fully explained. A positive family history of eczema, a younger age at the onset of the disease, the clinical picture of AD and multiple exposure to allergens certainly increase the risk.

AD is caused by complex pathogenetic mechanisms and therefore represents a multifactorial heterogeneous disease. The skin in these patients is extremely dry and dull, with increased permeability. It is constitutionally irritable, and pruritus is the earliest symptom of the disease (due to elevated histamine)—it is regularly present and can be so strong that the vicious cycle of itching-scratching-itching occurs (11).

Clinical manifestations

It is clinically characterized by erythema, edema, vesicles and wetting in the early stage of the disease, and lichenification, desquamation and hyperkeratosis in the later chronic stage.

Skin manifestations change continuously, with periods of exacerbation and remission, and are usually associated with various provocative factors (12).

Typical predilection sites, as well as clinical manifestations, change during the life of AD patients. As a result, AD is classified into 4 stages:

1. Atopic dermatitis in infants—Eczemainfantum

Babies can get symptoms as early as 2–3 months of age. The rash usually appears suddenly, making the skin dry, cracked, and itchy. It typically appears on the face—especially on the cheeks and scalp (known as the "cradle cap"), knees and elbows, while the central part of the face remains unaffected.

A yellowish layer of seborrheic, hard scales on the scalp in the first months of life in babies is usually an early presentation of AD. These scales can rarely be found on the folds and in the ankle area. In severe cases, the disease becomes generalized (Figure 2).

In babies, atopic skin is also very rarely found in the diaper area. Although diaper rash may look similar, that area is too wet for AD to occur. The changes are of the exudative and eczematous type and consist of vaguely limited beaches with erythema, edema, papulovesicles, wetting and crusts. In 50% of the babies, the symptoms disappear spontaneously at the end of the second year of their lives.

2. Childhood atopic dermatitis—Besnier's Prurigo presents a clinical picture from 3 to 11 years of age. Predilection places for the appearance of changes on the skin are the cubital and popliteal folds, on the neck and around the joints.

There are two potential scenarios—that the changes have developed as a transition from the previous form to a chronic form or that they have occurred suddenly. They represent ill-defined plaques with lichenification and desquamation.

3. Atopic dermatitis of adolescents and young adults—usually, a dry rash with scaly patches that itch appears first. The skin is often uneven, thickened, and rough to the touch.

The inner sides of the elbows and knees, neck, wrists, ankles and/or the folds between the buttocks and thighs are most commonly affected.

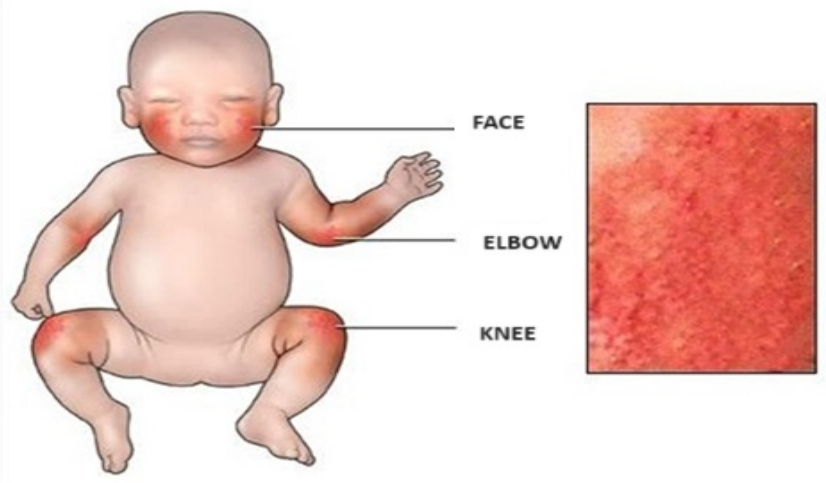

Figure 2. Predilection sites for AD in infants

In addition, pruritic nodules, scratching marks, chronic eczema of the hands and feet, inflammation around the eyes, which corresponds to the clinical picture of diffuse atopic dermatitis, are often found as well.

4. Atopic dermatitis in adulthood remains active in a small number of patients and rarely occurs for the first time. It is characterized by lichenified plaques that appear on the entire skin, affecting the face, folds, and anorectal region (13).

The course of the disease is chronic, accompanied by improvements and reactivation of the disease. In most patients, remission occurs after puberty or by the age of 30. In a smaller number of patients, the chronic relapsing course is maintained throughout life.

Complications are caused by an infection with staphylococci (colonization) and viruses (reduced cellular immunity) (14).

Aim of the Research

The aim of the study was the examination of the frequency of atopic dermatitis in children and its association with other disorders belonging to the type of atopic diseases.

Respondents and Methods

A retrospective analysis of the documentation of children who were treated from 2018 to 2019 at the Children's Internal Medicine Clinic of the Niš University Clinical Center was performed.

Anamnestic data, clinical manifestations, and laboratory parameters obtained from the medical records of the subjects were analyzed.

The value of specific IgE to inhalant and nutritional allergens in examined children was also assessed for each age group.

Results

The total number of examined children was 40—21 male (53%) and 19 female (47%).

Three groups of patients were divided into three age groups, ranging from 2 months to 7 years:

Group 1: Children under 2—10 children
Group 2: 2-year-olds—19 children
Group 3: 2-7-year-olds—11 children

Anamnestic data indicated the association of AD with other disorders belonging to the type of atopic diseases. Out of 40 children, 25 had comorbidities—in 9 cases AD came with asthma, in 6 with allergic rhinitis, in 8 with respiratory infections, and in 17 with milk allergy.

This indicates that an average of 27.25 out of 40 subjects with atopic dermatitis suffered from another atopic disease.

The value of specific IgE was tested in the groups of 2-year-olds and children under 2—59% to milk (Figure 3).

It was also tested in the group of children from 2 to 8—43% to mites, 39% to gluten, 15% to animal hair, and 3% to grass (Figure 4).

There were no elevated values for other allergens in the examined patient groups. In 32% of children in the 2–8 age group, immunoglobulin class A values were decreased, whereas other values did not show deviations in all age groups.

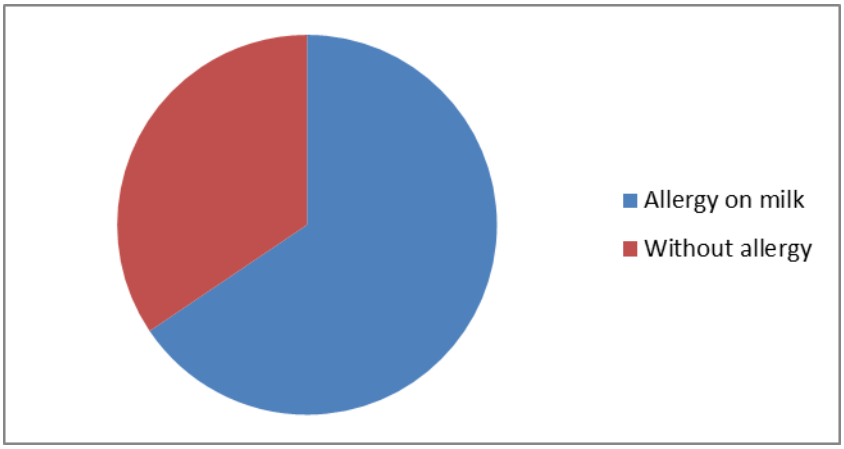

Figure 3. Allergy on milk in children from 2 to 8 years old
*59% of children have allergy on milk

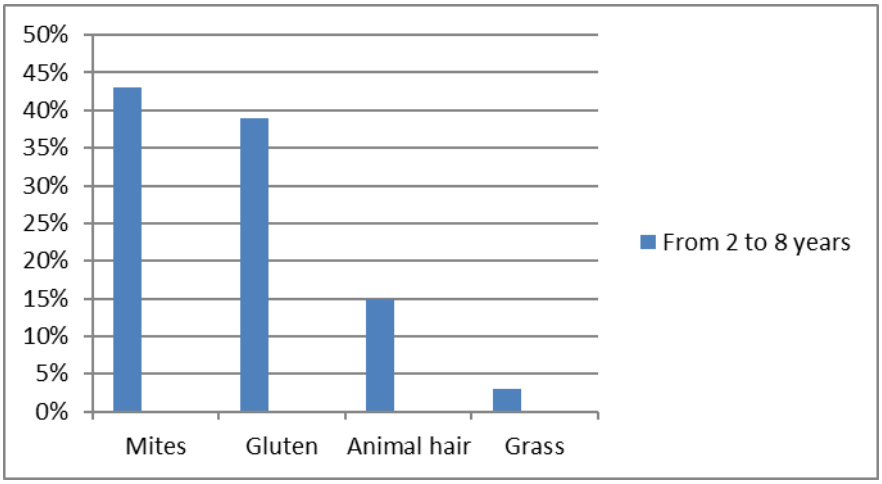

Figure 4. IgE value to specific inhalant and nutritional allergens

Discussion

Atopic dermatitis is closely related to asthma and allergic rhinitis. Although there is a general consensus that the existence of a diagnosis of atopic eczema increases the chances of developing asthma and rhinitis, the risk of developing these diseases should be determined in different populations according to precisely determined methods, which was the aim of this research (15).

Based on the questionnaire of the International Study of Asthma and Allergy in Childhood (ISAAC), a survey which included all schoolchildren of the city of Cartagena (Murcia) was conducted in Spain. The association between the severity of atopic dermatitis and asthma, and allergic asthma and allergic rhinitis was analyzed. The conclusion was as follows: it was shown that schoolchildren with atopic eczema have a three-fold higher risk of developing allergic rhinitis (OR: 3.33; 95% CI: 2.45–4.54), a 4-fold higher risk of developing asthma (OR: 3.85; 95% CI: 2.74–5.42) and a fivefold risk of allergic asthma (OR: 4.91; 95% CI: 3.17–7.59) compared to school-age children without atopic eczema. Thus, a direct connection between AD and allergic rhinitis and asthma was observed (16).

In a German longitudinal study of atopy in 1,300 children, it was found that patients with atopic dermatitis are at a higher risk of developing asthma at the age of 7 years. However, patients with atopic dermatitis and no wheezing during the first 3 years of life are not at increased risk of developing wheezing or bronchial hyperreactivity at the age of 7 years. Atopic dermatitis and asthma are thought to be related, but atopic dermatitis does not precede asthma, whereas allergic rhinitis is a risk factor for asthma and may precede asthma.

A cross-sectional study in five Mexican cities with a sample of almost 15,000 children aimed to determine the prevalence of asthma, allergic rhinitis and atopic dermatitis in six- and seven-year-olds. In order to determine the prevalence of allergic diseases and their symptoms, parents had to fill in the questionnaire of the International Study of Asthma and Allergy in Childhood. Ninety-five percent of confidence intervals (CI) were estimated for proportions. Of the total sample, 7,466 (52.5%) were boys, and 7,463 (47.5%)

were girls. Overall, the prevalence of asthma and exercise-induced asthma was 6.1% (95% CI = 5.7%–6.5%) and 2.1% (95% CI = 1.9%–2.3%), respectively (17).

Conclusion

Studies have shown that dysregulation of innate and acquired immunity plays a key role in the occurrence of AD. However, recent genetic

and molecular research has focused on the fact that what precedes the appearance of the disease is a disruption of the skin barrier function. The etiology of AD emphasizes the important role of disruption of the epidermal barrier, which leads to increased epidermal permeability leading to pathological inflammation of the skin and percutaneous sensitization to allergens.

Therefore, most new treatment strategies aim to strengthen specific aspects of the skin barrier or skin inflammation. Several studies have shown that in the prevention of AD, the early use of emollients in high-risk infants is necessary.This may have wider implications in terms of halting the progression of atopic comorbidities, including food allergies, asthma and allergic rhinitis.

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ATOPIJSKI DERMATITIS

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Atopijski dermatitis je hronična, nezarazna, multifaktorijalna upalna dermatoza sa pruritusom kao glavnim nalazom. Patofiziologija atopijskog dermatitisa je kompleksna. Uključuje genetske poremećaje, defekt epidermalne barijere, izmenjen imuni odgovor i poremećaj mikrobne ravnoteže kože, koji oštećuju epidermis izazivajući lezije kože sa svrabom. Prevalencija varira, ali je generalno prisutan kod 15% – 30% dece, a 85% slučajeva manifestuje se pre pete godine života. Atopijski dermatitis, alergijski rinitis i astma čine trijadu atopičnih bolesti. Retrospektivnom analizom dokumentacije dece koja su lečena na Klinici za pedijatriju Univerzitetskog kliničkog centra Niš u periodu od 2018. do 2019. godine analizirani su anamnestički podaci, kliničke manifestacije i laboratorijski parametri dobijeni iz medicinske dokumentacije ispitanika. Ukupan broj ispitivane dece je 40 – 21 ispitanik bio je muškog pola, a njih 19 bilo je ženskog pola. Podeljeni su u tri grupe po uzrastu (od dva meseca do sedam godina). Anamnestički podaci ukazuju na postojanje udruženosti AD sa drugim poremećajima po tipu atopijskih bolesti – astmom, alergijskim rinitom, respiratornim infekcijama i alergijama na mleko. *Acta Medica Medianae 2015; 54(3):54-60.*

***Ključne reči**: atopijski dermatitis, astma, alergijski rinitis*