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An Overview on Atopic Dermatitis in Children

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SUMMARY Atopic dermatitis (AD) is a chronic recurring inflammatory skin disease divided into at least two different forms: atopic (extrinsic) and non-atopic (intrinsic) dermatitis. Genetic epidemiological studies have unraveled several chromosomal loci with putative candidate genes, some of which are localized on chromosomes 3, 17 and 20, and most recently on 1q21. AD represents a large and continuous spectrum of one disease where different contributions from epidermal, immunologically relevant genes and their interactions with environmental signals dictate the outcome of sensitization. AD appears early in childhood and has a typical clinical picture with characteristic remissions and exacerbations. The variability of the clinical picture is related to the complex etiopathogenesis of the disease and patient's age, and is accompanied by moderate to strong itch. This review outlines recent standpoints on the etiopathogenesis, diagnosis, treatment and prevention of AD.

KEY WORDS: atopic dermatitis, children, etiology, pathophysiology, clinical evaluation, diagnosis, treatment

INTRODUCTION

Atopic dermatitis (AD) (constitutional neurodermatitis, atopic eczema, endogenous eczema, atopic eczema/dermatitis syndrome, AEDS) is a chronic recurring inflammation of the skin that can occur in all ages but is more common in children. The disease is determined by genetic predisposition localized on chromosomes 1q21, 3, 17 and 20. Due to the progress in research of AD, a new picture emerges in which the natural history of AD is divided into three stages: an initial intrinsic form (eczema) occurring in early infancy, in 60%-80% of cases followed by sensitization to food and/or environmental allergens with the development of the extrinsic stage (true AD). In this form, it is speculated that antigen presenting cells expressing the high affinity receptor for IgE (FcεRI) play a major role in the control of inflammation. IgE sensitization to self-proteins is observed in children and adults with AD. The clinical picture is typically characterized by remissions and exacerbations. The variability of the clinical picture is related to the complex etiopathogenesis and interactions with environmental signals and relevant genes, age of the patient and itch as well as to the family history positive for other atopic diseases such as asthma and/or allergic rhinitis (1-7). Atopic eczema in childhood is a common disease, the incidence of which is increasing (8). AD has been reported to

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affect 10% of children (9). Although the symptoms of AD resolve by adolescence in 50% of affected children, the condition can persist into adulthood.

AD is the most common skin disease in children. Recent epidemiological studies have shown that the prevalence of AD in the 0-7 year age group falls within the range of 5%-20%, while in adults the incidence, as reported by various authors, is between 1% and 3%. AD is equally represented in both sexes, although in childhood it more frequently affects boys and in adulthood women. The condition typically starts in the first year of life, usually between the 3rd and 6th month. Some 60% of all AD cases develop before the fifth birthday. Just 2% of all AD cases manifest themselves at the age of 20 or more years. In around 30% of the affected individuals, complete remission occurs by the 2nd birthday, in another 30% by the 5th birthday, while 10%-15% of patients continue to suffer from AD symptoms even after puberty. AD is present worldwide and the number of affected people has increased in the last three decades, especially in the industrialized countries of Europe (10-15). From 50% to 80% of AD patients already have or develop asthma or allergic dermatitis (16). AD is a debilitating condition that can compromise the quality of life. Attempts at itch relief by scratching worsen the rash, thus creating a vicious circle.

ETIOLOGY AND PATHOGENESIS

The complex etiology and pathogenesis of AD remain incompletely understood and are a topic of many studies. The prevailing opinion is that the pathogenesis of AD is multifactorial. It is believed that the development of AD is the result of complex interactions in which genetic and immune factors (disorders of humoral and cellular immunity as well as conditions of the neurovegetative system), skin as the barrier (irritation, disorders of the skin function), stress (emotional, specific psychogenic personality structure) and environmental (climate, allergens) factors all play key roles (3,17,18).

Atopy is caused by multiple polygenic defects. If both parents suffer from the same atopic disease, the child will be affected by the same condition in 70% of cases. If the parents suffer from different conditions, the child's chance of developing the same disorder is around 30%. The frequency of AD in monozygotic twins is around 85%, and in dizygotic twins around 21% (13,15). Patients with AD inherit abnormalities of the immune response linked to multiple chromosomal loci, which explains the diversity of the clinical picture. These include the abnormality of the locus 5q31-33, which encodes interleukins (IL) -3, -4, -5 and -11 as well as granulocyte and macrophage colony-stimulating factor (GM-CSF); 3q21, which encodes co-stimulatory proteins (CD80 and CD86) involved in T-cell activity; 11q13, which encodes receptors with high affinity for IgE antibodies (FceRI); and 1q21, 17q25 and 20p, which are, together with psoriasis, joint candidate genes connected to the control of skin inflammation (7,19-24). A wide range of immune abnormalities have been described in patients with AD. These include T helper 2 (Th2) and T helper 1 (Th1) type cell perturbance, elevated serum immunoglobulin E (IgE) levels, hyperstimulatory Langerhans cells, eosinophilic and elevated production of prostaglandin E2 (PGE2) by peripheral monocytes (3,5,7,9,17,26).

The pathogenesis of AD includes allergic sensitivity types I and IV as well as the action of leukocytes, monocytes, macrophages, lymphocytes, eosinophils, mastocytes and keratinocytes. The currently accepted model proposes a predominant type 2 (Th2) cytokine milieu in the initiating stages or acute lesions of AD, and a mixed type 1 (Th1) and type 2 (Th2) pattern in chronic lesions (17,25,27-30). Patients with AD may have weakened cellular immunity and regulation of T and B lymphocyte activity as well as hyperreactivity to external antigenic stimuli such as inhalant and food allergens and insect antigens. These are low-molecular proteins, polysaccharides and haptens. The affected persons show low resistance to bacterial, viral and fungal infections. According to the current knowledge, the main immune abnormality in 80% of all AD cases involves excessive production of IgE proteins with predisposition for anaphylactic hypersensitivity and dysregulation of type 1 and 2 cytokines. Such cases are termed as 'extrinsic' AD, which, in addition to the increased IgE levels, is furthermore characterized by severe clinical symptoms and chronic pattern. Other cases are termed as 'intrinsic' AD; they are characterized by the same clinical picture but show normal levels of total IgE and absence of allergen-specific IgE, other atopic conditions and negative prick test (29-31). Both forms of AD are characterized by eosinophilia that stands in correlation with the severity of the clinical picture. In 'extrinsic' AD, excessive IgE antibodies production in the acute stage is a consequence of the activation of type 2 T-helper cells (Th2). These cells produce IL-4, IL-5 and IL-13, and induce differentiation of B lymphocytes and an increase in IgE synthesis. In chronic stage, the hyperproduction

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of IgE is caused by the biphasic model of T-cell activation, that is by the combined effect of type 1 T-helper cells (Th1) and IL-12-producing Th2 (IL 12). The production of Th2 type cytokine is linked to the membrane expression of glycoprotein CD30 on CD4+ and CD8+ T-cell clone. As the result of the described events, an excessive amount of histamine is released from mastocytes and basophils (7,19,22-31). IgE bound to Langerhans cells (Lc) *via* the high-affinity IgE receptor FcεRI is thought to bind aeroallergens, food allergens or autoantigens.

Environmental factors that play the key role in the development of AD include food, inhalant and infectious agents. Food allergens are especially significant in childhood because they may provoke eczematous exanthema in 40% children with moderate to severe AD. The most frequent food allergens that affect children with moderate to severe AD are egg-white, cow milk, peanuts, soy, flour and fish (1,3,6,32-34). Inhalant allergens induce peripheral eosinophilia and increase serum IgE concentration. The exacerbation of AD may be caused by inhalation of or direct contact with food allergens. Direct epicutaneous application of aeroallergens may induce eczematous reaction on unchanged skin in 30%-50% of AD patients. The most frequent inhalant allergens are house dust and mites, weed and grass pollen, cat epithelium and passive smoking (32-38). Patients with AD suffer from an increased incidence of bacterial, viral and fungal infections, the majority of which are located on the skin. In more than 90% of all AD cases, *Staphylococcus aureus* is isolated from skin lesions (39). In the healthy population, the same bacterium has been found in 5%-15% of cases. This bacterium secretes the so-called super-antigens that penetrate the inflamed skin and stimulate epidermal macrophages and T-cells. Fungal infectious agents affecting patients with AD include *Trichophyton rubrum*, *Malassezia furfur* and *Candida albicans*, as well as herpes simplex virus (eczema herpeticatum) and pox virus (eczema molluscatum, vaccinatum) (3,6,7,39-46).

The barrier function of the skin plays an important role in the development of skin lesions in AD. In physiological conditions, the skin acts as mechanical protection, thanks to corneocytes, as well as a permeable barrier, due to the extracellular lipid matrix. In patients with AD the skin loses water and contains a high level of free fatty acids and sterols; reduced amount of ceramides, gamma-linolenic and dihomo-gamma-linolenic acids as well as urea in the corneous skin layer; and fewer sebaceous glands. For this reason, the permeable function of the skin is disturbed, permitting the entry of allergens, infectious agents and irritants (3,4,10,42-46).

The increase in the incidence of AD in recent decades cannot be explained by genetic factors, which have remained constant, but rather by changes in the environment, especially the so-called “Western lifestyle”. This includes exposure to stress, hygiene (too frequent or too aggressive washing), vaccination that reduces the contact with infectious disease, and finally excessive use of antibiotics leading to reduced immunocompetence. A key role is furthermore played by staying in air-conditioned or ventilated space, inappropriate clothing, changes in nutrition and food additives, and exposure to cigarette smoke. Climate factors are also important, as a seasonal pattern of AD is registered in some 77% of patients, with up to 60% suffering from exacerbations in winter and up to 15% in summertime (1,3,6,10-12).

CLINICAL MANIFESTATIONS

The clinical picture of AD shows diversity in its morphology, distribution and severity. It ranges from mild to extremely severe changes, and it depends primarily on the age but also on the race of the patient, frequency of exacerbations, duration of disease and complications. There are three basic types of AD: infantile, childhood and adult. Each of them may be accompanied by acute, subacute or chronic skin changes. Acute lesions are characterized by the development of papules and vesicles on erythematous skin, accompanied by intense itch and consequent excoriations, erosions and serous exudate. In the subacute type, erythematous, excoriated, scaly papules are found, while chronic lesions show lichenification of the skin which becomes thick and fibric with papules and nodules within the plaques. All three stages of skin changes may coexist in the same patient (1,2,6-10). Lesions at any stage can develop secondary infections, which may resemble impetigo, with crusting and weeping lesions. Xerosis (dry skin) is a characteristic skin finding in AD patients. Because xerotic skin is unable to hold moisture, it is more likely to develop crack and fissure. The resultant skin barrier breakdown increases the susceptibility to irritation and infection. When the lesions resolve, areas of hyperpigmentation persist.

In infants, clinical manifestations of AD develop in the first six months of age, usually around the 3rd month. They are characterized by the develop-

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ment of symmetric, intensely itchy, erythematous macules located primarily on the face and scalp. As the disease progresses, macules are transformed into papulovesicles. This is followed by the development of infiltrated foci, which may secrete and produce scabs, poorly delineated scaly foci, erosions, excoriations, and hemorrhagic scabs. The changes may spread to the trunk and extremities, but the area of the nasolabial furrow, nose and diaper region are usually spared. This stage is often characterized by secondary infections (5-10,27,45-47).

In children aged 2 to 12 years, AD no longer has exudative character and becomes localized. At age 2-3 years, the clinical picture becomes increasingly polymorphous. It is characterized by the development of characteristic papules and plaques localized on the flexion sides of large joints: elbows, knees, neck, on the dorsal side of the hands and feet, wrists and ankles, cheeks and eyelids. They may persist there for long periods of time. Some children develop the nummular form of AD, which is characterized by coin-sized eczematous changes that may exhibit any of the clinical stages of AD and may be located on various parts of the body. Later childhood and adolescence are characterized by lichenification changes, along with hyper- and hypopigmented areas on the flexion sides of large joints, perioral region, nape, neck, forehead, thorax, shoulders, hands and feet (5,7,10,45-48).

DIAGNOSIS

The diagnosis of AD is based on patient history, clinical examination and laboratory findings. Unfortunately, there are no specific laboratory findings or histologic features to define AD. According to Hanifin and Rajka, the clinical picture supports the diagnosis of AD if at least 3 major and at least 3 minor out of 4 major and 23 minor criteria for AD are found (27). By contrast, Lillehammer bases the diagnosis of AD on the history, clinical and laboratory data, along with the set duration of the entire disease and each stage (infantile, childhood and adult) (3). Pruritus is a universal finding in AD on the scalp, neck, wrists and ankles, face, cheeks and extensor surface of the extremities (antecubital and popliteal fossa). Pruritus can be severe, sometimes causing sleep disrupting, irritability and generalized stress for affected patients and family members. Pruritus leads to scratching, which in turn results in secondary changes such as lichenification, excoriation and breakdown of the skin barrier.

The required laboratory tests include the concentration of eosinophils, the level of total and specific IgE (RIST, RAST), allergy skin tests (prick test, scratch test, intradermal, patch or epicutaneous test, atopy patch test), immunoelectrophoresis and histopathology (2,10,27,48,52).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis in the infant must first exclude infantile seborrheic dermatitis, then nummular eczematous dermatitis, contact dermatitis, scabies, psoriasis, dermatophytosis, reaction to medicaments, and atopiform dermatitis (5-10).

TREATMENT

The treatment of AD targets underlying skin abnormalities. Patients should be educated about the chronic nature of the disease and the need for continuous skin care. Xerosis is one of the key elements in the treatment of AD. Lubricants and topical corticosteroids are the mainstays of therapy. If pruritus does not respond on antihistamines, microbial overgrowth (bacterial or viral) should be considered. The treatment of AD must be individually adjusted to the patient and must take into account his/her age, stage of the disease, extent and localization of changes, presence of superinfection, and previous response to treatment. Modern treatment principles are based on the attempt to sufficiently hydrate the skin, eliminate the itch, inflammation and infection, if present, and to prevent sensitization. The treatment may be classified into topical, systemic and phototherapy (1,2,5-10,16,48,49,53-69). Alternative medicine has been termed as a means of therapy that has no scientific basis, but such medicine is increasing without the benefit of controlled clinical trials on the subject (64-66). In childhood eczema alternative therapies are reported: Chinese herbs, homeopathy, dietary restriction, massage therapy, hypnotherapy, and evening primrose oil. Alternative therapies are often used by pediatric dermatology patients (64).

Local therapeutic procedures include adequate hydration of the child's skin, which consists of the use of pH neutral soap and minimal degreasing effect during regular bathing. Bathing with warm (not hot) water must be as short as possible (5-10 min) except for oil baths in which water temperature should be by two degrees lower than usual. After "three-minute" bathing the skin should be treated with moisturizers/emollients, sometimes several times a day because they significantly alleviate itching and have an antiphlogistic effect

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(48,53). Ointments are preferred to creams and lotions, but they are greasy and are poorly tolerated. The frequency of their use depends on the level of skin dryness: the drier the skin, the more occlusive emollients should be used. Severely affected skin can be optimally hydrated by occlusion in addition to the application of an emollient. Small areas can be occluded with plastic wrap; the hands can be covered with gloves. However, this occlusive technique is not used with topical corticosteroids because of side effects. Soaks in sodium bicarbonate or colloidal oatmeal (Aveno) can be used to treat pruritus (16). Products with urea, omega fatty acids, lipids, zinc and copper are usually used in the treatment of AD, as they retain water in the corneous layer. Indifferent hydrophilic creams (oil/water emulsion) should be used in the acute stage, antiphlogistic creams and soft pastes in the subacute stage, and ointments (water/oil) and tars in the chronic stage of AD. In mild cases these preparations alone provide sufficient therapeutic effect (5,6,48,53-55). To avoid skin scratching, fingernails should be cut short.

Topical therapy for inflammatory stage of AD is based on the use of corticosteroids. The strength of products is adjusted to the severity of symptoms, so that the least potent but sufficiently effective product in a suitable base is applied. These products have anti-inflammatory, antimitotic and antiproliferative effects. They should be used intermittently in exacerbations, with a diary of use. As soon as the condition improves, corticosteroids should be substituted with emollients because in long-term use they may cause skin atrophy.

Using wet-wrap dressing with diluted steroids and/or emollients (WWT) is relative safe addition to the therapeutic treatment options in adults with severe and/or refractory AD. Specialized nursing care is essential, especially when using WWT for prolonged periods (59).

The greatest penetration occurs with steroid use on the groin and face; the longest penetration occurs with the application on the palms and soles. In children it is reasonable to use initially a group 6 or 7 (low potency) steroids for intertriginous areas. A general principle in treating AD in children with topical steroids is to use the least potent agent possible and to limit the frequency of application. The use of low-potency topical steroids is appropriate for non-intertriginous areas in children and adults. If the dermatitis is severe and a more potent steroid is needed, the patient should be closely monitored and the strength of steroid should be reduced as the skin lesions improve (1,16,48,53-56). Tar preparations are effective alone or with topical corticosteroids. Frequent superinfections of the skin, especially with *Staphylococcus*, may indicate the need to use local antibiotics (e.g., mupirocin) alone or combined with corticosteroids (7,49,53,56).

Recently introduced preparations in AD therapy include local immunomodulators: calcineurin inhibitors tacrolimus (as 0.01% and 0.03% ointment) and pimecrolimus (as 1% cream). These are the first immunosuppressive drugs that act locally on a specific immune event. By inhibiting calcineurin, they inhibit inflammatory cytokines and thus act selectively on T-cell activation and antigen-presenting cells. They are suitable for local therapy because, in contrast to corticosteroids, they do not cause skin atrophy; they are poorly absorbed through skin; and no cases of systemic toxicity have been hitherto registered. These preparations are indicated for use in moderate and severe cases of AD (57-61).

Systemic therapy of AD includes the use of antihistamines (62), corticosteroids, antibiotics and antiviral drugs as well as immunotherapy and phototherapy (16,63,67-69). The main purpose of antihistamines with sedative and non-sedative effect in AD (loratadine, terfenadine, diphenhydramine, astemizole, cetirizine, hydroxyzine) is to alleviate itch. More effective are sedating agents but they can effect the child's ability to learn. Tricyclic antidepressants such as doxepin (Sinquan) and amitriptyline (Elavil) also have an antihistaminic effect, induce sleep and reduce pruritus (16). Topical forms of antihistamines are not recommended. In children, short-term systemic use of corticosteroids, most frequently prednisone, is indicated for severe treatment-resistant cases and cases of acute AD. Because of the risk of rebound, their dose and therapy duration should be accurately titrated. Marked symptoms of superinfection are, if necessary, treated with systemic antibiotics (cephalosporins) and antiviral medication acyclovir (Zovirax) to prevent complications. In severe clinical pictures or in treatment-resistant cases, the treatment will include immunosuppressive drugs, in the first place cyclosporine (2.5-5 mg/kg/day for 8 weeks), which selectively inhibits IL-2 synthesis, as well as azathioprine (Imuran 2.5-3.5/day), and methotrexate. Interferon-gamma is effective in AD treatment, mycophenolate-mofetil, thalidomide, leukotriene inhibitors zafirlukast (Accolate in children older than 12 years), and montelukast (Singulair in children older than six years), Thymopentin, anti IgE antibodies and topical phospho-

diesterase inhibitors (Cipampylline 0.15% cream) and IVIG failed to show any significant beneficial effect in severe AD (67).

A particularly effective treatment is phototherapy, used in treating refractory AD to induce keratinocytes to produce anti-inflammatory cytokines, which in turn leads to reduction in lymphocyte count, mastocyte degranulation, *Malassezia furfur* and *Staphylococcus aureus* growth inhibition, and increase in epidermal lipid synthesis (67). UVA and UVB are used alone or in combined (UVA and UVB) in the form of narrow band UVB and PUVA therapy as well as extracorporeal photopheresis (16,53,54,63). In 2005, a group of experts published a proposal for treatment of AD in children and adults (68). In very severe cases of AD accompanied by some serious complications, the authors have good results with topical corticosteroids (0.3% prednisone valerate acetate), oral ketotifen fumarate and sodium cromoglycate (69).

Finally, the elimination of trigger factors has therapeutic significance. It is necessary to avoid clothes that may irritate the skin (wool, synthetics), heat and sweating. Depending on the results of allergy tests, patients should avoid exposure to specific allergens (certain foods, house dust mite, animal hair and feathers) and cleansing agents that may irritate the skin. They should also avoid longer stay in smoky and air-conditioned spaces.

CONCLUSION

AD is a chronic relapsing skin disease that typically occurs in early childhood and in pediatric population, and has a complex etiology and pathogenesis. The manifestation of the disease, its severity and extent of skin lesions may vary considerably among patients. As different cases often exhibit variation in laboratory parameters, a precise definition of AD requires a consensus on new criteria, which should take into account recent knowledge about the etiopathogenesis of the disease. With the constant increase in the prevalence of the disease in mind, the importance of prevention, early diagnosis and optimal treatment must be stressed. While further development of safer and more effective treatment is necessary, a precondition for successful treatment of AD remains appropriate skin care.

References

1. Lipozenčić J. Atopijski dermatitis. In: Lipozenčić J *et al*., eds. Dermatovenerologija. Zagreb: Medicinska naklada; 2004. pp. 163-71.
2. Ring J, Huss-Marp J. Atopic eczema. Karger Gazette 2004;64:7-9.
3. Paštar Z, Lipozenčić J, Ljubojević S. Etiopathogenesis of atopic dermatitis – an overview. Acta Dermatovenerol Croat 2005;13:54-62.
4. Leung DYM, Boguniewicz M, Howell MD, Nomura I, Hamid QA. New insights into atopic dermatitis. J Clin Invest 2004;113:651-7.
5. Ruzicka T, Ring J, Przybilla B. Handbook of atopic eczema. Heidelberg: Springer; 2005.
6. Lipozenčić J. Natural history of atopic dermatitis. Practical Workshop on Atopic Dermatitis, Kloster Seeon, July 1-3, 2005;1-5.
7. Leung DY, Bieber T. Atopic dermatitis. Lancet 2003;361:151-60.
8. Williams H. Epidemiology of atopic dermatitis: recent advances and future predictions. Curr Probl Dermatol 1999;83:464-70.
9. Leung DY, Diaz LA, DeLeo V, Soter NA. Allergic and immunologic skin diseases. JAMA 1997;278:1914-23.
10. Turner JD, Schwartz RA. Atopic dermatitis. A clinical challenge. Acta Dermatovenerol Alp Panonica Adriat 2006;15:59-67.
11. Schultz-Larsen F, Diepgen T, Svensson A. The occurrence of atopic dermatitis in north Europe: an international questionnaire study. J Am Acad Dermatol 1996;34:760-4.
12. Laughter D, Istvan JA, Tofte SJ, Hanifin JH. The prevalence of atopic dermatitis in Oregon school children. J Am Acad Dermatol 2000;43:649-55.
13. Williams H, Robertson C, Stewart A, Ait-Haleld N, Anabwani C, Anderson R, *et al*. Worldwide variations in the prevalence of symptoms of atopic eczema in the International Study of Asthma and Allergies in Childhood. J Allergy Clin Immunol 1999;103:125-38.
14. Darsow U, Lubbe J, Taieb A, Seidenari S, Wollenberg A, Calza AM, *et al*, for the European Task Force on Atopic Dermatitis. Position paper on diagnosis and treatment of atopic dermatitis. J Eur Acad Derm Venerol 2005;19:286-95.
15. Hofer MF. Atopic dermatitis: the first allergic step in children. Rev Med Suisse Romande 2000;120:263-7.

16. Correale ChE, Walker C, Murphy L, Craig TJ. Atopic dermatitis: a review of diagnosis and treatment. Am Fam Physician 1999;60:1191-210.
17. Lugović L, Lipozenčić J. Immunologic mechanisms in atopic dermatitis. Acta Dermatovenerol Croat 1996;4:21-9.
18. Lugović L, Lipozenčić J. Are respiratory allergic diseases related to atopic dermatitis? Coll Antropol 2000;24:335-45.
19. Lee YA, Wahn U, Kehrt R, Tarani L, Busineo L, Gustafsson D, *et al*. A major susceptibility locus for atopic dermatitis maps to chromosome 3q21. Nat Genet 2000;26:470-3.
20. Coleman R, Trembolt RC, Harper JI. Chromosome 11q13 and atopy underlying atopic eczema. Lancet 1993;341:1121-2.
21. MacLean JA, Eldelman FJ. The genetics of atopy and atopic eczema. Arch Dermatol 2001;137:1474-6.
22. Kawashima T, Noguchi E, Arinami T, Yamakawa-Kobayashi K, Nagakawa H, Otsuka F, *et al*. Linkage and association of an interleukin 4 gene polymorphism with atopic dermatitis in Japanese families. J Med Genet 1998;35:502-4.
23. Forrest S, Dunn K, Elliot K, Fitzpatrick F, Fullerton J, McCarthy M, *et al*. Identifying genes predisposing to atopic eczema. J Allergy Clin Immunol 1999;104:1066-70.
24. Folster-Holst R, Moises HW, Yang I, Fritsch W, Weissenbach J, Christophers E. Linkage between atopy and the IgE high-affinity receptor gene at 11q13 in atopic dermatitis families. Hum Genet 1998;102:236-9.
25. Grewe M, Bruijnzeel-Koomen CA, Schopf E, Thepen T, Langeveld-Wildschut AG, Ruzicka, *et al*. A role for Th1 and Th2 cells in the immunopathogenesis of atopic dermatitis. Immunol Today 1998;19:359-61.
26. Hamid Q, Boguniewicz M, Leung DY. Differential *in situ* cytokine gene expression in acute *versus* chronic atopic dermatitis. J Clin Invest 1994;94:870-6.
27. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. Acta Derm Venereol (Stockh) 1980;92:44-7.
28. Leung DYM, Soter NA. Cellular and immunologic mechanisms in atopic dermatitis. J Am Acad Dermatol 2001;44:11-2.
29. Schmid-Grendelmeier P, Simon D, Simon HU, Akdis CA, Wuthrich B. Epidemiology, clinical features and immunology of the "intrinsic" (non-IgE-mediated) type of atopic dermatitis (constitutional dermatitis). Allergy 2001;56:841-9.
30. Lugović L, Lipozenčić J, Jakić-Razumović J. Prominent involvement of activated Th1-subset of T-cells and increased expression of receptor for IFN-gamma on keratinocytes in atopic dermatitis acute skin lesions. Int Arch Allergy Immunol 2005;137:125-33.
31. Wuthrich B, Schmid-Grendelmeier P. The atopic eczema/dermatitis syndrome. Epidemiology, natural course and immunology of the IgE-associated ("extrinsic") and the nonallergic ("intrinsic") AEDS. J Invest Allergol Clin Immunol 2003;13:1-5.
32. Husar K, Lipozenčić J. Alergijske manifestacije na hranu kod djece s atopijskim dermatitisom. Pediatr Croat 2001;45:183-5.
33. Guillet G, Guillet MH. Natural history of sensitization in atopic dermatitis. A 3-year follow-up in 250 children: food allergy and high risk of respiratory symptoms. Arch Dermatol 1992;128:187-92.
34. Burks AW, Mallory SB, Williams LW, Shirrelli MA. Atopic dermatitis: clinical relevance of food hypersensitivity reactions. J Pediatr 1988;113:447-51.
35. Darsow U, Laifaoui J, Kerschenlohr K, Wollenberg A, Przybilla B, Wuthrich, B, *et al*. The prevalence of positive reactions in the atopy patch test with aeroallergens and food allergens in subjects with atopic eczema: a European multicenter study. Allergy 2004;59: 1318-25.
36. Sporik R, Hill DJ, Hosking CS. Specificity of allergen skin testing in predicting positive open food challenges to milk, egg, and peanut in children. Clin Exp Allergy 2000;30:1540-6.
37. Sampson H. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. J Allergy Clin Immunol 2001;107:891-6.
38. Oranje AP, van Gysel D, Mulder PGH, Dieges PH. Food-induced contact urticaria syndrome (CUS) in atopic dermatitis: reproducibility of repeated and duplicate testing with a skin provocation test, the skin application food test (SAFT). Contact Dermatitis 1994;31:314-8.
39. Bunikovski R, Mielke MEA, Skarabis H, Worm M, Anagnostopoulos I, Kolde G, *et al*. Evidence for a disease-promoting effect of *Staphylococcus aureus*-derived exotoxins in atopic dermatitis. J Allergy Clin Immunol 2000;105:814-9.

40. Jappe U, Schnuch A, Uter W. Frequency of sensitization to antimicrobials in patients with atopic eczema compared with nonatopic individuals: analysis of multicentre surveillance data, 1995-1999. Br J Dermatol 2003;149: 87-93.
41. Lever R. Infection in atopic dermatitis. Dermatol Ther 1996;1:32-7.
42. Leung DYM. Atopic dermatitis: the skin as a window into the pathogenesis of chronic allergic diseases. J Allergy Clin Immunol 1995;96:302-19.
43. Melnik B, Plewig G. Atopic dermatitis and disturbances of essential fatty acid and prostaglandin E metabolism. J Am Acad Dermatol 1991;25:859-60.
44. Sator PG, Schmidt JB, Honigsmann H. Comparison of epidermal hydration and skin surface lipids in healthy individuals and in patients with atopic dermatitis. J Am Acad Dermatol 2003;48:352-8.
45. Bonifazi E, Meneghini CL. Atopic dermatitis in the first six months of life. Acta Dermatol Venerol (Stockh) 1989;144:20-2.
46. Mortz CG, Lauritsen JM, Bindlev-Jensen C, Andersen KE. Prevalence of atopic dermatitis, asthma, allergic rhinitis, and hand and contact dermatitis in adolescents. The Odense Adolescence Cohort Study on Atopic Diseases and Dermatitis. Br J Dermatol 2001;144:523-32.
47. Aoki T, Fukuzumi T, Adachi J, Okano M. Reevaluation of skin lesion distribution in atopic dermatitis. Acta Derm Venereol Suppl (Stockh) 1992;176:19-23.
48. Hanifin J, Chan CS. Diagnosis and treatment of atopic dermatitis. Dermatol Ther 1996;1:9-18.
49. Eichenfield L, Hanifin J, Luger T, Stevens SR, Pride HB. Consensus conference on pediatric atopic dermatitis. J Am Acad Dermatol 2003;49:1088-95.
50. Majamaa H, Moisio P, Holm K, Turjanmaa K. Wheat allergy: diagnostic accuracy of skin prick tests and specific IgE. Allergy 1999;54:851-6.
51. Niggemann B, Reibel S, Wahn U. The atopy patch tests (APT) – a useful tool for the diagnosis of food allergy in children with atopic dermatitis. Allergy 2000;55:281-5.
52. Turjanmaa K. The role of atopy patch tests in the diagnosis of allergy in atopic dermatitis. Curr Opin Allergy Clin Immunol 2005;5:425-8.
53. Tofte SJ, Hanifin JM. Current management and therapy of atopic dermatitis. J Am Acad Dermatol 2001;44:313-6.
54. Sidbury R, Hanifin JM. Atopic dermatitis: old, new and emerging therapies for atopic dermatitis. Dermatol Clin 2000;18:1-11.
55. Hornstein OP. Topical treatment. In: Ruzicka T, Ring J, Przybilla B, *et al*., eds. Handbook of atopic eczema. Berlin: Springer-Verlag, 1991:334-53.
56. Kuokkanen K, Sillartaka I. Aclometasone dipropionate 0.05% *vs* hydrocortisone 1%: potential to induce cutaneous atrophy in children. Clin Ther 1987;9:223-31.
57. Lipozenčić J. Pimecrolimus – a safe and effective local immunomodulator in the treatment of inflammatory skin diseases. Acta Dermatovenerol Croat 2005;13:63-9.
58. Meurer M, Fartasch M, Albrecht G, Vogt T, Worm M, Ruzicka T, *et al;* CASM-DE-01 Study Group. Long-term efficacy and safety of pimecrolimus cream 1% in moderate atopic dermatitis. Dermatology 2004;208:365-72.
59. Oranje AP, Devillers ACA, Kunz B, Jones SL, Deraeve L, Van Gysel D, *et al*. Treatment of patients with atopic dermatitis using wet-wrap dressings with diluted steroids and/or emollients. An expert panel's opinion and review of the literature. J Eur Acad Derm Venereol 2006;20:1277-86.
60. Allen BR, Lakhanpaul M, Morris A , Lateo S, Davies T, Sao HG, *et al*. Systemic exposure, tolerability, and efficacy of pimecrolimus cream 1% in atopic dermatitis patients. Arch Dis Child 2003;88:969-73.
61. Kapp A, Papp K, Bingham A, Folster-Holst R, Ortone JP, Potter PC, *et al*. Long-term management of atopic dermatitis in infants with topical pimecrolimus, a nonsteroid anti-inflammatory drug. J Allergy Clin Immunol 2002;110:277-84.
62. Hagermark O, Wahlgren C-F. Itch in atopic dermatitis: the role of histamine and other mediators and the failure of antihistamine therapy. Dermatol Ther 1996;1:75-82.
63. Krutmann J, Morita A. Photo(chemo)therapy for atopic dermatitis. In: Krutmann J, Honigsmann H, Elmets CA, Bergstresser PR, eds. Dermatological phototherapy and photodiagnostic methods. Berlin: Springer-Verlag; 2001. pp. 93-108.

64. Hughes R, Ward D, Tobin AM, Keegan K, Kirby B. The use of alternative medicine in pediatric patients with atopic dermatitis. Pediatr Dermatol 2007;24:118-20.
65. Johnston GA, Bilbao RM, Graham-Brown RA. The use of complementary medicine in children with atopic dermatitis in secondary care in Leicester. Br J Dermatol 2003;149:566-71.
66. Madsen H, Andersen S, Nielsen RG, Dolmer BS, Host A, Damkier A. Use of complementary/alternative. medicine among paediatric patients. Eur J Pediatr 2003;162:334-41.
67. Akhavan A, Rudikoff D. The treatment of atopic dermatitis with systemic immunosuppressive agents. Clin Dermatol 2003;21:225-40.
68. Akdis CA, Akdis M, Bieber T, Bindslev-Jensen C, Boguniewicz M, Eigenmann P, *et al*, for the European Academy of Allergology and Clinical Immunology/American Academy of Allergy, Asthma and Immunology/PRACTALL Consensus Group. Diagnosis and treatment of atopic dermatitis in children and adults: European Academy of Allergology and Clinical Immunology/American Academy of Allergy, Asthma and Immunology/PRACTALL Consensus Report. Allergy 2006;61:969-87.
69. Katoh N, Hosoi H, Sugimoto T, Kishimoto S. Features and prognoses of infantile patients with atopic dermatitis hospitalized for severe complications. J Dermatol 2006;33:827-32.

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