Review paper

Microorganisms in the etiopathogenesis of atopic dermatitis

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Abstract

Atopic dermatitis (AD) is a chronic, recurrent inflammatory skin disorder, which is accompanied by characteristic appearance of skin lesions and intense pruritus. The etiopathogenesis of the disease has not been fully elucidated. An important role in pathophysiology of AD seems to be associated with genetically related disturbances of both structure and function of the epidermal barrier, disorders in innate and adaptive immunity, the surrounding environment (airborne allergens and also food allergens – at the younger age) and infectious factors. The article presents current knowledge on the role of different microorganisms (*Staphylococcus aureus*, *Malassezia species*, *Candida species*, *Herpes simplex virus*) in initiating, exacerbation and maintaining skin lesions typical of atopic eczema.

Key words: atopic dermatitis, etiopathogenesis, *Staphylococcus aureus*, *Malassezia species*, *Candida species*, *Herpes simplex virus.*

Introduction

Atopic dermatitis (AD, endogenous eczema) is a chronic relapsing inflammatory skin disorder, which develops on the base of atopic diathesis. It is estimated that approximately 800 000 people in Poland suffer from AD. The incidence of that disease in children under 7 years of age is approximately 15-20%. Skin lesions persist in less than 10% of 10-year-old patients [1].

Both etiology and pathogenesis of AD are very complex in nature. Coexistence of immune disorders (acute phase of the disease is dominated by Th2 response, whereas the chronic phase – by Th1 response), neurovegetative disorders and functional impairment of epidermal barrier has been reported [2]. The key role in AD development is played by genetic predispositions and environmental factors (including microorganisms, whose antigens contribute to development, intensification and persistence of skin lesions typical of AD) [3]. As a result of colonization of patients' skin with different strains of microorganisms the so-called "mechanism of the vicious circle" occurs, which can be interrupted with the use of antibacterial, anti-fungal or antiviral drugs.

Bacterial infections in atopic dermatitis

Staphylococcus aureus

Changes in both the quantity and composition of skin bacterial flora have been observed in the course of atopic dermatitis. According to numerous studies, *Staphylococcus aureus* has frequently been isolated from the skin surface of AD patients [4].

The following factors seem most significant for skin colonization by this microorganism in atopic dermatitis:

- Disruption of the epidermal barrier. Establishing the association between mutations in the filaggrin coding gene (key protein in the final differentiation of skin and forming the skin barrier) and AD development was particularly significant. It is worth mentioning that about 40 different loss-of-function mutations have been determined so far (in Europe) in the gene coding filaggrin, whose locus occurs within 1q21 chromosome. However, two independent genetic variants of function loss (R501X and 2282del4) in this gene, are most frequent, which are strong factors predisposing to AD development (especially association with exogenous AD char-

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acterized by high serum IgE antibody levels and accompanying allergies). These variants occur in approximately 9% of people in Europe (in 30% of AD patients) and also show a relevant connection with asthma [5]. It is worth pointing out that research conducted in Asia showed the occurrence of different mutations in filaggrin gene in these populations than in European people [6].

- Innate and acquired immune deficiency.
- Increased adhesion of *S. aureus* to the keratinocytes and its impaired elimination due to characteristic receptors, which are present on the surface of the bacterial cell, i.e. microbial surface components recognizing adhesive matrix molecules (MSCRAMMs) and show marked affinity to the proteins of the extracellular matrix (mainly fibrinogen and fibronectin). Th2-type cytokines (mainly IL-4 and IL-13), which dominate in the acute phase of the disease, increase the expression of those proteins and facilitate Staphylococcus adhesion within inflammatory skin lesions [7].
- Alkaline pH.
- Decreased number of ceramides, free fatty acids and polar surface lipids within the atopic skin.
- Low levels of immunoglobulin A in the sweat gland secretion.
- Natural antimicrobial peptide deficiency in the skin (cathelicidin, β-defensin 2 and dermicidin) [8]. The cause of lower expression of antimicrobial peptides in the skin has not been elucidated; it may be associated with predominance of Th2 cytokines in the microenvironment (since IL-4 and IL-13 inhibit synthesis of those peptides by the keratinocytes) [9].

The statistics show that *S. aureus* occurs in the skin lesions of 75-100% of untreated patients and in 30-50% of patients – within the normal skin [10]. Strains that produce staphylococcal toxins with superantigen properties account for 30-60% [11]. These microorganisms have rarely been isolated from the skin of healthy subjects (< 5% of patients) [12]. In the study by Leyden *et al.*, density of the pathogens in the skin lesions of AD patients was 1000 fold higher than in apparently healthy skin and exceeded 10^6 CFU (colony forming units)/cm^2 [13].

It is worth pointing out that the nose vestibule and throat are common reservoirs of the bacteria in AD patients (the incidence of *S. aureus* carrier state in the nose vestibule is estimated as approximately 60%, whereas it is 20% in healthy people) [14]. Results of recent studies showed that patients in the close environment of an AD patient could also be the reservoir of staphylococcus (occurrence of the bacteria in the nose vestibule has been demonstrated in approximately 46% of patients described as "close contacts"). Genetic investigations concerning staphylococci isolated from AD patients and persons from their close environment showed homology in the microbe morphology that reached nearly 81% [15].

The grade of colonization (of both the skin and other ontocenoses) by *S. aureus* in patients with AD correlated with the clinical progression of the disease, levels of total and specific IgE antibodies and peripheral eosinophilia [16]. Studies that have been performed so far (despite a vast number of these) have not shown any association between the existence of a specific strain of *Staphylococcus* producing a specific enterotoxin and severity of AD [17].

The effect of *S. aureus* on the etiopathogenesis of AD has been proven by the fact that oral or local antibiotic therapy resulted in the improvement of skin lesions in a large number of patients [18]. In the course of treatment, *S. aureus* is eliminated from the skin of 70% of patients. However, it seems worth noticing that recolonization occurs promptly after therapy with antibiotics has been withdrawn and patients from a close circle frequently are the source of Staphylococcus [19].

One of the recently conducted studies, which aimed to determine whether colonization of mucous membranes or skin by Staphylococcus in newborns correlates with the occurrence of AD later in life, deserves attention. Swabs from the nose vestibule and the area of the perineum of newborns and 1-year-old children (of asthmatic mothers) were taken and analyzed. *Staphylococcus aureus* positive cultures were found in 53.3% of 1-month-old children and in 11.3% of 1-year-old children. Out of the group of children qualified for the study, 42% developed symptoms of AD in the first 3 years of life. However, no correlation between early colonization by *S. aureus* and occurrence of AD was found. However, it was found that colonization of the nasal cavity by the following bacteria: *S. pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* showed a positive correlation with occurrence of asthma or recurrent cough in the early childhood [20].

The role of *S. aureus* colonization in the development of AD seems to be the result of a direct pro-inflammatory effect (*S. aureus* is a source of pro-inflammatory proteins: protein A and α-toxin) and superantigen properties of secreted enterotoxins such as SEA, SEB, SEC, SED, SEE (*Staphylococcal enterotoxin A*, *B*, *C*, *D*, *E*) and TSST-1 (toxic shock syndrome toxin) [21].

Results of the most recent study conducted by Wichmann *et al.* demonstrate that α-toxin is produced by about 30% of different strains of *S. aureus* isolated from AD patients. It also showed that besides inducing proliferation of T lymphocytes, α-toxin could contribute to the epidermal barrier disruption by damaging keratinocytes [22]. The research also showed that *Staphylococcus* strains that produce α-toxin occurred statistically more frequently in patients with specific IgE antibodies against pollens of grass and birch.

As far as the superantigen properties of some Staphylococcal exotoxins are concerned, the definition of a superantigen should be reminded. Superantigens are proteins characterized by a large molecular mass, which cause polyclonal activation of lymphocytes (some superantigens can activate as much as 5-30% of all lympho-

cytes, which is even a hundred times more than the proportion of lymphocytes induced in the reaction with a classic antigen). This is due to the fact that superantigens react with only a short variable segment of TCR (T cell receptors) in the β chain [23]. Superantigens are capable of:

- inducing proliferation of T lymphocytes and production of cytokines,
- activating expression of the skin lymphocyte antigen – CLA (cutaneous lymphocyte antigen), which belongs to the group of the so-called homing receptors that determine preferential shift of lymphocytes towards skin,
- stimulating Langerhans cells, keratinocytes and macrophages to secrete for instance IL-1, IL-12 and tumour necrosis factor α (TNF-α),
- modulating functions of the eosinophil (i.e. inhibiting its apoptosis, increasing expression of activation markers on its surface and stimulating *in vitro* respiratory burst),
- it is also worth mentioning that superantigens contribute to generating resistance to conventional therapy with steroids through sensitizing T-cell to the suppressive effect of these drugs.

Simultaneously, superantigens can function as allergens and induce synthesis of specific IgE antibodies [24].

Development of chronic AD in patients who underwent septic shock induced by TSST-1 demonstrates the role of superantigens in initiation, intensification and persistence of the inflammatory process in AD. It is also proved by the fact that application of staphylococcal enterotoxin SEB to the altered/unaltered skin in AD patients can induce or intensify lesions typical of this disease [25].

Staphylococcal superantigens and α-toxin are also capable of inducing synthesis of IL-31 *in vivo* in AD patients and increasing the number of receptors for this cytokine on monocytes, macrophages and dendritic cells [26]. Interestingly, stimulation of histamine receptors type 4 located on T CD4+ lymphocytes (mostly Th2 subpopulation) can also result in increasing secretion of IL-31 in patients with atopic dermatitis, which was reported by Gutzmer *et al.* [27].

Interleukin 31 is a newly discovered cytokine, which is produced by T lymphocytes and belongs to the IL-6 family. Experiments conducted on animals showed that applying cytokine IL-31 (exogenously supplied) stimulated changes characteristic of AD. Increased expression of mRNA for IL-31 has been found in biopsy specimens of unaltered skin from AD patients [28]. This cytokine can probably play an important role in development of inflammatory lesions (through inducing synthesis of IL-1β, IL-6, IL-18 by monocytes and macrophages) and in the pathogenesis of pruritus (by its binding to the IL-31 receptor in the cells of the sensory nerves). Moreover, IL-31 stimulates expression of some chemokines (CCL17, CCL22, CCL1), which results in T-cell movement towards skin and in producing IL-31 by this lymphocyte [29].

The role of lipoteichoic acid (LTA) in the development of typical skin lesions in AD is also worth mentioning. Lipoteichoic acid is a component of cell walls of gram (+) bacteria including *S. aureus*. It can exert biological effects by binding mostly with TLR-2 (type 2 Toll-like receptors). The most recent studies conducted by Jeffrey *et al.* demonstrated that LTA could contribute to worsening of skin inflammatory lesions in the course of AD. It has also been confirmed by results of the experiments conducted on mice, which revealed that application of LTA on the animal skin surface resulted in the development of lesions typical of atopic dermatitis. It has also been shown that intracutaneous injection of LTA caused increase in mRNA expression for some cytokines, such as TLF-α, IL-6 and IL-8 [30].

Similarly, Jeffrey *et al.* reported that patients, whose skin samples contained MRSA (Methicillin-resistant *S. aureus*) showed significantly higher values of the EASI (eczema area and severity) index compared with patients, in whom MSSA strains (Methicillin-sensitive *S. aureus*) were detected [30].

Fungal infections in atopic dermatitis

Malassezia sp.

Malassezia yeast species are naturally found as human skin physiological component of the microbiological flora [31, 32]. Most commonly, the fungi occur on the areas of skin, which are rich in sebaceous glands, such as the trunk, back, face and hirsute regions of head skin, where they form colonies in the horny layer [33, 34]. The *Malassezia* genus is divided into several species: *M. globosa*, *M. restricta*, *M. obtusa*, *M. slooffiae*, *M. sympodialis*, *M. furfur*, *M. japonica*, *M. yamatoensis*, *M. dermatitis* and *M. pachydermatis* [35]. All the species show different morphological characteristics but molecular biology techniques are necessary to assign them to a correct taxonomic position [36].

Malassezia fungi are detected in approximately 56% of AD patients (they mostly colonize the hirsute skin of the head in these patients) [37]. Most commonly, these species include: *M. globosa*, *M. restricta*, *M. sympodialis*, *M. furfur*, *M. dermatitis* and *M. slooffiae* [38]. The most frequently occurring species (both in the group with AD and in the group of healthy people) is *M. sympodialis* [39, 40]. *Malassezia globosa*, *M. restricta* and *M. furfur* have been significantly more frequently isolated in AD patients than in healthy subjects [41].

It is worth noticing that *Malassezia* fungi have been significantly more frequently found in the skin lesions compared to the areas of unaltered skin of AD patients [42]. *Malassezia sympodialis* and *M. furfur* predominate in the skin lesions, whereas *M. globosa* prevailed in the seemingly unaltered skin [43, 44].

Based on the results of research carried out so far, no statistically significant relationships between colo-

nization of skin by *Malassezia* sp. and severity of the disease symptoms expressed in SCORAD scale have been found. Results of one of these showed that those yeast-like fungi were isolated from 59.8% of patients with a severe course of the disease (SCORAD > 40): *M. sympodialis* from 30.8% of patients, *M. restricta* from 25% of patients, whereas *M. globosa* was isolated from 19.2% of patients. In the group with SCORAD lower than 40, those fungi were found in 48.4% of patients (*M. sympodialis* – in 32%, *M. furfur* – in 23.3% and *M. restricta* – in 20.4%) [45].

Malassezia yeast-like fungi seem to play a role in deteriorating the disease course in patients with AD [46]. It has been particularly noticeable in adult AD patients with skin lesions located in the skin of head and neck [47, 48]. That finding has been confirmed by a noticeable increase in the number of AD patients, in whom applying anti-fungal treatment (which led to decrease in the number of *Malassezia* colonies) caused improvement of the existing skin lesions [49].

Malassezia sp. has been shown to induce allergic response. Structure of some of its antigens has been determined using molecular methods. The most frequent of them are: protein compounds with 67 kD and 37 kD molecular masses, carbohydrate component – 14 kD and allergens known as Mal f1, Mal f2, Mal f4, Mal f7 and Mal f9 [50]. The 14 kD antigen seems to occur both in *Malassezia* and *Candida albicans*, which results in cross-reactions between them [51].

Malassezia sp. antigens induce synthesis of IgE antibodies; therefore, they are connected with type 1 hypersensitivity response [52]. According to Gupta *et al.*, specific antibodies against *Malassezia* sp. are found in 20-100% of patients (40-65% of patients have antibodies directed against *M. furfur*) [42]. Presence of specific IgE immunoglobulins correlates with total levels of IgE and with a more severe course of the disease. Attention has also been drawn to the fact that the incidence of specific IgE antibodies against *Malassezia* sp. is lower in children that in adults (the highest incidence was found in adults with AD, in whom skin lesions were located mainly in the skin of head and neck – 79%). IgE-dependent allergy within the aforementioned range seems to be specific of AD patients and that observation has not been confirmed in any studies concerning patients with allergic rhinitis or bronchial asthma [53].

Atopic dermatitis patients have positive results of prick tests for *Malassezia* antigens much more frequently than healthy people [54]. The number of positive results differs with the age of patients (these are positive in 39% of patients under 10 years of age, in 64% of patients over 10 years of age and in 84% of adult patients) and location of lesions (in Swedish studies, positive results have been found in 56% of patients with atopic skin lesions located in the skin of head and neck and only in 36% of patients with no lesions on the head and neck).

Positive results of intradermal tests and patch tests for *Malassezia* antigens were also noted in a considerable percentage of AD patients. In the Swedish studies, the patch tests for Mal f1, Mal f5 and Mal f6 antigens extract were positive in 38% of patients (response to Mal f5 antigen was strongest) [55].

Simultaneously, it should be emphasized that the disrupted skin barrier in AD patients enables allergens of *Malassezia* species to contact with Langerhans cells, which causes growth of the latter and induces their production of specific cytokines. As a result, stimulation of Th2 cell response occurs [56]. Th2 cells produce IL-4, which subsequently stimulates synthesis of IgE immunoglobulin by the plasma cells. *Malassezia* sp. also exert an inflammatory effect by activating alternative complement pathways stimulating keratinocytes to produce pro-inflammatory cytokines, such as IL-6, IL-8 and TNF-α. Therefore, stimulation with *Malassezia* sp. antigen extracts results in increase in the synthesis of IL-4 and IL-6 cytokines, and decrease in IL-10 and IFN-γ synthesis. It seems to confirm the role of *Malassezia* in intensifying AD symptoms by causing and maintaining the inflammatory process in the skin [57].

Candida sp.

Candida genus consists of approximately 50 species. *C. albicans*, *C. glabrata*, *C. guilliermondii*, *C. tropicalis* and *C. dubliniensis* occur most frequently in humans [58]. Fungi of this genus colonize mainly mucous membranes of the gastrointestinal tract and vagina without causing disease symptoms [59]. However, they become pathogenic factors in some conditions (especially in immune deficiency, immunosuppression, diabetes mellitus, pregnancy, endocrine disorders, antibiotic therapy and treatment with steroids). Both non-specific immune mechanisms (skin barrier, integrity of mucous membranes, macrophages, granulocytes, system of complement, NK cells) and specific mechanisms (antibodies and cell-mediated immunity) are engaged in the defense against *Candida* [60].

It is worth emphasizing that *Candida* genus has been found significantly more frequently in AD patients than in healthy people, both within the skin (altered by the disease or apparently unaltered) and in the gastrointestinal tract [61]. *Candida albicans* has been the most commonly isolated species (70% of cases) [62].

Similarly to *Malassezia* sp., *Candida* sp. may intensify symptoms of AD [63]. Moreover, colonization of the gastrointestinal tract by these can result in constant release of allergens and be responsible for the development of chronic atopic dermatitis. Mannan, a polysaccharide, is the main *Candida* antigen that contributes to the development of AD (being also responsible for the occurrence of cross-reactions between *Candida* sp. and *Malassezia* sp.) [64]. According do Savolainen *et al.*, mannan induced synthesis of IL-2, IL-4, IL-5 and IFN-γ in

patients with atopic dermatitis. At the same time, the authors noticed that IL-4 and IL-5 levels were similar in the controls, whereas concentrations of Th1 cytokines (such as IL-2 and IFN-γ) induced by mannan were significantly higher in AD patients than in healthy subjects. Furthermore, their study demonstrated that IL-2 level correlated with the total level of IgE antibodies and level of specific IgE antibodies as well as with the level of the lymphoproliferative response [65].

To conclude, both *Malassezia* sp. yeast-like fungi and *Candida* sp. are engaged in AD pathogenesis, being factors that intensify the course of the disease. *Malassezia* fungi induce mainly Th2 immune response (significantly stimulating IL-4 synthesis), while *Candida* sp. induces Th1 response (by strongly inducing IFN-γ synthesis). Lasting exposure to *C. albicans* antigens in AD patients leads to development of immediate-type hypersensitivity with a subsequent decrease or atrophy of delayed-type hypersensitivity towards *Candida* allergens [66].

Viral infections in atopic dermatitis

Herpes simplex virus (HSV)

Patients with AD show increased susceptibility to viral infections. It is probably associated with lower levels of dendritic cells (DC), which are found in AD patients and play a crucial role in the defense against viral infections [67]. Moreover, those cells differ from dendritic cells of healthy people in expressing a greater number of receptors with a high affinity to IgE immunoglobulins (FcεRI) and a lower amount of molecules such as CD62L and CLA (cutaneous lymphocyte-associated antigen) on their surface. A large number of FcεRI receptors inhibit the ability of dendritic cells to produce IFN-α and IFN-γ. Additionally, activation of those receptors contributes to an increase in IL-10 synthesis, which results in their apoptosis [68].

Patients with AD are particularly prone to *Herpes zoster virus* (HSV) infections, which are observed in as many as 7-10% of patients [69]. The most frequently recognized complication of skin HSV infections in AD patients is eczema herpeticum (EH), which is also called eruptio varicelliformis Kaposi [70]. It is an extensive HSV skin infection, which sometimes causes complications such as conjunctivitis, corneal inflammation and may even involve internal organs (including meninges and brain), which can result in patient's death [71]. The disease can be caused both by primary or secondary HSV infection (patients with primary infection are much younger than those with the secondary type) [72]. Clinical manifestations of *Eczema herpeticum* infection are characterized by monomorphic dissemination of dome-shaped follicles, which is accompanied by fever, discomfort and lymphadenopathy. The follicles can turn into pustules in the course of the disease. The lesions dry up into eschars within approximately 2 weeks and then heal over after 2-6 weeks. The most frequent locations are the head, neck and upper trunk [73]. *Eczema herpeticum* has been observed with identical frequency in males and females, usually between the age of 20 and 29 years [74]. Early onset of AD is considered an important risk factor for its occurrence [75]. In 58% of AD and EH patients, the first lesions typical of AD occurred in the first decade of life (before the age of 5 in most cases).

According to one of the hypotheses, increased susceptibility of AD patients to HSV infections is caused by predominance of Th2 lymphocytes and deficiency of Th1 cells, which results in decreased production of antiviral peptides [76]. Th2 cytokines (due to their inhibitory effect on epidermal barrier proteins and cell-mediated immunity) are characterized by weak immune effect against various microorganisms, including viruses [77]. According to another hypothesis, local treatment with steroids could be a risk factor for EH; however, it has not been proven in clinical studies [78].

It is also worth noticing that AD patients with the history of EH are characterized by polisensitization, which is an allergy to many different allergens commonly occurring in the environment (such as pet dander, dust mite excretion, wood and weed pollens or foods). Pet dander, dust mite excretion and food allergy (which can be factors predisposing to the occurrence of EH) seem to play a particular role. Moreover, the history of AD and EH patients revealed a significantly higher risk of other atopic diseases; asthma was found in 64% [79, 80].

Positive correlation between occurrence of EH and development of other skin infections, especially caused by *S. aureus* in AD patients is also worth noticing. This finding suggests existence of a common immune response defect in AD patients, which affects both viral and bacterial infections [81].

Conclusions

Complex interactions among genetically conditioned disorders of structure and functions of epidermal barrier, defects in primary and adaptive immune response and environmental factors play an important role in the etiopathogenesis of AD. Different microorganisms, including *S. aureus*, *M. species*, *Candida species* or *Herpes simplex virus* also play a significant role. Infections are well-documented factors, which can initiate, intensify and contribute to persistence of lesions typical of atopic dermatitis, therefore should be considered in case of worsening of symptoms.

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