

Development of childhood eczema and its classification

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Two main forms of childhood eczema exist: atopic eczema [AE] and infantile seborrhoeic dermatitis [ISD] (1). ISD is a disorder that is easily confused with early AE. Mixed forms are not uncommon. Some consider ISD as an infantile candidid (2). Others have different opinions and consider ISD as a *Pityrosporum ovale* infection (3) or as an early presentation of AE (4). Podmore found that ISD could be distinguished from AE. However, these children with ISD have more chance to develop atopic diseases (3). Recently, we concluded the same from a retrospective study [Aarden, pers. comm.]. In this article the development and the classification of AE are discussed in detail.

Atopic eczema

AE is the commonest chronic inflammatory dermatosis in children (1). The term eczema is often used incorrectly. By definition, eczema is a dermatosis with more than 2 primary elements together. AE belongs to the manifestations of the atopic syndrome. Therefore, the best name for this disorder is AE, instead of atopic dermatitis or constitutional eczema, neurodermitis and several others.

The prevalence of atopic diseases such as atopic eczema and asthma, is increasing for unknown reasons (5). Possible explanations are smoking, outdoor pollution, early exposure to allergenic foods and others. The prevalence of AE has increased from 3–5% to approximately 10–20% (6, 7).

Development of atopic eczema

Pathogenesis

AE is genetically determined. When both parents have the same expression of atopic disease (for example AE), their child has a 70% chance of developing the same manifestations (the same phenotype). In other cases and in which both parents are atopic (different phenotypes), there is a 30% chance for the child to develop atopic disease (8). The overall chance for a newborn to develop atopic disease is 10%. The genetic mapping of AE is complicated. Cookson & Young observed linkage for a gene on chromosome 11q13 in atopic patients with respiratory disease (9, 10). Coleman et al. investigated 95 families with AE, but were unable to confirm genetic linkage in these cases (11). The chances for children to develop AE, increase if their mother is atopic (12).

The histopathology of AE is the same as that of allergic contact dermatitis. Most investigators feel that although AE is an immunologic type IV skin reaction, IgE-mediated mechanisms play a primary role (13). The pro and contra arguments are listed in Table 1. Production of IgE antibody is dysregulated in atopic diseases.

AE is often associated with high levels of IgE and eosinophilia. Cytokines produced by T-lymphocytes, regulate the switch of B-lymphocytes to antibody-secreting cells. Production of IgE antibody is promoted by interleukin [IL]-4 and IL-13.

In the early development of AE, eosinophils are attracted by IL-3, IL-5 and platelet activating factor [PAF]. Eosinophils have several membrane receptors including that for the Fc part of IgE. These

Table 1. Arguments for IgE-mediated mechanisms in atopic eczema

Positive	Negative
Increased levels of IgE in 80% of the patients	Normal levels of IgE in 20% of the patients
Specific IgE to food- and aero-allergens	Increased levels of IgE in other dermatoses
Positive prick tests	
Positive family history	
Transfer by bone marrow transplantation	

receptors have an important function. Eosinophils contain granules, encompassing major basic protein [MBP] and eosinophilic cationic protein [ECP] as the main proteins (14, 15). After activation eosinophils degranulate rapidly, producing mediators such as prostaglandines, leukotriens and PAF. ECP is probably a marker of disease activity. ECP levels are significantly increased in AE (15). This protein is detectable in the involved AE skin, but eosinophils are disrupted and not present anymore.

Cellular immunity is diminished in AE (13). AE is frequently complicated by cutaneous viral and bacterial infections. Skin lesions of such immune-deficiency syndromes as Wiskott-Aldrich syndrome, Di-George syndrome, Nezelof & Job syndrome (hyper IgE syndrome) closely resemble those of AE.

IgE-bearing Langerhans cells [LC] play an important role in the triggering of AE (16, 17). The pathomechanism is comparable with that of contact allergic dermatitis. In contrast to that observed in contact allergic dermatitis, in AE Th2 cells are predominantly observed.

The mast cell is also important in the pathogenesis of AE. The mast cell is loaded with IgE. Allergens may reach cutaneous mast cells and LC via the skin or by way of the blood circulation after entering the mucosal surfaces (13). After contact with allergens, the mast cells degranulate (Fig 2). Then several mediators such as histamine, prostaglandines, serotonin, leukotriens, cytokines (IL-3, IL-5) and PAF are released. The direct response results in urticaria. Both IL-3 and IL-5 in combination are a strong signal inducing maturation of the mast cell and for recruiting eosinophils. Eosinophils play an important role in the initiation of the early- and late-phase skin reactions. Both IL-3 and IL-5 are also produced by Th2 cells.

The resulting mononuclear infiltrate consists of T cells. The majority of the T-cells belongs to the Th2 subset, whereas a minority belongs to the Th1 subset. Cells of the Th2 subset have a high, while Th1 cells a low IL-4/IFN-gamma ratio. IL-4 stimulates IgE production, while IFN-gamma inhibits it.

Contributing factors in atopic eczema

Several contributing factors (irritants and allergens) can be recognized in AE. It indicates, that they play a causal role in the development or in the aggravation of AE. Food and inhalation allergens, animal products and many other factors can aggravate or even induce AD. However, there are conflicting opinions on the extent to which these factors influence the course of AD (1).

The serum IgE level is elevated in about 80% of the patients. Specific IgE antibodies may be directed against food allergens, inhalant allergens (house dust mite and others), *Staphylococcus aureus* and *Pity-*

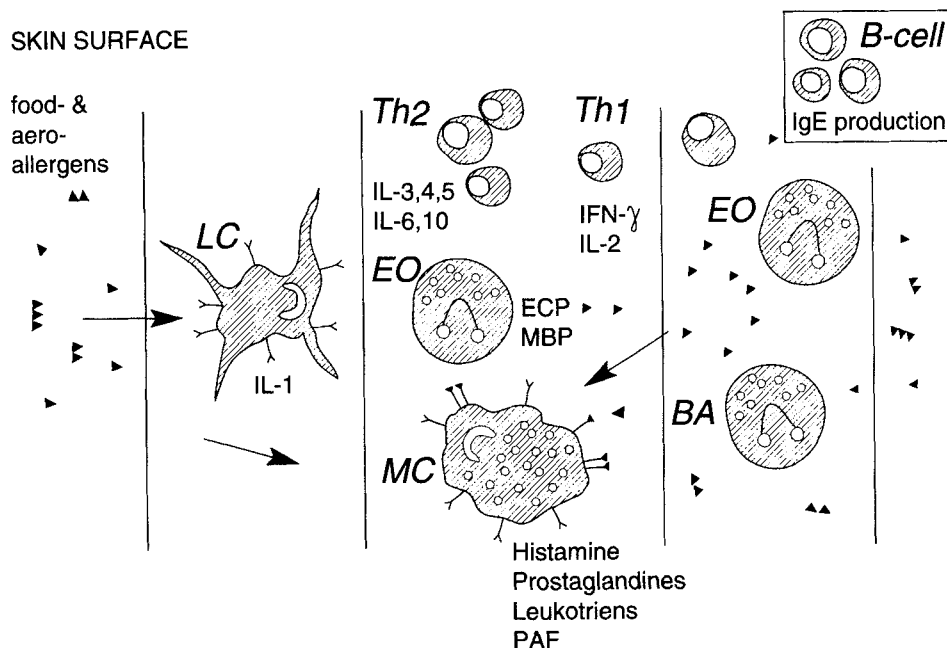
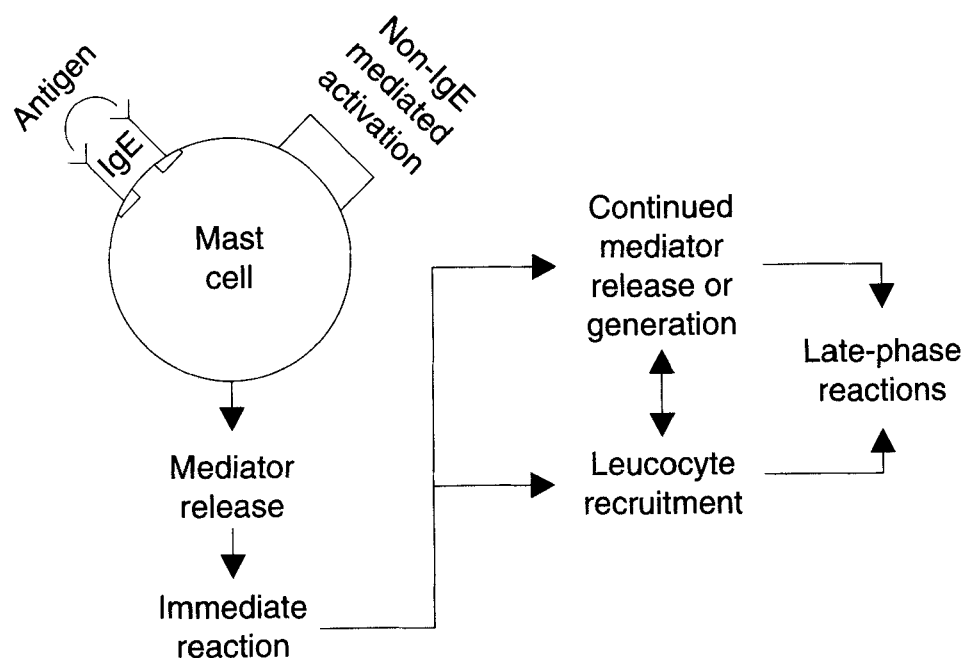


Fig. 1. Pathogenetic model in atopic eczema. The small arrows indicate allergenic molecules.

Fig. 2. Mast cell, direct and late reactions.



rosporum ovale. The possible routes of sensitization are via the skin, the gastrointestinal tract and the respiratory tract.

Food allergy – Food allergens may play an important role in inducing or aggravating AE (18, 19). However, only some of the children with AE experience an exacerbation of dermatitis after consuming foods.

Food allergy [FA] varies as a chameleon in presentation. The reaction pattern depends partly on the releasability of the mast cells and on the target organ(s) involved. In AE, of course, the skin is the target organ. Skin-related symptoms include rashes, urticaria, quinkes oedema and contact urticaria (syndrome) [CUS]. Often, vomiting and diarrhoea are also present. Food allergy is observed in 20% of the children with AE, attending the out-patients department of paediatric dermatology at Sophia hospital in Rotterdam. Nearly half of these children responds to elimination diets.

CUS occurs in about half of the patients with AE and FA. The term CUS was introduced by Maibach et al. in 1975. CUS is a wheal-and-flare response to rapidly absorbable agents to an intact skin. For many years CUS was not recognized. The role of IgE in CUS and childhood AE is important (20). Based on this mechanism, Oranje developed a simple, cheap and child-friendly test system, called skin application food test [SAFT], for investigating infants and toddlers with AE (20).

Inhalant allergy – The exact role of aeroallergens in inducing AE is still subject to controversy. CUS may be induced not only by foods, but also by aero-

allergens and allergens from animals. House dust mite allergy is frequently observed in older children with AE. It is still controversial whether direct contact and inhalation play an aggravating role in AE. The role of grass pollen allergy is even more controversial (1).

Delayed contact allergy – Delayed contact allergy plays a role in AE persisting after the age of 5 years. However, it has also been reported in children as young as 2 years or more (21, 22). Oranje et al. observed delayed-type contact allergy in 47% of the children aged 5 years or more with AE (23).

Evaluation of AE – The influence of the different contributing factors should be scored using an index-system to obtain an objective evaluation. Many homemade systems exist, that cannot be compared with each other (20). Therefore an international system called SCORAD-index was developed by the European Task Force Group on Atopic Dermatitis. It is a combination of objective and subjective (sleep loss, pruritus) evaluations. The extent of eczema counts for 20% (A), the intensity of the mean lesion for 60% and the subjective symptoms for 20% (24).

Course and prognosis of atopic eczema

The course of AE is marked by exacerbations and remissions, often unexplained. It clears in one-third of the patients after 2 years and in another one-third after 5 years of age. However still many patients who suffered from infantile and juvenile AE, still suffer from eczema during adult life. If AE persists

Table 2. Diagnostic criteria of Hanifin & Rajka, selected upon age groups for practical reasons (Oranje)

a> Diagnostic criteria for infants and toddlers
Basic features (must have 3 or more)
* Pruritus
* Typical facial or extensor or nummular eczematous lesions (infants)
Typical flexural slightly lichenified or nummular lesions (toddlers)
* Chronic relapsing course of eczema
* Positive first-degree family history for atopy
Minor features (must have 3 or more)
* Dry skin
* Perifollicular accentuation
* Peri-auricular fissures
* Chronic scalp scaling
* Dennie-Morgan folds
* Dry skin on lateral surfaces of distal lower legs
* IgE antibodies directed to foods or animal allergens
b> Diagnostic criteria for older children and adults
Basic features (must have 3 or more)
* Pruritus
* Typical flexural lichenification and hand/foot eczema
* Chronic relapsing course of eczema
* Positive first-degree family history for atopy or other symptoms of atopic syndrome
Minor features (must have 3 or more)
* Dry skin
* pale desquamating face
* dry cheilitis with perleches
* head & neck dermatitis, neck folds
* IgE antibodies directed to aero- or food allergens

in the typical form in the teens, most of these patients also will suffer from it during adulthood (25).

The relationship with asthma makes AE even more important. About 40% of the children with AE also develop asthma later on. If they also suffer from food allergy [FA], the chance of developing asthma, is even increased to 50% or more (26).

Classification of atopic eczema

Definition and diagnostic criteria of atopic eczema

AE is defined as a multifactorial inflammatory dermatosis influenced by a variety of triggering factors. With asthma and allergic rhinitis, it belongs to the atopic syndrome. The lesions of AE are variable and non-specific. Elements observed in AE include erythema, excoriations, papules, vesicles, oozing, crusts, lichenification and dryness. More than 2 elements together are often present. Pruritus and itching, chronic relapsing course and a typical distribution of lesions (according to the patient's age) are characteristic. Most patients suffer more from pruritus than from the skin lesions themselves. Usually, AE begins in early infancy. Eighty percent of the children are affected in the first year of life. Diag-

nosis is based on the international criteria defined by Hanifin & Rajka (1). For practical reasons these criteria are by us selected upon practical usefulness for the diagnosis of AE in different age groups (Tables 2a, b). The modified list provides a good guideline for diagnosing AE.

An interesting, to date poorly understood, phenomenon is the age-related distribution of the skin lesions. In young infants, the lesions predominantly involve the head, the face and the extensor surfaces of the extremities. Often, oozing lesions are observed in infantile AE, but not in ISD. In ISD especially the flexural surfaces and other body folds are involved. After the age of 2½ the localization of the skin lesions changes to the flexural surfaces of the arms and the legs. Then, the hands also may be involved, but not often. The flexural lesions show lichenification, but not as profound as that in the older children, in whom the face is often pale and scaly.

Conclusion

Atopic eczema [AE] is the most common form of eczema in children. Infantile seborrhoeic dermatitis [ISD] does not belong to the early manifestations of atopy. However, children that suffered from ISD, are more at risk to develop atopic diseases. The diagnostic criteria for AE of Hanifin & Rajka can be simplified.

The pathomechanism of AE is complex and still not fully elucidated. AE is genetically determined, but the genetic pattern is complicated. It is likely that more than one gene predisposes to atopy and to the target organ involved. Disturbed immunologic cellular interactions are the likely underlying mechanism in AE. Langerhans cells, mast cells and eosinophils play an important role in the pathomechanism.

Several observations suggest that food allergens and inhalant allergens (in particular house dust mite) may play an inducing and aggravating role in AE. Food-induced contact urticaria syndrome [CUS] occurs in about half of the patients with AE and food allergy [FA]. In persisting AE delayed-type contact allergy may play an aggravating role. It is important to evaluate these triggering factors using a standardized evaluation system, such as the SCORAD-index.

The course and the prognosis of AE is less favourable than formerly thought. If AE is still manifest in the teens, most of these patients suffer from AE during adulthood. The risk of asthma is increased in AE complicated by FA.

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References

1. RAJKA G. Essential aspects of atopic dermatitis. Springer Verlag 1989.
2. ORANJE AP, DZOLJIC-DANILOVIC G, MICHEL MF, et al. The role of candidal infections in infantile seborrheic dermatitis. *Pediatr Dermatol News*, 1987; 6: 82-6.
3. PODMORE P, BURROWS D, EADY DJ, et al. Seborrheic eczema-a disease entity or a clinical variant of atopic eczema. *Br J Dermatol* 1986; 115: 341-50.
4. VICKERS CFH. The natural history of atopic eczema. *Acta Derm Venereol Suppl* 1986; 92: 113.
5. ZELLWEGER JP. Asthma and the environment. *Essentialia*. 1992; 21:1-8.
6. HATTEVIG G, KJELLMAN B, BJORKSTEN B, et al. The prevalence of allergy of allergy and IgE antibodies to inhalant allergens in Swedish school children. *Acta Paediatr Scand* 1987; 76: 349-55.
7. WILLIAMS HC. Is the prevalence of atopic dermatitis increasing? *Clin Exp Dermatol* 1992; 17: 385-91.
8. Björkstén B, Kjellmann NIM. Perinatal factors influencing the development of allergy. *Clin Rev Allergy* 1987; 5: 339-47.
9. COOKSON WOCM, SHARP PA, FAUX JA, et al. Linkage between immunoglobulin E responses underlying asthma and rhinitis and chromosome 11q. *Lancet* 1989; i: 1292-95.
10. YOUNG RP, SHARP PA, LYNCH JR, et al. Confirmation of genetic linkage between atopic IgE responses and chromosome 11q13. *J Med Genet* 1992; 29: 236-38.
11. COLEMAN R, TREMBATH RC, HARPER JJ. Genetic heterogeneity in atopy underlying atopic eczema. *Lancet* 1993; 341: 1121-2.
12. COOKSON WOCM, YOUNG RP, SANDFORD AJ, et al. Maternal inheritance of atopic IgE responsiveness on chromosome 11q. *Lancet* 1992; 340: 381-4.
13. SAMPSON HA. Pathogenesis of eczema. *Clin Exp Allergy* 1990; 20: 459-67.
14. RING J, BIEBER T, VIELUF D. Atopic eczema, Langerhans cells and allergy. *Int Arch Allergy Appl Immunol* 1991; 94: 194-201.
15. JAKOP T, HERMANN K, RING J. Eosinophil cationic protein in atopic eczema. *Arch Dermatol Res* 1991; 283: 5-6.
16. BRUYNZEEL-KOOMEN CAFM, VAN WICHEM L, TOONSTRA J, et al. The presence of IgE molecules on epidermal Langerhans cells from patients with atopic dermatitis. *Arch Dermatol Res* 1986; 278: 199-205.
17. BIEBER T, BRUYNZEEL-KOOMEN CAFM. La cellule de Langerhans dans la physiopathologie de la dermatite atopique. *Ann Dermatol Venereol* 1990; 117: 185-93.
18. ATHERTON DJ. The role of foods in atopic eczema. *Clin Exp Dermatol* 1983; 8: 227-232.
19. BURKS AW, MALLORY SB, WILLIAMS LW, et al. Atopic dermatitis: clinical relevance of food hypersensitivity reactions. *J Pediatr* 1988; 113: 447-451.
20. ORANJE AP, AARSEN RSR, MULDER PGH, et al. Food immediate-contact hypersensitivity and elimination diet in young children with atopic dermatitis. Preliminary results in 107 children. *Acta Derm Venereol [Stockh]* 1992; 176: 41-4.
21. GONCALO S, GONCALO M, AZENHA A, et al. Allergic contact dermatitis in children. *Contact Dermatitis* 1992; 26: 112-5.
22. PAMBOR M, KRUGER G, WINKLER S. Results of patch testing in children. *Contact Dermatitis* 1992; 27: 326-8.
23. ORANJE AP, BRUYNZEEL DP, STENVELD HJ, et al. Direct and delayed type contact hypersensitivity in children, older than five years, with atopic dermatitis. *Pediatr Dermatol* 1994; 11: 209-15.
24. European Task Force on Atopic Dermatitis. Severity scoring of atopic dermatitis: the SCORAD Index. *Dermatology* 1993; 186: 23-31.
25. LAMMINTAUSTA K, KALIMO K, RAITALA R ETAL. Prognosis of atopic dermatitis. A prospective study in early adulthood. *Int J Dermatol* 1991; 30: 563-8.
26. GUILLET G, GUILLET MH. Natural history of sensitizations in atopic dermatitis. A 3-year follow-up in 259 children: food allergy and high risk of respiratory symptoms. *Arch Dermatol*, 1992; 128: 187-192.