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Review
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ATOPIC DERMATITIS

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Summary

Variable terminology used for atopic dermatitis, definition of this chronic inflammatory disease with hereditary component characterized by severe itch, typical clinical picture, and quite common association with other atopic diseases such as asthma and/or rhinitis are presented. The prevalence of this atopic disease is on a constant increase, now ranging from 0.6% and 20.5%. The course of the disease is relapsing with remissions of variable length. Remission is observed after the second or fifth year of life in one third of patients. About 40% of children with atopic dermatitis develop bronchial asthma later in life. It is considered to be caused by exposure to pollen, minor sources of infection, pets, older maternal age and numerous food allergens. Environmental factors and microbial agents (bacteria, fungi, *Malassezia furfur*, dermatophytes, viruses, etc.), psychosomatic factors, clinical picture in different age groups, other associated dermatoses, diagnostic and therapeutic procedures are described in detail.

Keywords: atopic eczema; neurodermatitis constitutionalis; Besnier's prurigo; atopic dermatitis

SYNONYMS

The various names such as atopic dermatitis (AD); atopic eczema, endogenous eczema, dermatitis atopica, neurodermitis constitutionalis, intrinsic allergic dermatitis, eczema flexurarum, Besnier's prurigo, diathetic prurigo, asthma-eczema, hay fever-eczema.

DEFINITION

AD is a chronic inflammatory skin disease due to genetic predisposition, characterized by pruritus, typical age-specific clinical picture, and frequently associated with

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other atopic diseases such as asthma and/or allergic rhinitis. The prevalence of AD is rather high, mostly involving children.

Table 1. Diagnostic features of atopic dermatitis according to Hanifin and Rajka (ref. 8)

MAJOR FEATURES (must have 3 or more)

Pruritus

Typical morphology and distribution of skin lesions

- flexural lichenification and linearity in adults
- facial and extensor involvement in infants and young children

Chronic or chronically relapsing dermatitis

Personal or family history of atopy (asthma, allergic rhinoconjunctivitis, atopic dermatitis)

MINOR FEATURES (plus must have 3 or more)

Xerosis

Ichthyosis/palmar hyperlinearity/keratosis pilaris

Immediate (type I) skin test reactivity

Elevated total serum IgE

Early age of onset

Susceptibility to repeated cutaneous infection (especially *Staphylococcus aureus* and Herpes simplex and other viral infections, warts, molluscum, dermatophytes)/impaired cell-mediated immunity

Tendency toward nonspecific hand and/or foot dermatitis

Nipple eczema

Cheilitis

Recurrent conjunctivitis

Dennie-Morgan infraorbital fold

Keratoconus

Anterior subcapsular cataract

Orbital darkening

Facial pallor/erythema

Pityriasis alba

Anterior neck folds

Pruritus when sweating

Intolerance to wool and lipid solvents

Perifollicular accentuation

Food intolerance

Course influenced by environment/emotional factors

White dermographism/delayed blanch

HISTORIC ASPECTS

Atopy was adopted from the Greek word *atopos*, meaning “strange” or “unusual”. This disorder was probably first described by Robert Willan in 1808, as a prurigo-like



condition. In 1844. Hebra noted the flexural distribution of the rash, which was postulated to precede pruritus. In 1923 Coca and Cooke introduced term "atopy" to designate phenomena of hypersensitivity in human. In the 1930's Wise and Sulzberg first proposed the term "atopic dermatitis". They discussed in the 1933 *Year Book of Dermatology and Syphiology* the conditions of eczema, neurodermatitis, lichenification, and "prurigo diathésiques" described by French dermatologist Besnier and Brocq. In the follow-up studies, by Schwartz and Schnyder, first seen with infantile eczema, supported close association of bronchial asthma, hay fever, perennial rhinitis, atopic dermatitis, and some forms of food allergies with classic atopic disease. In the 1960s Ishizaka and Johanson identified a new class of immunoglobulins, the IgE antibodies, as carrier of reaginic activity, raised in atopic individuals. In the 1980's Hanifin and Rajka proposed a list of characteristic features (criteria) of AD (table 1).

EPIDEMIOLOGY

There is great worldwide variation in the prevalence of AD, ranging from 0.6 to 20.5%.

The accumulative incidence of AD before the age of 7 years has increased dramatically in recent years and the prevalence rates of AD range from 10-12% with a insignificantly greater prevalence in females compared to males (ratio 1:4). Epidemiological studies in school children show the prevalence of AD to be 15%-17%. In the last decade, the number of AD patients in Europe has been on an increase, yielding a prevalence of 20%. In 80% of patients, the onset of disease occurs before 1 year of age, and in only 2% after age 20. The course of the disease is characterized by exacerbations and remissions that cannot be etiologically explained. Complete remission has been estimated to occur in one third of patients after 2 years of age, and in another one third after 5 years of age. However, many patients with infantile AD or juvenile AD experience discomforts up to their adult age. About 40% of AD children develop bronchial asthma later in life. There are probably several reasons for the increased incidence of AD, including higher exposure to air pollution, smaller families with less exposure to infections, more pets, higher maternal age, and a wider range of foods.

Genetic aspects of atopy and atopic dermatitis

There is clearly also an important hereditary component of atopic eczema. Atopy is a condition caused by multiple gene defects. Thirty genes responsible for expression of AD have been demonstrated. Several chromosomal regions contain pathophysiologically relevant candidate genes, especially on chromosome 5q31-33. A defect on chromosome 5q31-33 in the β_2 -adrenergic gene region was found in AD patients suffering from asthma. Several studies have found the linkage of serum IgE levels to an extended region



on chromosome 5q encoding for IL-3, IL-4, IL-5, IL-13, and granulocyte-macrophage colony-stimulating factor (GM-CSF). There is genotypic association between the T allele of 590C/T polymorphism of the interleukin 4 gene promoter region with atopic dermatitis. This suggests that it might affect atopic dermatitis predisposition. AD has been linked to markers at chromosome 11q13, including the gene encoding for β chain of the high affinity receptor for IgE. Variants of interleukin 13 coding region, a gain-of-function polymorphism in the α subunit of the interleukin 4 receptor (16q12), and a functional mutation in the promoter region of RANTES (17q11) have a role in expression of atopic dermatitis. A gene for mast cell chymase, a key element in atopic or allergic inflammation of the skin, resides with the region on chromosome 14q11 which is thought to be specifically linked to AD.

Hanifin's group demonstrated a cyclic adenosine monophosphate (cAMP) defect with a marked increase of cAMP-phosphodiesterase in leukocytes of AD patients. Mutations of $\hat{\alpha}_2$ -adrenergic receptors and their reduced number on lymphocytes and keratinocytes, and impaired function of $\hat{\alpha}_2$ -adrenergic receptors with L-phenylalanine have been identified.

Although many genes are involved in the development of allergic diseases, particular interest is in: 1q21, 3q21 (candidate genes CD86, CD 80), 5q23-31 (asthma, atopy, total IgE), 17q-25, 20p. When both parents have the same atopic disease, their child is at a 70% risk to develop the disease. The prevalence of AD in children is 56% when only one parent has AD. When parents have different atopic diseases (different phenotypes, for example: one parent has AD and other respiratory allergy), the probability for their child to develop the disease is around 30%.

PATHOGENESIS

Atopic constitution is more frequently transmitted by maternal inheritance. Various environmental factors influence clinical expression of AD, e.g., allergens, irritants, climatic and geographical conditions, body structure, psychological stress, secondary infections, etc. AD is frequently associated with immunodeficiency (selective IgA and IgM). Numerous factors are implicated in the onset of the disease. Hyperimmunoglobulinemia E is characteristic of atopic diseases, however, AD is also a consequence of immune response type IV. The cells infiltrating the skin are predominated by CD4+ Th2 cells that produce IL-4/IL-10/IL-13 and enable differentiation of B-lymphocytes and production of IgE. It has been demonstrated that Langerhans cells (LS), dendritic cells of dermis, and peripheral blood monocytes of atopic patients can bind monomeric IgE via high-affinity IgE receptors ($F_{ca}RI$), representing allergen binding molecules on antigen presenting cells. In the same way, they translate and present the allergen to T lympho-



cytes. Mastocytes also play a major role in the genesis of AD, via allergen stimulation of the secretion of mediators (histamine, prostaglandin and cytokines including interleukins IL-3, IL-4, IL-5, IL-6, and TNF- α). Thus, the function of suppressor lymphocytes (CD8) is impaired due to the underlying gene defect. In atopic individuals, T lymphocytes are mostly of Th2 type, secrete more IL-4 and IL-5, and induce IgE synthesis, IgE hyperproduction, and eosinophilia. There is a significant coordination between AD disease activity and skin eosinophilic cationic protein (ECP) deposition. AD patients have impaired metabolism of fatty acids, i.e. decreased levels of gamma-linolenic acid (GLA) and digamma-linolenic acid (DGLA). Borage (*Borago officinalis*) is a natural source of GLA, containing 24% of this acid. Inhalation allergens have a substantial role in AD. Aeroallergens penetrate the epidermis and bind to IgE expressed on Langerhans cells (LCs) *via* F ϵ ₁ receptors (e.g., dermatophagoides). The pathogenesis of AD has not yet been fully clarified. The CD4+ T lymphocytes are most frequently found in the skin of AD patients. Inhalation allergens can trigger cellular response in atopic skin predominated by Th2 cells. A decreased interferon gamma (IFN- γ) secretion from activated lymphocytes and an increased interleukin 4 (IL-4) secretion are found in AD patients. Elevated level of IgE, eosinophilia, activated macrophages with an increased secretion of the granulocyte-macrophage colony-stimulating factor (GM-CSF), prostaglandin E2 (PGE2), interleukin 10 (IL-10), IL-4 and IL-5 (by Th2 cells), decreased secretion of IFN- γ (by Th1), and enhanced spontaneous basophile release of histamine have been demonstrated in atopic skin. A correlation of elevated eosinophilic protein (ECP), soluble E-selectin with eosinophilia has been reported.

The Role of Trigger in the Expression and Exacerbation of Atopic Dermatitis

Besides genetic there are other factors such as the environmental influence which consists of the climate itself, air pollution, airborne allergens (plant, animal allergens) and psychological and emotional factors which play an important role in the course of the disease.

Environmental factors

The importance of environmental factors in the development of AD has been increasing. The majority (40-65%) of AD patients experience deterioration in the winter, probably due to decreased humidity of the air outdoors (due to cold), as well as indoors due to the heating. The climate itself may influence dermo-epidermal barrier by humidity, temperature of the air and ultraviolet radiation. The aggravation by sun exposure is probably due to a non-specific intolerance of heat caused by impaired function of sweating in affected skin and induction of itch by sweating. It also differentiates the animal and plant characteristics of various geographical regions, forming specific allergenic condition. Outdoor pollution seems to be one of the major causes of the dramatic in-



crease of atopy in recent years. Chemical compounds and exhaust particles are released into the air and may have indirect effects on the allergic sensitization by favoring IgE sensitization and development of allergic disease. It has been observed that diesel exhaust particles, but not gaseous elements enhance allergy to birch pollen and nitrogen oxide and ozone have been shown to effect mucous membranes and their protective effects against penetration of allergens into the body.

Irritants

Irritants, such as soaps, detergents, disinfectants and prolonged exposure to water have and excitatory effect on the impaired barrier layer of atopic's skin. Daily washing with soap and water or noxious agent may elicit an irritant contact reaction in atopic individuals. Saliva frequently induces perioral eczema. Contact with wool is common trigger of irritant contact dermatitis in AD. Other textiles especially synthetics or dyed fabrics, are sometimes incriminated. Tobacco smoke is also potent irritator of atopic skin.

Alimentary allergens

Controlled studies have shown that nutritive allergens may lead to exacerbation of skin lesions in some AD patients. Nutritive allergens are primarily important in children. The most common allergens in children are egg-white, cow's milk, peanuts, soya, shellfish and flour. The prevalence of food allergy in AD varies widely according to different studies from 25-60%. There are also non-specific irritant reactions predominantly to acid fruit (citrus fruit, tomatoes) and salty or spicy items. Aggravation of eczema may also be provoked by food additives. The term contact urticaria syndrome (CUS) was introduced in 1975, and denotes the occurrence of urticaria and erythema as a reaction to food substances absorbed through intact skin. The IgE mediated nutritive CUS plays a significant role in AD patients. Therefore, the skin application food test (SAFT) has been developed for use in the diagnosis of this syndrome. The test has proved useful in the diagnosis of food hypersensitivity in small children with AD. However, the test sensitivity declines after the age of 4 years.

Aeroalegens

Among airborne allergens the most important are grass, weeds and tree pollen allergens, animal epidermis and dander allergens, house dust mites. Airborne allergy in AD varies widely according to different studies from 50-90%. It seems that airborne allergy is mainly IgE-mediated, and the skin lesions may be provoked by direct contact of aeroallergens with atopic skin, involving the immediate and delayed type of allergic reaction. Epicutaneous application of aeroallergens (e.g. house dust mites, weeds, animal dander, and moulds) by atopy patch test on unaffected atopic skin elicits eczematous reaction in 30-50% of the patients with atopic dermatitis.



Microbiological factors

1. Bacterial

Staphylococcus aureus

Great attention has been paid to skin colonization and infection with *Staphylococcus (S.) aureus*. This bacterium can be isolated in nostrils and intertriginous regions in 5%-15% of normal individuals, but is found in 64-100% of skin lesions in AD patients. Although the majority of patients with AD are colonized by *S. aureus*, its presence does not necessarily indicate that it acts as a pathogen. Antibiotic treatment is indicated only when there is evidence of overt clinical infection or superantigen effect is suspected. It influences the course of the disease via different mechanisms: exotoxins, enzymes, superantigen and protein A.

Impetiginization is characterized by honey-colored crusts, extensive oozing, folliculitis and pyodermal lesions indicate bacterial infection. The bacterium produces a number of toxins (enterotoxin A and B, toxic shock syndrome toxin 1), known as superantigens that activate T cells and macrophages. Children with AD develop a significantly higher proliferative response to *S. aureus* itself and its toxins, enterotoxin B in particular, as well as to the decreased production of IFN- γ and increased production of IL-4. Bacterial toxins act as superantigens aligned along MHC II and can directly stimulate massive T cell proliferation. This discovery has entailed introduction of antistaphylococcal antibiotics.

Other bacteria

Other bacteria, such as streptococcal species, may be important, but little clinical or investigative information exists to document their role

2. Fungal infections

a. *Candida albicans*

It is the most common yeast. There are no reports of increased or more severe *C. albicans* infection in AD patients. However, positive prick tests with *C. albicans* occur more frequently in patients with AD than in healthy individuals.

b. *Malassezia furfur (Pityrosporum ovale)*

M. furfur yeasts may be a trigger factor for AD. This organism may produce positive skin prick reactions in a higher rate (49%) in patients with AD of the head, scalp and neck region. It can be also detected in the serum (specific immunoglobulin E to *P. ovale*), and could provoke positive patch-test reaction. *M. furfur* can induce an eczematous reaction in sensitized AD patients and may trigger factor for AD.



c. Dermatophytes

Dermatophytes (eg. *Trichophyton*) are suspected of occurring more frequently in atopic patients.

Viruses

Patient with AD have a minor deficiency problem in defending against viruses. However, some viral skin infections can have dramatic course. Kaposi's herpetiform and varicelliform eruptions are caused by spread of *herpes and varicella* viruses. Epstein-Barr virus, parainfluenza virus, respiratory syncytial virus and cytomegalovirus infections have been reported to trigger exacerbation of AD.

Psychosomatic factors

Atopic patients often respond to stress, frustration, embarrassment, or other upsetting events with increased pruritus and scratching. Between 22-80% of patients or their parents report worsening of the skin condition due to emotional tension, nervousness of conflicts in the family, mostly via induction of itch. Children with AD have been shown to be more susceptible to stress-induced skin eruptions because of a hyporesponsive hypothalamus-pituitary-adrenal axis, which blunts the body's natural ability to produce cortisol and suppress inflammation in response to stress. The presence of AD causes anxiety and depression. Evidence that mood disturbances increase and decrease as result of fluctuation of disease severity can be found in studies demonstrating that mood symptoms correlate with AD symptoms and decrease following successful AD treatment. When the higher cortical centers are activated by stress, there is an increased secretion of substance P from adrenal glands. They serve as brain peptides that are easily released by psychosocial stress, triggering or exacerbating itching, especially in patients with AD.

Hormones

One third of young female patients reported premenstrual flare-ups of their AD. Pregnancy also was noted to have an adverse effect on 52% of pregnant patients with AD during first and second trimester, but improvement was noted in the third trimester. Hormonal analyses showed a significant reduction in serum cortisol levels compared with nonpregnant women.

CLINICAL FEATURES

Atopic dermatitis is a multifaceted disease. The clinical picture, morphology and distribution of the skin lesion, varies greatly depending on the age of patient, the ethnic group he or she belongs to, the course and duration of the disease, aggravating factors



and possible complications such as superinfection. Its manifestations ranges from very mild to severe disease.

There are three classical stages of disease-infantile, childhood, and adulthood-each of which may show acute, subacute and/or chronic skin reaction. Acute lesions are characterized by intensely pruritic, erythematous papules and vesicles over erythematous skin, erosions and serous exudate. Subacute lesions form erythematous, excoriated scaly papules, whereas chronic lesions show skin thickening with pronounced skin markings (lichenification) and nodular papules. All three stages of skin lesions may frequently be present in the same patient.

Infantile phase

In more than half of AD patients, the disease begins during infancy, and in 90% of patients the onset is before 5 years. Problems with the skin usually start around the second month.

In infancy, the characteristic lesions consist of symmetrical, dry, erythematous, scaly plaques with follicular papules on the face, mostly involving the cheeks and forehead, scalp but not the perioral region. When child starts to crawl the lesions extend to upper trunk, extensory aspect of upper and lower extremities, and dorsal aspects of the hands and feet. Diaper region is usually spared due to the moisture retention of nappies. However, diaper region may be involved by contact irritant dermatitis.

Childhood phase

As children begin to move around, the eczema becomes more localised and thickened, during the second and third year of life, the clinical picture is being modified, showing characteristic papules and plaques localized primarily in large joint flexures, especially on the neck, elbows, wrists, knees and ankles. The disease may disappear at age 2 or 3 years, however, other atopic diseases and relapses may develop. Later in childhood and adolescence, lesions involving flexural areas persist, including eyelids, hands and feet, where pustules are frequently observed. Many children develop "nummular" pattern of AD. This refers to small coin-like areas of eczema scattered over the body. The appearance of these eczematous lesions may be altered in any stage of disease due to pruritus and scratching. Then, excoriations and lichenification with hyperpigmentation and hypopigmentation are seen. Mostly, AD improves during school years and it may completely clear up by the teens, although the barrier function of the skin is never entirely normal.

Adult phase

In adults, the disease is characterized by lichenification, chronic course, thickened areas in flexures, on the neck and eyelids, with chronic facial edema (Fig. 1, 2). Some

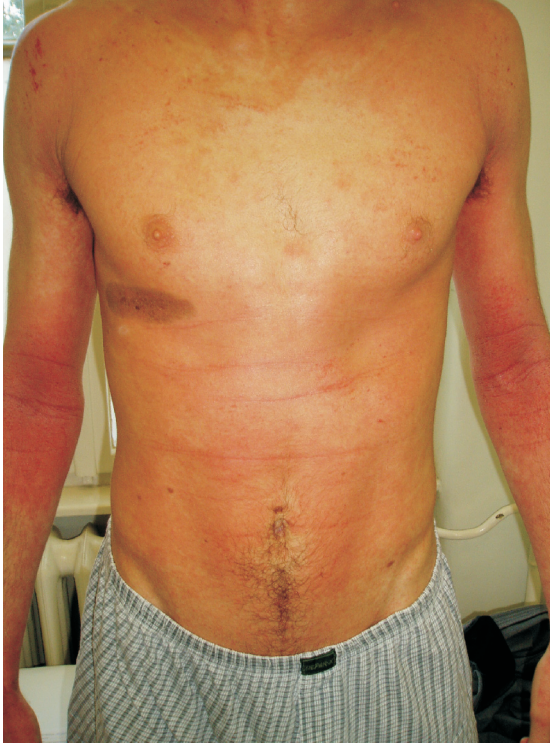


Figure 1. Adult phase, distribution



Figure 2. Erythematous facial skin, with scaliness, particularly periorcular region in adult patient.

adults have prominent head and neck distribution and they manifest severe periocular and eyelid involvement (Fig. 2). Other adults show more extremity-based disease. AD is major contributing factor to occupational irritant or allergic contact dermatitis. This often affects hands that are frequently exposed to water, detergents and/or solvents. Localized patches of AD can occur on the nipples, especially in adolescent and young women. The disease has a chronic or chronic-relapsing course, with alternating periods of regression and exacerbation of skin changes with pruritus. In some patients, a seasonal variant of the disease is present, with exacerbations mostly in spring and autumn. About 80% of patients with AD will develop allergic rhinitis, conjunctivitis or asthma.

Subtypes of atopic dermatitis

Although most patients with AD have high concentrations of total and allergen-specific serum IgE levels and positive skin prick tests reactions to common environmental allergens, a subgroup of AD patients, both children and adults suffer from skin disease with clinical features that clinically resemble the skin lesions and distribution patterns found in AD. Clinical term for such clinical features is "pure" type of AD and is characterized without concomitant respiratory allergies. "Mixed" type of AD is characterized by concomitant respiratory allergies such as asthma or rhinoconjunctivitis, polyvalent IgE sensitization against inhalants and foodstuff. Pure AD can further be subdivided into an *intrinsic* (IAD) and an *extrinsic* type (EAD). Extrinsic type affects 70-80% of patients and an intrinsic type affects 20-30% patients. In IAD is characterized by: clinical phenotype of AD, according to Hanifin and Rajka; absence of other atopic diseases such as rhinoconjunctivitis, asthma, acute urticaria, or food allergy; negative skin prick and intracutaneous tests to common aero- and food allergy; total serum IgE levels in normal ranges for infants, children, and adults; negative in vitro screening for specific IgE to common aero- and food allergens. In EAD type patients are not presented with respiratory symptoms, but IgE sensitization against inhalant and/or food allergens in the skin test or serum is present. Patients with IAD tend to have a late onset of the disease, but family history and disease duration seem to be similar in IAD and EAD. The distribution and clinical picture of the skin lesions do not differ. The classification to the two types is not just academic because in the case of IAD pharmacological prevention of asthma with long term medication is not indicated because onset of respiratory disease is quite improbable. In 2001 in an attempt to harmonize the allergy-related relevant definitions in the various fields, a task force of European Academy for Allergology and Clinical Immunology (EAACI) proposed to use as an umbrella the term *atopic eczema/dermatitis syndrome* (AEDS). AEDS is further subdivided into allergic, IgE associated group (AAEDS) and nonallergic one (NAAEDS).



Associated clinical features

Pruritus

Severe pruritus is the main characteristic of AD. The more so, pruritus with consequential scratching is an important factor for the occurrence of typical eczematoid changes in these patients. It worsens in the evening, during sweating and by wearing wool clothing. The pathogenesis of pruritus is rather complex. Histamine is not believed to be the essential mediator of itch in AD. Proteases, kinins, prostaglandins, neuropeptides, acetylcholine, cytokines, and opoids can cause itch or potentiate histamine release when injected into atopic skin.

Keratosis pilaris

Keratosis pilaris is seen most commonly during childhood and presents as small, rough, raised lesions (papules). It is regarded as a defect of keratinization at the xerotic hair follicles, in which the follicular openings are filled with horny plugs making skin feel like sand paper or chicken/turkey skin. These papules are described as "spiny and keratotic" and are typically skin colored. It occurs in 55% of atopic patients with or without AD. It is frequently noted during childhood, peaks during adolescence, and becomes less apparent during adulthood. The papules are usually found on the outer surface of the upper arms and thighs, buttocks, and face, although it may occur elsewhere on the body. The roughness is accentuated by dry skin and the condition is often worse in the winter. It tends to be inherited and may be associated with atopic dermatitis. Keratosis pilaris is asymptomatic but cosmetically disturbing.

Xerosis cutis

Xerosis cutis is considered to be the most common condition dermatosis of atopic individuals. It can persist for life, independent of the activity of atopic symptoms. The seasonal variations are noted in 75% of the patients. Due to the xerotic epidermis, skin barrier is abnormal and that provokes and sustains inflammation by activation of an epidermis-initiated cytokine cascade. The impaired barrier function of atopic skin allows great absorption of irritant agents and contact allergens. It is also easier access for bacteria, viruses, and dermatophytes.

Pityriasis alba

Pityriasis alba (PA) is a benign, chronic skin disorder that affects some children, usually between the ages 6 to 12 years, but may occur up to age 20-30. Synonyms are: pityriasis streptogenes, pityriasis simplex, pityriasis sicca facies, erythema streptogenes, furfuraceous impetigo. It is characterized with small white patches of lighter skin main-



ly on the face, although the neck, upper chest, and arms are sometimes involved. They sometimes have pinpoint-size white papules. The light colored patch seems to blend gradually into normal appearing skin, so the borders of the lesions are not clearly visible. The etiology and pathogenesis of pityriasis alba are still poorly understood. Recent studies have found direct correlation between the incidence of pityriasis alba and atopy, amount of sun exposure, lack of sunscreen use, and bathing frequency. Ultrastructurally the number of melanocytes is reduced, as are the melanosomes within both melanocytes and keratinocytes. Pityriasis alba may be interpreted as resolving atopic dermatitis in which the inflammation has subsided, thereby unveiling hypomelanosis. It is often an incidental finding on physical examination because it is usually asymptomatic. It appears to get worse when the skin is dry. It is often thought of as a mild form of eczema. During the summertime when the surrounding skin gets tanner, white patches become more visible, because it remains the same colour. In the winter months the skin is drier and the patches are more flakier. Differential diagnosis includes: pityriasis versicolor (alba), which is an autoimmune response to a fungus on the skin, and the diagnosis can be ruled out by KOH examination. Sometimes pityriasis alba can be confused with vitiligo. The vitiligo patches have very distinct border with a sharp line between normal and lighter-colored skin. Psoriatic leukoderma is rarely located on the face and the active psoriatic lesions can be found elsewhere. Treatment of pityriasis alba is not necessary since it will resolve on its own. Using moisturizer or hydrocortisone may make the patches go away faster. However, even with treatment, it may take months to years for white patches to resolve. Usage of sunscreen or protective clothing to prevent sunburn in affected areas is recommended.

Ichthyosis vulgaris

The most common disorder of keratinization with diffuse scaling and highly variable degree of involvement. The skin changes are usually not present at birth. They can be seen from early infancy to the teens. There is clear association with atopic dermatitis (25-33%). When a patient with ichthyosis vulgaris has severe pruritus and flexural involvement, usually has atopic dermatitis.

Dennie-Morgan lines

Dennie-Morgan lines are symmetrical, prominent folds, extending from medial aspect of the lower eye lid. It is most often seen in the patients with Down's syndrome, and in 60-80% of atopic individuals. These folds are usually present at birth, or appear shortly thereafter, and persist for life. Patients tend to have more than one fold, especially at the early age. The sign is present in about 70% of atopic children.



Palmoplantar hyperlinearity

People with atopic dermatitis frequently have thickening of the skin on the palms and soles with an increase number of lines in the skin (hyperlinearity). This characteristic is closely associated with genetic predisposition (atopy).

Cheilitis

Cheilitis is noted as a persistent scaliness, usually restricted to the vermilion, but often extending onto the perioral skin. It often starts in winter during childhood and appears as dry scaly lips and is often attributed to frequent licking to hydrate the dryness (cheilitis sicca). It also occurs as a result of food allergy, and in the children with no known atopy or allergy. It may become secondary infected and crusted. It can easily be transformed to a true perioral dermatitis by repeated application of potent corticosteroids.

Lichen simplex chronicus

Lichen simplex chronicus also known as circumscribed neurodermatitis or lichen Vidal, is a common pruritic skin disorder, usually sharply localized and characterized by skin thickening and prominent skin markings. Lichenification is a common phenomenon-it describes the response of the skin to repetitive irritation with thickening and more prominent skin markings. A minor itch may encourage scratching, which increases the irritation, leading to more scratching. This ultimately results in a rough, scratched (excoriated), thickened skin surface which may develop increased pigmentation (hyperpigmentation) as seen on the front part of the foot, just below the leg, nape, distal extremities, genitalia and upper eyelids. Many patients have atopic dermatitis and some have defined lichen simplex chronicus as part of the atopic diathesis.

Prurigo nodularis

Prurigo nodularis is a very pruritic dermatosis characterized by persistent nodules. In the past it was considered pathognomonic for uremia and renal transplantation patients. Probably the biggest group are patients with severe atopic dermatitis or at least an atopic diathesis. Elevated serum immunoglobulin E and increased incidence of immediate reactions to pollens, dust and house dust mites support the role of underlying atopy. Underlying emotional stress (depression, psychosocial problems) is also applied here. The lesions are almost limited to distal aspects of extremities. The face and trunk are spared. There are usually a modest number of symmetrically distributed, isolated firm nodules.



Nipple dermatitis

Nipple dermatitis is noted in 12-23% of patients with AD. It is most common in postpubertal girls. The very sensitive areolar skin Koebnerizes with the slightest rubbing or friction of clothing. It is frequently symmetrical, scaly, oozing, and papulovesicular, and it may extend onto the adjacent breast skin.

Complications of atopic dermatitis

Any chronic illness can have a major impact on the patient's life. Young children often suffer sleep disturbances which are difficult for parents and may cause behaviour problems in the child. Older children may become shy and withdrawn due to the embarrassment of a visible skin condition. Adults also suffer shyness and withdrawal due to the appearance of the eczema. Long lasting AD may lead to pronounced psychical trauma. *Retarded grow* can be associated with atopic dermatitis-it used to be seen in severe cases of AD before advent of corticosteroid therapy, and can therefore be attributed to the disease.

Because of frequent scratching and fissuring of the skin, *secondary infection* is not uncommon. The potential complications include: 1) bacterial infections (staphylococcal, streptococcal); 2) fungal infections (trichophytosis, candidiasis); 3) viral infections (warts, molluscum contagiosum, eczema herpeticum Kaposi; and 4) contact allergic dermatitis to fragrance mix, parabene, nickel, plastics components, rubber, etc.

Eczema herpeticum: Herpes simplex may produce widespread lesions in patients with eczema. Clinical picture is characterized by multiple grouped vesicles with associated fever.

Exfoliative dermatitis: Eczema may be the underlying disorder in this diffuse warm erythematous dermatitis that affects the entire body. Hospital admission is usually required.

Ocular problems: Eye complications are associated with severe AD. *Eyelid dermatitis* (Fig. 2) or *chronic blepharitis* are commonly associated with AD and may result in visual impairment from corneal scarring. *Cataracts* are more common in patients with atopic dermatitis. It occurs in up to 10% of the severe adolescent and adult cases. Atopic cataracts may resemble those induced by topical or systemic therapy. *Keratokonius* is a rare condition. It is due to degenerative changes in cornea, which is forced outwards by the intraocular pressure, to give rise to marked visual disturbances.

Atrophy or striae occur if fluorinated corticosteroids are used on the face or in skin folds. Systemic absorption of steroids may occur if large areas of skin are treated, particularly if high-potency medications and occlusion are combined.



HISTOPATHOLOGY

A biopsy is rarely used to diagnose AD, but occasionally performed to exclude other disorders. *Acute eczematous lesions* are characterized by marked epidermal intercellular oedema (spongiosis), antigen-presenting cells (eg. Langerhans cells, inflammatory dendritic epidermal cells, and macrophages) to a lesser extent in dermis. In the dermis with acute lesions, there is striking infiltration of CD4 activated T cells. *Chronic lichenified lesions* are characterized by an acantholytic epidermis with elongation of the rete ridges, parakeratosis, and only minimum spongiosis. Those chronic lesions have an increased number of IgE-bearing Langerhans cells and inflammatory dendritic epidermal cells in the epidermis, and macrophages dominate the dermal mononuclear cell infiltrate. These lesions also contain eosinophiles.

DIAGNOSTICS

Clinical Diagnostic

Elements contributing to the establishment of the diagnosis of AD are compiled from patient history, clinical finding, skin tests and laboratory investigation. Hanifin and Rajka were the first to attempt a systematic approach towards the standardization of the diagnosis of AD by proposing four major and 23 minor criteria for AD in 1980 (table 1). They argued that a diagnosis of AD could be established if three of the major and three of the minor criteria were present. The Lillehammer Criteria of 1994 are based on the idea that the distribution of the atopic dermatitis may differ in the infantile, childhood, and adult phase (table 3). Diagnostic Lillehammer criteria are visible eczema in at least one of the regions, and at least one positive of the anamnestic or laboratory criteria, and at least three of the clinical, anamnestic, or laboratory criteria. In addition, as fourth criteria, the skin disease should always have a duration of at least 6 weeks in the infantile phase or 3 months in the childhood and the adult phase.

Laboratory diagnostics

There are currently no single laboratory tests for the diagnosis of AD, there has been substantial progress in the past decade toward understanding the basis of the immune response in allergic diseases such as atopic dermatitis. Laboratory tests are chosen according to history data and physical examination. The aim of laboratory testing is identification of the respective allergen. In vitro tests are: 1. tests for detection of IgE antibodies: (a) radioimmunoassays for total IgE (RIST), specific IgE (RAST), (b) enzyme-linked immunosorbent assay (ELISA) for detection of IgE; 2) tests for detection of IgG antibodies: RAST and ELISA; 3) tests for lymphocyte determination; 4) tests for immunoglobulin determination: RIST; Immunoelectrophoresis is of utmost importance in the diagno-



sis of AD because low concentrations of immunoglobulins can be found in immunodeficient conditions.

Skin tests

In vivo tests in the diagnosis of immediate hypersensitivity are *prick test*, *scratch test* (*scarification test*) and *intradermal tests*. Intradermal tests are recommended only if skin prick test are negative. Despite the dilution, the allergen concentration is 100-1000-fold higher than prick testing and the risk of systemic allergic reaction is greater. Standard series with common aeroallergens and food allergens are employed. *Patch test* or *epicutaneous test* is used to determine delayed (type IV) hypersensitivity. In *Atopy patch test* aeroallergens, rarely food allergens are used for patch testing.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of AD includes most conditions listed in this chapter. Despite the long lists, in the most cases the diagnosis is easy. The table 2 lists a number of inflammatory skin diseases, immunodeficiencies, skin malignancies, genetic disorders, infectious diseases and infestations that might be considered as differential diagnosis

In infants problems includes seborrheic dermatitis, candidiasis, diaper rash, scabies, Langerhans cell histiocytosis. *In children and adults* it includes: contact dermatitis (allergic and nonallergic), seborrheic dermatitis, ichthyosis, scabies, lichen simplex chronicus, generalized mycosis, dermatitis herpetiformis, medicamentous exanthema, atopy-form dermatitis (atopic dermatitis-like dermatitis) associated with immunodeficiency syndrome.

TREATMENT

Successful management of atopic dermatitis requires a different approach involving skin care, identification and elimination of flare factors, and anti-inflammatory treatment.

General measures

In AD, the disturbed function of the skin barrier is the result of reduced ceramide concentrations and results in dry skin and enhanced transepidermal water loss. General measures of prevention and treatment of AD include avoiding those factors that have been identified as potential causes of the disease exacerbations. This implies avoidance of skin contact with wool, synthetic materials, and foods that can induce irritation, e.g., citrus fruit or tomato. Patients are advised to avoid staying in smoky areas, to reduce exposure to house dust, feather, and animal hair. Perspiration and itch increase with



heat exposure, while dry air contributes to skin dryness. Staying in mountains at 1500 m above sea level is useful. Staying at seaside, sea bathing and sun exposure usually prove beneficial in AD patients. However, skin sun protection is necessary, i.e. avoiding most intensive sun exposure (between 11.00 a.m. and 5.00 p.m.), along with application of sun protecting preparations and daily skin care. Skin care includes appropriate skin hygiene, which is of paramount importance. Patients with hypersensitivity to a nutritive allergen are recommended appropriate dietary regimen. On prescribing diets for children, it should be borne in mind that inappropriate diet may lead to malnutrition while even a minimal dietary deficit may cause changes in immune response.

It should be emphasized that hypersensitivity to food allergens is mostly diagnosed in children, whereas hypersensitivity to inhalative allergens and development of contact allergic dermatitis predominate in older patients.

Local therapy

Skin care preparation should be applied on the skin within three minutes (3-minute rule) of bathing, otherwise bathing will lead to skin drying instead of desirable skin hydration. *Bathing* is also important because the penetration of corticosteroids into the hydrated skin is best after bathing. Soaps with minimum defatting activity and a neutral pH are preferred. The use of oily baths followed by neutral preparations for skin ointment and hydration (creams, ointments and emulsions) several times a day is necessary in most AD patients. The higher the degree of skin dryness, the greater is required frequency of preparation usage. Preparations with the addition of urea, omega fatty acids, lipids, zinc and copper are used for this purpose. Local therapy for AD is tailored to the stage of disease: in acute stage, *indifferent creams*, bases (hydrophilic creams, oil/water emulsions); in subacute stage, mild *antiphlogistic creams* and *soft pastes*; and in chronic stage, water/oil ointments and tar preparations are used. Keratolytics and rehydrating ointments (salicylic acid, urea) applied by occlusive technique for 4-12 hours are used for hyperkeratoses/rhagades. *Water-alcohol compresses*, *soft zinc pastes* or *zinc oil* are applied in case of moist, macerated lesions, whereas oil baths and occasional use of corticosteroid preparations are recommended for all stages. *Local corticosteroid* preparations remain the most important agents in the management of AD patients for their antiinflammatory and antipruritic action. The potent corticosteroids should be avoided on the face, the genitalia, and the intertriginous area. With mild disease activity a small amount of topical corticosteroids two-three times weekly (monthly amounts in the mean range of 15 g in infants, 30 g in children and up to 60-90 g in adolescents and adults) achieves good maintenance. *Local antihistamines* are not recommended because of potential cutaneous sensitization. *Topical calcineurin inhibitors* are steroid-free preparation: tacrolimus and pimecrolimus. Most promising are macrolide derivatives for local appli-

cation, tacrolimus (Protopic® 0.1% and 0.03%) and pimecrolimus (ascomycin, SDZ.ASM981, Elidel®), which have an immunomodulatory effect. Their main advantage over corticosteroids is that these agents do not cause skin atrophy and telangiectasia because they do not affect collagen synthesis. They are especially useful for facial and intertriginous lesions. *Tar preparation* may have antipruritic and anti-inflammatory effects on the skin. They may be useful in reducing the potency of topical corticosteroids required in chronic maintenance of AD. Tar preparations should not be used on acutely inflamed skin, since this often results in skin irritation. *Capsaicin*, 0.025% cream acts on substance P release and has an antipruritic effect. In case of localized pyodermal lesions, local antibiotics, mostly mupirocin, is applied. The yeast *Pityrosporum ovale* is efficiently eliminated by use of a ketoconazole shampoo, or with miconazole alone or in combination with hydrocortisone.

Systemic therapy

Infectious agents

Skin infections with *Staphylococcus aureus* are rather common in AD patients, manifesting as madidations of skin lesions, pustules and crusts. Therefore, therapy with oral antibiotics, mostly erythromycin, azithromycin and cephalosporin preparations, is quite frequently justified.

Antihistamines

Systemic antihistamines are widely used in acute flares against itch. They may be helpful to decrease pruritus and permit sleep during flares. Antihistamines H1 receptor antagonists, especially those with sedative effect (diphenhydramine) are frequently prescribed for AD patients, however, their efficacy is variable. These agents (hydroxyzine, terfenadine, loratadine, astemizol, cetirizine) are efficacious in the control of reactions generated by mastocyte degranulation but not of T-lymphocyte mediated inflammatory processes. Yet, prolonged use of antihistamines (cetirizine, sodium chromglycate in combination with an antihistamine has a much better effect in AD children) has proved efficient. Tricyclic antidepressants, high-potent antagonists (doxepine, amitriptyline) are also useful. Leukotriene inhibitors have received considerable word-of-mouth testimonial support.

Systemic corticosteroids

The use of systemic corticosteroids, such as oral prednisone, may be required in the treatment of severe chronic AD. The dramatic clinical improvement that may occur with systemic corticosteroids may be also associated with an equally dramatic rebound flaring of atopic dermatitis after discontinuation of systemic corticosteroids. In children are used seldom only in acute phase.



Ultraviolet light

Natural sunlight is frequently beneficial to patients with AD. However, if the sunlight occurs in the setting of high heat and humidity, thereby triggering sweating and pruritus, it may be deleterious to patients. *Heliotherapy* (sun and sea therapy) is also useful. *UV B* or combined *UV AB* exposure is efficacious in AD patients. High daily doses of *UV A1* (340-400 nm) are even more efficacious. Photochemotherapy with oral photosensitizer methoxypsoralen (Meladinin tablets) followed by the *UV A* exposure (*PUVA therapy*) may be indicated in patients with severe, widespread AD with failure of topical steroid therapy or significant corticosteroid side-effects. Topical application of 0.3% 8-MOP ointment (*PUVA cream therapy*) could be used to treat palmo-plantar AD lesions.

Cyclosporine

Cyclosporine is a potent immunosuppressive drug that acts primary on T cells by suppressing cytokine transcription. Severe AD patients, refractory to topical corticosteroid therapy, can benefit from treatment with oral cyclosporine (5 mg/kg/per day). Discontinuation of treatment frequently results in rapid relapse of skin disease.

Interferons

INF- γ is known to suppress IgE responses and downregulate T_H2 proliferation and function. The treatment with recombinant INF- γ results in clinical improvement and decreases total circulating eosinophil counts.

Extracorporeal photopheresis

This treatment consists of passage of psoralen-treated leukocytes through an extracorporeal *UVA* light system. It could be used in severe, resistant to therapy AD patients.

Allergen immunotherapy

Available evidence of the effectiveness of immunotherapy with aeroallergens in the treatment of AD is mixed. Immunotherapy with aeroallergens must be proven for efficacy in the treatment of AD.

Other

Systemic immunosuppressants such as *methotrexate*, *azathioprine*, *mycophenolate mofetil* (*MMF*) are indicated in the management of resistant forms of AD and are behind cyclosporin in AD management. *MMF* odds with a better safety profile than cyclosporine or azathioprine, but controlled studies are needed to prove efficacy. *Thalidomide* (25-200

mg/day) is efficacious in resistant cases of AD, even in children. *Phosphodiesterase inhibitors* are agents intended for generalized forms of the disease.

AD develops as a consequence of complex etiology and pathogenesis. The severity and extent of skin lesions, and deviation in laboratory parameters, especially immunologic ones, may greatly differ from patient to patient. A consensus will have to be established in the near future on the new criteria defining AD, on the model of those set 25 years ago by Hanifin and Rajka. The ever growing prevalence of the disease worldwide underlines the role of prevention, timely recognition, and optimal treatment of the many patients with AD.

WHAT DO YOU NEED TO KNOW ABOUT THIS DISEASE?

- chronic, recurrent disease with intense pruritus, associated with personal or family history of atopy
 - predisposition and trigger factors are genetic, environmental factors, irritants, alimentary allergens, aeroallergens, microbial factors (*Staphylococcus aureus*, *Malassezia furfur*, *Herpes and varicella viruses*), psychosomatic factors and hormones
 - three classical stages of the disease: infantile, childhood and adult
 - subtypes of AD: pure (intrinsic and extrinsic) and mixed
 - associated clinical features are pruritus, keratosis pilaris, xerosis, pityriasis alba, ichthyosis vulgaris, Dennie-Morgan lines, palmoplantar hyperlinearity, cheilitis, lichen simplex chronicus, prurigo nodularis and nipple dermatitis
 - treatment involves general measures, local neutral, hydrating preparations (emollients), corticosteroids and immunosuppressive local treatment, and in severe cases phototherapy, peroral corticosteroid and other immunosuppressive agents therapy
-



Table 2. Differential diagnosis of atopic dermatitis

IMMUNODEFICIENCIES	
Wiskott-Aldrich syndrome	Ataxia-telangiectasia
DiGeorge syndrome (congenital thymic aplasia)	Bruton syndrome (X-linked hypogammaglobulinemia)
Hyper-IgE syndrome	Selective IgA deficiency
Severe combined immune deficiency	Chronic granulomatous disease
GENODERMATOSES	
Comél-Netherton syndrome	Biotin deficiency
Phenylketonuria	Hartnup disease
Hypohidrotic ectodermal dysplasia	Acrodermatitis enteropathica
METABOLIC DISEASES	
Pyridoxine (vitamin B ₆) and niacin deficiency	Multiple carboxylase deficiency
Tyrosinemia	Essential fatty acid deficiency
Histidinemia	Zinc deficiency
IMMUNOLOGIC DISORDERS	
Dermatitis herpetiformis	Dermatomyositis
Pemphigus foliaceus	Lupus erythematosus
Graft-versus-host disease	
NEOPLASTIC DISEASES	
Cutaneous T-cell lymphoma (mycosis fungoides/Sézary syndrome)	
Langerhans cell histiocytosis	
INFECTION AND INFESTATION	
Candida (chronic mucocutaneous candidiasis)	<i>Staphylococcus aureus</i>
Neonatal mucocutaneous candidiasis	<i>Sarcoptes scabiei</i>
Impetigo	HIV-associated dermatitis
<i>Herpes simplex</i>	Congenital syphilis
DERMATITIS	
Contact (allergic or irritant)	Nummular
Seborrheic	Lichen simplex chronicus
Psoriasis	Asteatotic eczema
OTHER	
Drug eruption	
Photoallergic contact dermatitis	
Chronic actinic dermatitis	



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Table 3. The Lillehammer criteria for diagnosing atopic dermatitis (adopted from ref. 27)

I. THE INFANTILE PHASE (age <2 years)

A. CLINICAL

- eczema over the face or neck
 - eczema on the trunk
 - eczema on the arms or legs (extensor or flexural sites)
 - itching or scratch effects, including lichenification of impetigo
-

B. ANAMNESTIC

- a history of relapsing course or seasonal variation
 - a history of dry skin
 - a history of itching when sweating or wool intolerance
 - a history of respiratory atopy or positive family history of atopy in first-degree relatives
-

C. LABORATORY

- elevated serum IgE or positive skin prick tests
-

D. DURATION

- duration of more than 6 weeks
-

II. THE CHILDHOOD PHASE (age 2-12 years)

A. CLINICAL

- eczema over the face or neck
 - eczema in the elbows or the kneefolds
 - eczema at the wrists or ankles
 - eczema on the hands or feet, including dermatitis sicca
 - pityriasis alba or reversed eczema above (below) elbows/knees or toilet seat dermatitis
 - itching or scratch effects, including lichenification or impetigo
-

B. ANAMNESTIC

- a history of relapsing course or seasonal variation
 - a history of dry skin
 - a history of itching when sweating or wool intolerance
 - a history of respiratory atopy or positive family history of atopy in first-degree relatives
-

C. LABORATORY

- elevated serum IgE or positive skin prick tests
-

D. DURATION

- duration of more than 3 months
-



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III. THE ADULT PHASE (age >12 years)

A. CLINICAL

- eczema over the face or neck
 - eczema in the elbows or the kneefolds
 - eczema at the wrists or ankles
 - eczema on the hands or feet, including dermatitis plantaris sicca
 - pityriasis alba or nummular eczema on the arms or legs, or eczema on the upper trunk, including nipple eczema
 - itching or scratch effects, including lichenification or impetigo
-

B. ANAMNESTIC

- a history of relapsing course or seasonal variation
 - a history of dry skin
 - a history of itching when sweating or wool intolerance
 - a history of respiratory atopy of positive family history of atopy in first-degree relatives
-

C. LABORATORY

- elevated serum IgE or positive skin prick tests
-

D. DURATION

- duration of more than 3 months
-

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Sažetak

Atopijski dermatitis

U radu se iznose različito nazivlje za atopijski dermatitis, definicija ove kronične upalne bolesti s nasljednom sklonošću koju obilježava izraziti svrbež, tipična klinička slika i često udruženost s drugim atopijskim bolestima kao što astma i/ili rinitis. Ova atopijska bolest je u stalnom porastu broja oboljelih i učestalost se kreće između 0,6 – 20.5%. Tijekom bolesti je recidivirajući s različito dugim remisijama. U oko trećine bolesnika remisija je nakon 2. godine života, odnosno nakon 5. godine života. Oko 40% djece s atopijskim dermatitisom razvije kasnije u životu bronhijalnu astmu. Smatra se da je uzrok tomu izloženost peludima, manjim izvorima infekcija, kontaktu sa kućnim ljubimcima, starija životna dob majke i brojni alergeni u hrani. Detaljno se navode svi faktori okoliša kao i mikrobijelni uzroci (bakterije, gljive, *Malassezia furfur*, dermatofiti, virusi), psihosomatski faktori, klinička slika u različitim dobnim skupinama, te druge udružene dermatoze kao i dijagnostički i terapijski postupak.

Ključne riječi: atopic eczema; neurodermatitis constitutionalis; prurigo Besnier; dermatitis atopica

