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ATOPIC DERMATITIS: FROM ETIOLOGY AND HISTORY TO TREATMENT

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Abstract. *Atopic dermatitis (AD) is a chronic recurrent inflammatory skin disease in patients with atopy. Atopy itself, is defined as a predisposition to develop immune response with overproduction of immunoglobulin E to low doses of allergens. AD is one of the most common skin disorders in the developed world, affecting up to 20% of children and about 3% of adults. The pathogenesis of the disease is complex, with both genetic and environmental factors playing a significant role in it. Clinically, hallmarks of atopic dermatitis include dry, itchy skin and various cutaneous efflorescence, compatible to dermatitis or eczema. Atopic dermatitis subdivides into three morphological variants manifesting during infancy, childhood and adulthood. Various environmental factors and associated diseases may have serious influence on the clinical course or may trigger disease relapses. The aim of this review article is to serve as a comprehensive overview of the etiology, pathogenesis, clinical course and diagnosis, as well as potential challenges facing the successful treatment of atopic dermatitis.*

Key words: *atopic dermatitis, history, epidemiology, pathogenesis, clinical presentation, diagnosis and differential diagnosis, treatment*

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INTRODUCTION

Atopic dermatitis (AD) is a relatively common, chronic recurrent inflammatory skin disease in patients suffering from atopy. Atopy itself, is defined as a predisposition to develop Th2 immune response and overproduction of immunoglobulin E to low doses of allergens. It manifests clinically by bronchial asthma, allergic rhinitis, conjunctivitis, and atopic dermatitis [1].

Atopic dermatitis is a disease known since Hippocrates times. In the treatise The Twelve Caesars, the Roman historian Suetonius described that Emperor Octavian Augustus had dry skin and rashes on his body, and added that he suffered from a chronic respiratory disease by passing this suffering on to his grandchildren [2]. In medical literature, atopic dermatitis was first mentioned in *"De morbis cutaneis"* by Girolamo Mercurialis, published in 1572 [2]. In 1808, Robert Willan made the detailed description of atopic eczema as the "eruption of small, grouped vesicles as a result of irritation that turns into crusts" [3]. Half a century later, in Vienna, Ferdinand von Hebra described an itchy dermatosis in children, name it *"von Hebra prurigo"* [4]. In the 1890, Erasmus Wilson mentioned in his lectures that acute eczema developed erythema and excoriation, and chronic eczema developed lichenifications and hyperkeratosis, which

he compared to psoriasis. French dermatologists Ernest Besnier and Emile Vidal describe the juvenile *"prurigo diathésique"* [5] and the chronic variant of atopic dermatitis, *"lichen simplex chronicus"*, respectively. Moreover, Besnier describes in detail the clinical picture of many forms of prurigo, the association with emphysema, asthma and allergic rhinitis and suspects a familial predisposition to the disease. Focusing on the itchy nature of the disease and its influence by various psychotic factors, Louis Brocq imposed in 1891 the term *"neurodermitis"* and later *"eczema constitutionale"*.

A significant breakthrough in understanding the etiology and pathogenesis of atopic dermatitis occurred in the twentieth century with the introduction of the term *"allergie"* by Clemens von Pirquet, and *"atopia"* by the Americans Arthur Coca and Robert Cooke [6]. The German school of dermatology continued to adhere to the terminology of "eczema" and in 1932 Heinrich Gottron launched the diagnosis of *"eczema endogens"* [7]. A few years later, Marion Sulzberger defined *"atopic dermatitis"* as a disease beginning in childhood, affecting the face and folds in individuals with a family history of atopy [8]. Bruno Wüthrich reported that the high levels of IgE observed in patients with AD are not an accidental phenomenon, but play a role in the pathogenesis of the disease, adds to the understanding of atopic dermatitis [9]. In 1980 Jon Hanifin and Georg Rajka propose a single classification of AD, including four basic and 23 minor features [10].

EPIDEMIOLOGY

Atopic dermatitis affects about 20% of children (10-12% in the United States) [11] and 1-3% (according to other data up to 10%) of adults [12]. In Germany, 23% of children, 8% of students and 2-4% of adults are diagnosed and/or treated for this disease, making it the most common chronic skin disease [13]. It occurs in all races, with a male/female ratio of 1:1,4 [12].

The initial manifestation of the disease is between the third and sixth month of birth, and in 60% of cases the disease manifests itself by the first year, and in 80-90% – by the fifth year after birth [14, 15]. Less than 20% of patients develop atopic dermatitis after puberty [16]. The majority of children and adolescents with AD enter complete clinical remission upon entering adulthood, however up to 30% continue to have lifelong relapses.

The incidence of disease is higher in economically developed countries, among the urban population and in individuals with so-called „Western type" diet, poor in fresh vegetables and fish and with excess of carbohydrates [17]. Evidence suggests that there is no relationship between obesity and asthma although such association was observed for atopic dermatitis [18]. The severity of disease is positively affected by latitude and UV irradiation and negatively correlates by annual temperature fluctuations [19]. Other environmental factors give insignificant differences, except for active and passive exposure to tobacco smoke, that are associated with a significant prevalence increment [20].

ETIOLOGY AND PATHOGENESIS

The pathogenesis of atopic dermatitis is complex, with both genetic and environmental factors playing a significant role in it. There are two hypotheses for the development of the disease. The first involves primary immune dysregulation occurring with IgE sensitization and secondary disruption of epithelial and epidermal barriers, whereas in the latter the initial disruption of epithelial and cutaneous barriers leads to secondary IgE sensitization.

Studies have discovered a three to five-fold increased risk of developing atopic dermatitis in children whose mother and father have had or are suffering from the disease [21]. This directs the search for a genetic predisposition in the development of the disease, such as a change in the function of the gene encoding the synthesis of filaggrin (FLG), located on chromosome 1q21.3 [22]. The FLG gene is responsible for the synthesis of filaggrin, a structural protein that plays an important role in maintaining the integrity of the epidermal barrier in the keratinocytes. Filaggrin performs protein packaging in the keratohyalin matrix of granular layer keratinocytes. Impaired filaggrin synthesis leads to increased trans epidermal water loss and an increased risk of environmental antigens entering the skin. About 10% of the Caucasian population is heterozygous for the FLG gene, leading to 50% lower filaggrin expression and ultimately a threefold increased risk of developing atopic dermatitis [23, 24]. Other gene polymorphisms relevant to the pathogenesis of atopic dermatitis are those of the genes encoding the IL-4, IL-4 receptor, IL-5 and IL-13 in the 5q31-33 region of the fifth chromosome [25].

The immune hypothesis defines the onset of the disease as a disorder in the immune regulation of Th cells. This results in the production of Th2 mediated cytokines, leading to increased plasma synthesis of IgE. The skin is dominated by the Th1 and Th17 immune responses involving IL-11, IL-12 and TGF-β1 mediated lymphocyte taxis to the epidermis [26]. Th2-stimulated IL-31 plays a particularly important role in the pathogenesis of pruritus in atopic dermatitis [27]. Another cytokine overex-

pressed in AD is IL-33 [28]. IL-33 stimulates various cells to produce IL-5 and IL-13, and induces IL-31, thereby promoting pruritus and scratching in AD [28]. It is expected that blocking the action of IL-31 and IL-33 will affect not only the itching but also the clinical manifestation of atopic dermatitis. In the later stages of the disease, Th17 and Th22 lymphocytes, chemokines and cytokines from keratinocytes and fibroblasts carry out tissue remodeling leading to hyperkeratosis in the epidermis and fibrosis in the dermis.

Epidermal keratinocytes also influence inflammatory processes in the skin by increasing the skin levels of proinflammatory chemokine RANTES (CCL5), eotaxin (CCL11), MCP-4 (CCL13) and TARC (CCL17) [29], and can mediate the influx of T cells and neutrophils into the epidermis producing interleukin IL-8 and IL-6 [30]. Keratinocytes synthesize thymic stromal lipoprotein (TSLP), that activates Th2 lymphocytes and affect innate immunity through the expression of Toll-like receptors on cytokines and antimicrobial peptides. Moreover, TSLP downregulates filaggrin expression in normal keratinocytes [24].

Atopic dermatitis is a disease with a chronic-recurrent course, and many environmental factors influence the relapses. Viral, bacterial and fungal infections, pollen, house dust, cigarette smoke, industrial pollutants, preservatives, food allergens, climate change can cause the onset, trigger another relapse or complicate the course of atopic dermatitis [31]. The role of food allergens in the pathogenesis of atopic dermatitis is controversial. On the other hand, UV irradiation have a beneficial effect both because of their immunosuppressive effect on the skin and because of their participation in the synthesis of vitamin D3. Others suspect that vitamin C can stimulate ceramide production in keratinocytes and improve overall epidermal barrier function in AD [32].

CLINICAL PRESENTATION AND COURSE

Clinically, hallmarks of atopic dermatitis include dry, itchy skin and various cutaneous efflorescence, compatible to dermatitis or eczema. Acute dermatitis is represented by erythematous macules, papules and plaques, subsequently small vesicles formation and oozing, erosions and excoriation. The exudate dries into crusts. Subacute dermatitis is characterized by plaques, lichenifications, excoriations and desquamation. In the chronic stage, erythema, edema and excoriations are rare, plaques are hyperpigmented and hyperkeratotic, lichenifications and rhagades predominate.

Atopic dermatitis is subdivided into three morphology variants, manifesting during different periods of the patient‘s life. In the infancy AD usually occurs by the end of the first year of life, with skin lesions affecting exclusively the face and the scalp and rarely the limbs and the body. It is characterized mainly by acute dermatitis, with erythematous macules, papules and plaques appearing on the initially dry and desquamated skin of the cheeks and scalp, subsequently transformed to small vesicles with oozing and crust-covered erosions. The nasolabial folds are usually unaffected, in opposite to seborrheic dermatitis in childhood.

In children and adolescents, the skin of the whole body is usually dry (xerosis cutis). On the chicks these patients may have whitish papules and plaques with fine scaling termed as pityriasis alba. The predilection sites of the rash are the folds (cubital, popliteal, etc.), however, the neck, wrists and the ankles are also affected. Typical cutaneous lesions are licheninfications, but in moments of exacerbation an erythematous papules, erosions and excoriations with exudation and crusts appeared. The perifollicular papules termed keratosis pilaris are frequently observed on the lateral surfaces of the forearms in some children and adolescents.

Adult type AD subdivides in localized or disseminated form. Localized variant affects district areas of face and neck, back, palms and soles, the anogenital zone and the skin around the ankles. Usually the lesions are limited, the manifestations of subacute and chronic dermatitis predominate: lichenified plaques with hyperkeratosis, fissures and scars. The face of AD patients is pale. An infraorbital line, named Dennie-Morgan fold occurres in about 25-70% of patients [10, 33] (Figure 1). When scratched, a white instead of red dermographism on skin appears. Other specific manifestations of atopic dermatitis are: atopic cheilitis, involvement of the ear lobules and periareolar dermatitis (Figure 2). On the limbs, around the ankles, pigmented lichenified or hyperkeratotic plaques termed lichen simplex chronicus are observed (Figure 3). The dryness of skin on the extremities might be pronounced, with the appearance of hyperpigmented hyperkeratotic lamellae, resembling the fish scales and termed as ichthyosis. In case of extended emotional stress or other irritating conditions, flashes appear on the face and neck and cutaneous lesions disseminate. The tendency to exacerbate atopic dermatitis under the influence of stressors is the basis of the archaic term „neurodermitis“. The severe irritation can provoke the generalization of the skin rash up to atopic erythroderma (Figure 4) [34].

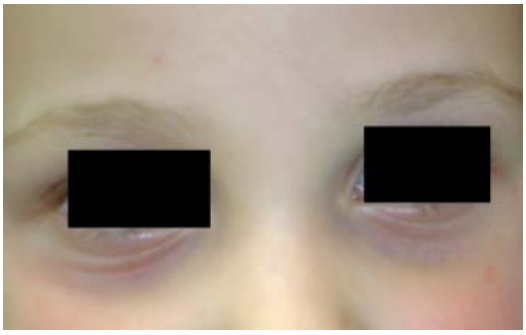

Fig. 1. Dennie-Morgan infraorbital fold in a 3-years-old boy with atopic dermatitis

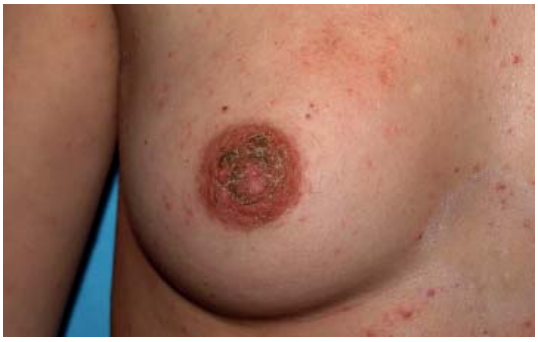

Fig. 2. Periareolar dermatitis in 23-years-old women with atopic dermatitis and pompholyx

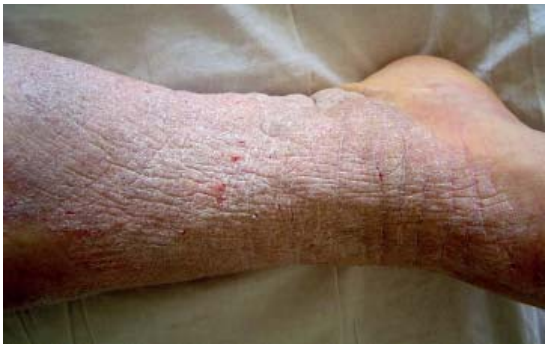

Fig. 3. Lichen simplex chronicus

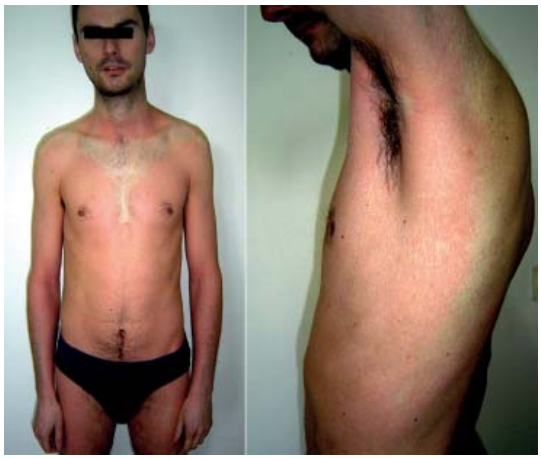

Fig. 4. Atopic erythroderma in a 21-years-old patient

At the same time, itching in varying degrees of manifestation is characteristic of all age variants of atopic dermatitis. It is triggered or intensified by sweating, contact with wool, stress or certain foods.

In about 30% of patients, AD is associated with allergic rhinitis, bronchitis or asthma and these associations are termed as an atopic triad or atopic march [35]. Sometimes the sequence of occurrence of the three conditions is reverce and asthma patients subsequently develop atopic dermatitis. Various food allergens can provoke an exacerbation of atopic dermatitis. The frequency of association with urticaria and anaphylaxis is increased. Keratoconjunctivitis, keratoconus and cataracts are more common in people with atopy. Other concomitant conditions are attention deficit, emotional disorders, insomnia, headaches and epilepsy [36].

Superimposed infection with bacteria, viruses and fungi worsens the course of atopic dermatitis and can trigger new relapses. The skin of AD patients is colonized by *Staph. aureus* in about 90% of patients, with the increased number of bacteria on the skin corresponding to the severity of the clinical manifestation of the disease [37]. Atopic dermatitis is found to be associated with increased risks of S. pyogenes infections, that may require active local or systemic antibiotic treatment [38].

The superinfection with *herpes simplex virus* in AD patients, may cause herpetic eczema, occurring clinically with the typical herpetiform-grouped vesicles, pustules, erosions or crusts on dermatitis plaques [39]. The cutaneous lesions are most often located on the face, scalp and chest, the ocular involvement is rare and addition of active antiviral therapy is necessary for effective treatment [40].

Atopic dermatitis is associated with a number of genodermatoses clinically manifested with dry skin. Wiskott-Aldrich syndrome is an X-linked, recessive disease resulting from a mutation in the WASP gene. It manifests with immune deficiency, susceptibility to autoimmune diseases, thrombocytopenia and atopic dermatitis [41]. Hyper IgE or Job syndrome is an autosomal dominant congenital disease caused by mutation in the STAT3 gene, that clinically represents with severe recurrent pyoderma, frequent bronchitis and pneumonias, high levels of serum IgE and atopic dermatitis [42]. Netherton syndrome is an autosomal recessive genodermatosis due to a mutation in the SPINK5 gene, that manifests with ichthyosis linearis circumflexa, trichorrhexis invaginata (hairless hair) and AD [43]. Down syndrome is associated with an increased incidence of cutaneous manifestations such as atopic dermatitis [44].

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Since 1980s the classification of Hanifin and Rajka [10] is used to diagnose atopic dermatitis. At least 3 of the main and 3 of the secondary criteria are required. Another, newer and simpler is the classification of the American Academy of Dermatology [45] (Table 1).

The SCORAD index is used to objectify the severity of symptoms and determine the area of involvement in atopic dermatitis [46]. The main criteria are erythema, edema, exudation, excoriation, lichenification, dryness of the skin, which are counted in 4 degrees (0-3) and adds the affected area in different anatomical areas according to the rule of the nines. Another scale for determining the severity of atopic dermatitis is the Eczema Area and Severity Index (EASI) [47]. A visual rating scale is used to determine the severity of the itching, and software has been developed to assess the severity and duration of the itching. The SCORAD and EASI indices and the VAS scale have been used in comparative studies of the severity or effect of treatment in patients with atopic dermatitis.

The diagnosis is confirmed by skin biopsy for active lesions, which shows parakeratosis, intercellular edema (spongiosis) in the epidermis and perivascular lymphocytic infiltrate in the dermis compatible with histology of acute dermatitis. In chronic dermatitis, hyperkeratosis, acanthosis and diffuse lymphocytic dermal inflammatory infiltrate are found.

There are no specific biochemical markers for diagnosing atopic dermatitis. Over 80% of patients have high serum IgE levels, however, they do not always correlate with the severity of atopic dermatitis, and are observed in clinically healthy population [48]. Serum levels of CD30, IL-12, IL-16, IL-31 are currently considered as potential laboratory markers for the severity of atopic dermatitis, without currently having a definite diagnostic value [1,9,49]. The noninvasive

Table 1. Criteria for atopic dermatitis

<table>
<tr><th colspan="2">Hanifin and Rajka 1980 [10]</th><th colspan="2">American Academy of Dermatology 2004 [45]</th></tr>
<tr><td>Basic features</td><td>1. Pruritus;
2. Typical morphology and distribution:
● Flexural lichenification or linearity in adult;
● Facial and extensor involvement in infants and children;
3. Chronic or chronic-relapsing dermatitis;
4. Personal and family history of atopy (asthma, allergic rhinitis, atopic dermatitis);
(Must have 3 or more basic criteria)</td><td>Essential features</td><td>1. Pruritus and eczema (acute, subacute, or chronic);
2. Typical morphology and age-specific patterns;
3. Chronic or relapsing history;</td></tr>
<tr><td rowspan="2">Minor features</td><td rowspan="2">1. Xerosis;
2. Ichthyosis/palmar hyperlinearity /keratosis pilaris;
3. Immediate (type I) skin test reactivity;
4. Elevated serum IgE level;
5. Early age of onset;
6. Tendency toward cutaneous infections, due to impaired cell mediated immunity;
7. Tendency toward hand and foot dermatitis;
8. Nipple eczema;
9. Cheilitis;
10. Recurrent conjunctivitis;
11. Dannie-Morgan infraorbital fold;
12. Keratoconus;
13. Anterior subcapsular cataracts;
14. Periorbital pigmentation;
15. Facial pallor/facial erythema;
16. Pityriasis alba;
17. Anterior neck folds
18. Itching when sweating;
19. Intolerance to wool textiles and lipid solvents;
20. Perifollicular accentuation;
21. Food intolerance
22. Course influence by environmental/ emotional factors;
23. White dermographism
(Must have 3 or more minor criteria)</td><td>Important features</td><td>1. Early age of onset;
2. Atopy;
3. Personal and/or family history;
4. IgE reactivity;
5. Xerosis;</td></tr>
<tr><td>Associated features</td><td>1. Atypical vascular responses
2. Keratosis pilaris/pityriasis alba/hyperlinear palms/ichthyosis ocular/periorbital changes
3. Other regional findings (eg, perioral changes/periauricular lesions)
4. Perifollicular accentuation/lichenification/prurigo lesions</td></tr>
</table>

assessment of skin barrier functions and micro-morphology may help in future to better understand skin changes in atopic dermatitis [50].

The differential diagnosis includes a number of diseases as: contact dermatitis (allergic or irritative), nummular dermatitis, seborrheic dermatitis, psoriasis, insects bite dermatitis, cutaneous T-cell lymphoma, scabies, impetigo, tinea corporis, ichthyosis, etc. The diagnosis should be made carefully, as some diseases have overlapping clinical manifestations, but a different prognosis, while in others inaccurate treatment can lead to severe complications.

TREATMENT

Treatment of atopic dermatitis is usually long-term, and it is recommended to take into account the patient‘s age and the clinical severity of the disease [51]. Measures have to be adapted individually to the patient, taking in account also the subjective factors as pruritus as well as quality of life.

Local therapy

The main treatment of atopic dermatitis is aimed at improving the barrier function of the skin, impaired at birth or by the inflammatory process. It is important to select suitable emollients – cremes and ointments for dry skin, emulsions and milks for the face and folds, as well as in the exudation phase. Attention should be paid to the hygiene regime, as powerful detergents can dry and irritate the skin in patients with atopic dermatitis. It is recommended that the emollients prescribed by the doctor do not contain common contact allergens. The inclusion of urea in emollients enhances their hydrating effect, but in infants can irritate the skin [52].

Topical corticosteroids are the oldest modern medications of treating atopic dermatitis with repeatedly proven high therapeutic efficacy [52]. They are the drug of choice and are often monotherapy in patients with mild forms of the disease, and the benefit/risk balance must be taken into account. They are applied once or twice a day on skin lesions, and more frequent application and long courses are not recommended. In young children and in the areas of the face, folds and genitals, weakly and moderately potent corticosteroids are recommended, while in adults and on the limbs, palms and soles - powerful steroid ointments, if necessary, under occlusion. Potent corticosteroids are not suitable for treating children, for a long time and over a large area, due to the risk of systemic reactions and suppression of the hypothalamic-pituitary-adrenal axis. The choice of a topical corticosteroid preparation requires an individual approach, as one preparation may be ineffective in a particular patient, or the active substance or vehicle may cause allergic skin reactions.

Topical calcineurin inhibitors (CI), tacrolimus or pimecrolimus, have been introduced into clinical practice 25 years ago, and their main therapeutic indication is atopic dermatitis [52]. CI have a steroid-like anti-inflammatory effect, regardless of the different pathogenetic mechanism. They are recommended as a means of choice in case of failure of treatment with topical corticosteroids, as well as in the areas of the face, folds, genitals, where long-term treatment with corticosteroid creams is contraindicated. Another indication is long-term proactive treatment and control of lesions in atopic dermatitis. In terms of efficacy, calcineurin inhibitors have a similar effect to topical corticosteroids with a comparable safety profile [52]. It should be borne in mind that calcineurin inhibitors are not indicated for children under two years of age. On the other hand, the increased risk of malignancies described in the product characteristics has not been confirmed by numerous clinical trials [52].

The impaired barrier function of the skin determines the high degree of colonization with *Staphylococcus spp.* in atopic dermatitis. It is believed that in the absence of an acute inflammatory reaction from a topical corticosteroid, secondary impetiginization of the lesions should be considered and the addition of an antiseptic or antibiotic is necessary [51]. On the other hand, long-term use of a topical antibiotic is not recommended as long as it can cause selection of resistant microbiom on the skin. In lesions of the neck, neck and shoulders, a superimposed infection with *Malassezia spp.* may occur, requiring topical antifungal treatment [53].

Phototherapy

Modern phototherapy has been practiced since the 1970s and includes broad-spectrum ultraviolet B rays (BB-UVB), narrow bend (NB) UVB, narrow-spectrum UVA1 and psoralen and UVA (PUVA) therapy [54]. Phototherapy is recommended in combination with topical therapy in mild, moderate and severe forms of AD [55]. In the acute phase high doses of UVA1 or PUVA phototherapy are beneficial, while in the subacute and chronic disease all UVB, NB UVB and UVA1 are recommended [54-56]. NB-UVB is consider to be safe and effective for a number of AD in children and is often considered as a first line agent because of its ease of administration and safety profile relative to PUVA [56, 57].

Phototherapy is not recommended in combination with systemic therapy with cyclosporine and azathioprine and PUVA is unsafe for children under 12 years

of age [56]. As a late side effect, the increased risk of skin malignancies should be considered, especially in PUVA therapy [57].

Systemic therapy

Systemic corticosteroids are indicated in moderate to severe atopic dermatitis, in case of ineffective topical treatment. Short courses and a gradually decreasing dose to suppress exacerbations are recommended. High doses and prolonged courses of treatment increase the risk of severe side effects. In therapeutically resistant cases immunosuppressors can be added.

Cyclosporine is the drug of choice in the treatment of severe atopic dermatitis in adults, with a proven high therapeutic effect. It was introduced into clinical practice in 1997, and its efficacy and safety have been well studied. Courses are conducted with a dose of 2.5 mg/kg/24 hours, lasting 4-6 months. It is not recommended to combine cyclosporine with phototherapy due to the increased risk of malignant skin tumors and vaccination with live vaccines [58].

Azathioprine is an alternative to systemic corticosteroid treatment and cyclosporine therapy in patients with severe, therapeutically resistant atopic dermatitis. The therapeutic dose is 1-3 mg/kg/24 hours [59]. In a study, after 12 weeks, the azathioprine treated AD patients reported about 40% improvement, compared with 20% improvement in the placebo group [60]. It is contraindicated in AD treated with phototherapy, and patients have to be photo-protected.

Other immunosuppressants with proven efficacy in severe atopic dermatitis are mycophenolate mofetil and methotrexate. Methotrexate is recommended as a systemic agent for the treatment of refractory disease in adult AD patients, since there are almost no prospective data on its use in children for the treatment of atopic dermatitis [61]. Mycophenolate mofetil blocks the purine biosynthesis pathway of cells. It is an alternative therapy for refractory atopic dermatitis; however, its efficacy is inconsistent [57], and long duration of treatment is associated with increased risk of herpes infections [62].

Immunotherapy is an alternative in therapy resistant moderate to severe atopic dermatitis. High doses of intravenous immunoglobulins (IVIG) are highly effective in up to 90% of children with severe atopic dermatitis with elevated serum IgE, while in adults the results are less promising [63]. There have been isolated reports of successful treatment of severe atopic dermatitis with various biological agents: rituximab [64], ustekinumab [65], alefacept [66] and others. Anti-IgE humanized monoclonal antibody omalizumab is licensed for the treatment of severe asthma and urticaria. It is safe and well-tolerated, but shows week effectiveness in the treatment of atopic dermatitis comparing with alternatives [67].

The most promising results among biological therapies were achieved with dupilumab, a monoclonal antibody against IL-4 receptor-α, which is currently the only biological product registered for therapy of atopic dermatitis [68]. For 16 weeks treatment, dupilumab significantly improves the symptoms of severe AD, including pruritus, and the quality of life, as compared with placebo [68,69].

As symptomatic and adjuvant systemic therapy for atopic dermatitis, antihistamines are used to control itching, antibiotics – for superimposed bacterial infection, antifungals – for mycoses and antiviral drugs for herpetic superinfection [57]. Montelukast, cysteinyl leukotriene receptor antagonist, was found as an effective therapeutic option for moderate-to-severe atopic dermatitis treatment [70]. Alitretinoin is indicated in adult patients with chronic dermatitis of the palms and soles and lichen simplex chronicus [71]. Probiotics and prebiotics containing cultures of *Lactobacilus* and *Bifidobacterium spp.* applied in the prenatal period and during lactation show a certain protective effect of the development of atopic dermatitis in newborns and children [72].

Climatotherapy

The Bulgarian dermatologists are among the pioneers in climatotherapy. In 1962 Peter Popchristov organized the first international symposium on high mountain climatotherapy in Bulgaria [73]. For the treatment of patients with atopic dermatitis and urticaria, a high-altitude camp was built in the „Yellow lake" area of Rila mountain, which lasted until the mid-1990s [74]. Total of 2246 patients with atopic dermatitis were treated between 1967 and 1987. Seventy-seven percent of them showed various degrees of improvement and 22% were discharged healthy after climatotherapy [75]. Similar results have been obtained for chronic urticaria. Subsequently, groups of patients with atopic dermatitis were treated at the base near Belmeken, Rila mountain. It is believed that in order to be effective, the treatment should be carried out at an altitude above 1500 m, where the number of allergens is relatively small.

CONCLUSION

Atopic dermatitis is a chronic systemic disease that requires a strategy and a systematic approach to treatment. In the first place, it is important to avoid atopic triggers. This requires training of patients, career guidance and sometimes a change in their

lifestyle and work activity. Stress factors, industrial pollution, frequent and large temperature changes in the environment carry an increased risk of recurrence and must be taken into account when choosing a profession and workplace.

The second important measure is the everyday skin care aimed at restoring damaged skin barrier functions. Daily hydration and maintenance of the water-lipid skin barrier should be included in the daily hygiene regime, and if necessary, adequate drug therapy should be included.

Third, control of inflammatory reactions and skin infections is needed. Patients should be actively monitored by the physician, both in terms of clinical manifestations and paraclinical studies. Potential infections complications should be appropriately treated with the least potent and safe treatment method that achieves a therapeutic effect. An individual approach and personal assessment should be applied when choosing a therapeutic agent and duration of treatment. Proactive and intermittent therapies can reduce the risk of frequent and severe relapses.

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