

Original article

Immunoglobulin E- (IgE) and non-IgE-mediated reactions in the pathogenesis of atopic eczema/dermatitis syndrome (AEDS)

AEDS is a chronic, relapsing, highly pruritic inflammatory skin disease that commonly begins in childhood. Two forms of this disorder exist, i.e. an allergic (extrinsic) form and a nonallergic (intrinsic) form. There are clear genetic, humoral and cellular differences between the allergic and nonallergic forms of AEDS. The allergic variants express local IgE production in affected tissue and both allergic and nonallergic triggers play a major role in the expression of disease. The role of allergens is very important in the immunopathogenesis of AEDS. Nonimmunological triggers play a secondary modulatory role often hampering treatment effort and optimal response to therapeutic efforts.

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The term 'atopic eczema/dermatitis syndrome' (AEDS) was recently proposed by the European Academy of Allergology and Clinical Immunology (EAACI) Nomenclature Task Force to describe what was previously called atopic dermatitis (1). AEDS is a chronic, relapsing, highly pruritic inflammatory skin disease that commonly begins in childhood (2). It is well known that AEDS is not a single disorder, but rather a continuum of several disorders with a number of common clinical characteristics (3). Scientific evidence suggests there are at least two forms of 'atopic eczema/dermatitis', i.e. an allergic (extrinsic) form and a nonallergic (intrinsic) form of disease much as is seen in bronchial asthma.

The immunoglobulin E (IgE) -mediated variant is the most prevalent form of the disease and relates to about 70–85% of AEDS patients. These patients have high serum IgE levels and positive skin prick test reactions to common environmental allergens such as food and aeroallergens (4). Target organ challenge with allergens has been shown to precipitate worsening of skin lesions, and the extent of IgE sensitization is directly associated with the disease severity (5).

The non-IgE-mediated variant of AEDS is not associated with sensitization to food or aeroallergens and total serum IgE is within normal limits. Nevertheless, these patients manifest identical skin lesions to the allergic form of disease. This variant has a frequency of approximately 15–30% depending on the location of the study and the parameters used in defining the disorder (6). A higher incidence of intrinsic AEDS has been observed in female patients. It has been suggested that sex hormones

may contribute to the pathogenesis of disease in this instance (7).

Immunopathogenesis

The allergic form of AEDS is a T-cell-dependent disease largely induced by antigens. Allergic immune responses are characterized by the production of a distinct cytokine profile upon stimulation of allergen-specific T cells. In particular, interleukin-4 (IL-4), IL-5 and IL-13 are responsible for the initiation of allergic inflammation. The cellular infiltrate in the skin lesions is principally CD4⁺ and CD8⁺ cells, with a CD4 : CD8 ratio similar to that in the blood (4). Cutaneous T cells that produce IL-4, IL-5 and IL-13 dominate in the acute phases of AEDS. T cells that produce interferon- γ predominate in the chronic phase of the disease (8). A prominent feature of allergic AEDS is the cutaneous infiltration with highly reactive cells of dendritic lineage. These cells include Langerhans cells and dendritic epidermal cells both of which display the high-affinity receptor for the Fc region of IgE (Fc ϵ RI) on their surface (9).

In the nonallergic form of AEDS the skin T-cells appear to be similar in nature. However, their cytokine products are different. There is a lower Fc ϵ RI expression of epidermal dendritic cells in nonallergic AEDS. T cells from nonallergic AEDS produce similar amounts of IL-5 and interferon- γ ₁, but produce less of the T helper type 2 cytokines, IL-4 and IL-13, which increase IgE synthesis (10). As in allergic AEDS, the skin of patients with the

nonallergic variant contain a large number of epidermal dendritic cells which have decreased amounts of high-affinity receptor for IgE (11). Eosinophils play a significant role in both forms of AEDS by releasing eosinophilic granules and promoting inflammation.

The differences between the allergic and nonallergic forms of AEDS are softened by recent studies that show children with nonallergic AEDS developing skin test positivity to epicutaneous tests to allergens within a decade (12). It has been suggested that nonallergic AEDS may be a transitional form of the disease in the natural history of atopic dermatitis (13).

Natural history of AEDS

There is considerable variation in the progress of AEDS over time. Eighty-seven per cent of AEDS patients develop the disease before the age of 5 years, and less than 2% of patients have disease onset after 20 years of age (8). The skin manifestations can regress after infancy, in childhood, or in adulthood (14). Of children with allergic AEDS, 30–60% will develop allergic respiratory disease, i.e. 'the atopic march' (15). It has also been reported that children with the nonallergic AEDS rarely go on to develop asthma (12,16). Hence, the definition of the allergic and nonallergic forms of AEDS becomes an important clinical benchmark in the formulation of the basic management approach, i.e. avoidance of allergic triggers.

Triggers for AEDS

The symptomatic expression of AEDS, as with other atopic diseases, involves the interaction of multiple genes, the environment and the immune system. From its earliest descriptions AEDS has always been characterized by lesions that are intensely pruritic, which are exacerbated by a variety of triggers. This brief review will discuss some of the better known precipitants of this condition.

Immunologic triggers

Food allergens

Double-blinded, placebo-controlled food challenges have shown that food allergens are an important trigger of allergic AEDS in infants and young children (17). The prevalence of food allergy in children with moderate to severe AEDS ranged from 33 to 39% in various studies (17). As well, the severity of allergic AEDS has been found to correlate with the presence of food allergy (18). Numerous controlled studies in children with AEDS have incriminated seven food allergens (i.e. egg, milk, peanut,

soy, wheat, fish and tree nuts), as accounting for nearly 90% of the positive challenges in these patients (17–19). Egg sensitivity is the most prevalent of the food allergens. Challenges generally induce the typical pruritic, erythematous rash in the expected distribution skin sites of 75% of the patients. Following adherence to avoidance diets, patients generally improve (20).

Aeroallergens

The first definitive studies showing a causal effect between pollen and AEDS were performed by Tuft (21). Numerous subsequent studies have demonstrated positive prick skin tests and patch tests to prevalent pollens in individuals with seasonal AEDS (22). Evidence supporting a role for aeroallergens in AEDS includes both allergen-specific IgE antibodies and allergen-specific T cells (23). Most studies have relied upon epicutaneous application of aeroallergens using patch test techniques. Patch testing of uninvolved atopic skin has precipitated eczematoid reactions in 30–50% of patients with AEDS (24).

Indoor allergens

As with the aeropollens, extensive investigations have implicated a variety of indoor allergens in the immunopathogenesis of AEDS. House dust mite allergen has been the most intensively studied (25). An epidemiological survey of homes of patients with moderate to severe AEDS demonstrated substantially higher indoor dust mite concentrations than controls (26). Correlation between marked clinical improvement in mite-free environments and relapse with transfer to mite-infested environments has strengthened this association considerably (27).

Animal danders and cockroach allergen are also thought to participate in the induction of AEDS on an immunologic basis. However, the data are not as definitive as with other allergens. There have been studies showing the presence of sensitivity to animal danders and cockroach in children with AEDS, suggesting a definite role of these allergens in the induction of AEDS (28). Although these associations are likely to be true, further study is clearly needed to define the extent of animal dander and cockroach allergen in the pathogenesis of AEDS.

Fungal allergens have also been suspected in the etiology of AEDS. As with animal dander and cockroach, the data are largely inferential and need further study to reach a definitive level. However, Tuft et al. induced typical skin lesions in mould-sensitive patients using an inhalation challenge model with *Alternaria* and talc powder and pine pollen as controls (29). An interesting recent study found an almost exclusive sensitization to a fungus, *Malassezia sympodialis* (*M. furfur*) in patients with AEDS. This was not found in subjects with other allergic disorders or in normal

individuals (30). Specific IgE antibodies to *M. sympodialis* (*M. furfur*) have been detected in 70% of sera from *M. sympodialis*-sensitized patients with AEDS (31). The full extent of its contribution to AEDS requires further controlled studies.

Other yeast species have also been implicated in the pathogenesis of AEDS. *Pityrosporum ovale* and its gestational counterpart, *P. orbiculare*, are lipophilic yeasts that may reside in the skin of all humans. They are more commonly found over the face, neck and upper trunk in older children and adults rather than infants or younger children. There have been reports of significant correlations between active AEDS lesions and antibodies to *P. ovale* (32). The possible contribution of other yeasts, such as *Candida albicans* and *Trichophyton* sp., has also been implicated in the causation of AEDS, but the true extent of their contribution requires further controlled studies.

Micro-organisms

The role of micro-organisms in the pathogenesis of AEDS has been extensively studied. They are known to participate as complicating skin pathogens, as allergens, and as producers of superantigenic toxins (33). The most extensively studied micro-organism of importance in AEDS is *Staphylococcus aureus*. The colonization of both diseased and normal skin by *S. aureus* is increased in patients with AEDS. Studies have shown colonization in over 90% of lesions in some individuals with this condition (34). In addition, elevated IgE-specific anti-staphylococcal antibodies have been demonstrated in the sera of patients with AEDS. Recent studies have focused on the role of staphylococcal exotoxins in the disease process. It appears that these exotoxins function as super antigens perpetuating the immune response by stimulating T-cell proliferation independent of the usual allergic mechanisms (35). These super antigenic toxins may also contribute to the skin inflammation of nonallergic AEDS patients via the activation of T cells and the production of inflammatory cytokines (36). Other bacteria such as streptococcal species may play a role in the pathogenesis of AEDS, but there is a paucity of scientific data to document their precise role.

Autoantigens

Valenta et al. have observed the presence of IgE antibodies against human proteins in sera from patients with AEDS (37). Similar antibodies were not detected in patients with autoimmune disease, chronic urticaria, or graft-versus-host disease, or in healthy controls. Some of the autoallergens were cloned and found to be intracellular proteins (37). Later studies by Tan's group uncovered an IgE autoantibody against a transcription coactivator designated dense fine speckles (DFS) in 30% of sera from patients with AEDS when compared

to normal sera or sera from patients with autoimmune diseases (38). This autoantibody was also found in 16% of sera from patients with asthma. It is not yet clear whether these autoantibodies are merely an epiphenomenon or whether they play an active role in the immunopathogenesis of AEDS.

Non-immunologic triggers

Just as respiratory allergy may be affected adversely in a nonspecific manner, AEDS may also be secondarily affected by a variety of nonspecific environmental factors. They frequently act as triggers that exacerbate the disease, but are not involved in the primary pathogenesis of the condition. These nonimmunologic triggers of AEDS are briefly discussed below.

Irritants

Most patients with AEDS are aware that their skin is hyperresponsive to a variety of irritants. This is analogous to the nonspecific bronchial hyperresponsiveness seen in the asthmatic. Irritants can play a major role in flaring episodes of AEDS. Perhaps the most common source of skin irritation is bathing with hot water and detergent with vigorous scrubbing using a brush or washcloth (39). Cleansers with minimal defatting activity and neutral pH should be used rather than soaps. Clothing fabrics are also associated with varying levels of irritation. Chief among the fabrics with the potential to 'itch' or 'irritate' are coarse woollens (40). Synthetic fabrics such as polyester and rayon may also pose problems in patients with AEDS. Cotton is said to be the fabric with the highest potential for comfort. Nonsensitizing sunscreens should be used to avoid sunburn. A variety of household laundry detergents and cleaners (bleach, ammonia, laundry detergents, etc.) can act as irritants and cause AEDS to flare. Certain acidic foods can also act as irritants leading to pruritus, e.g. tomatoes, citrus fruits and strawberries.

Climatic conditions

Many patients with AEDS report seasonal variation with their disease. In general, most AEDS patients improve in the summer and worsen in the winter months (41). The improvement during summer months may be multifactorial in nature and related to improved sebum and perspiration, sun exposure, diminished exposure to micro-organisms causing infection, and possibly diminished exposure to indoor allergens. Heat- or exercise-induced perspiration are also common triggers in selected AEDS patients which may be related to an enhanced transepidermal water loss associated with an impaired function of the water permeability barrier (41). Patients with AEDS also have an abnormal pattern of

thermoregulation caused by an intrinsic disturbance of the parasympathetic system (42).

Psychological factors

Chronic dermatitis of any type can have significant impact on an individual's social interactions, psychological adjustment, work success, sexual relationships, and overall quality of life (43). One of the major problems for patients with AEDS relates to their poor sleep. They experience heightened pruritus at night and the resultant scratching is associated with frequent arousals. In turn, the nonrestorative sleep has a negative impact on daytime functioning including cognition and behaviour. A vicious cycle is established between the pruritus, scratching and intensification of dermatitis leading to heightened interpersonal stress and anxiety. There is evidence suggesting that stress and anxiety are associated with the release of neuropeptides as secretagogues of various effector cells which, in turn, secrete pruritogenic and proinflammatory mediators (44). It appears that psychological factors are especially important disease-modifying factors in children and adolescents.

Endocrine factors

There are reports of flare-ups in females with AEDS during the premenstrual period (45). Pregnancy has also been reported to have an adversely effect on AEDS in the first and second trimesters, improving in the final trimester (45). These studies suggest some endocrinological role in the pathogenesis of AEDS, but there is a paucity of corroborating data in this area.

Work-related factors

Based on everything that has been reviewed above, there is little question that some occupations will have a significant negative impact on the frequency and severity of AEDS. Factors which are a cause for concern include rapid changes in temperature, perspiration, almost all greases and greasy ointments, and work-related stress. Clinicians who treat patients with AEDS should advise them to seek occupations in which they can work without the constant hazard of skin irritation. It is preferable that counselling begin early during adolescence. However, patients can also change their occupation later in life with the assistance of rehabilitation agencies provided they possess a keen motivation to pursue this approach.

Summary

There are clear genetic, humoral and cellular differences between the allergic and nonallergic forms of AEDS as well as other atopic disorders. The allergic variants express local IgE production in the affected tissue and both allergic and nonallergic triggers play a major role in the expression of disease. The major immunologic triggers have been reviewed. In this respect, the role of allergens is very important in the immunopathogenesis of AEDS. However, though only playing a secondary modulatory role, many nonimmunological triggers can hamper treatment efforts and interfere with optimal response to therapeutic interventions.

References

- JOHANSSON SGO, HOURIHANE JOB, BOUSQUET J, BRUIJNZELL-KOOMEN C, DREBORG S, HOATELA T, et al. Position paper. A revised nomenclature for allergy. An EAACI position statement from the EAACI Nomenclature Task Force. *Allergy* 2001;**56**:813–824.
- LEUNG DYM. Atopic dermatitis: new insights and opportunities for therapeutic intervention. *J Allergy Clin Immunol* 2000;**105**:860–876.
- WOLLENBERG A, BIEBER T. Atopic dermatitis: from the genes to skin lesions. *Allergy* 2000;**55**:205–213.
- 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**:841–849.
- TAN BB, WEOLD D, STRICKLAND I, FRIEDMANN PS. Double-blind controlled trial of effect of housedust-mite antigen avoidance on atopic dermatitis. *Lancet* 1996;**347**:15–18.
- SCHAFER T, HEINRICH J, WJST M, ADAM H, RING J, WICHMANN HE. Association between severity of atopic eczema and degree of sensitization to aeroallergens in schoolchildren. *J Allergy Clin Immunol* 1999;**104**:1280–1284.
- STUBNER UP, GRUBER D, BERGER UE, TOTH J, MARKS B, HUBER J, et al. The influence of female sex hormones on nasal reactivity in seasonal allergic rhinitis. *Allergy* 1999;**54**:865–871.
- GREWE M, BRUIJNZEEL-KOOMEN CA, SCHOPF E, THEPEN T, LANGEVELD-WILDSCHUT AG, RUZICKA T, et al. A role for Th1 and Th2 cells in the immunopathogenesis of atopic dermatitis. *Immunol Today* 1998;**19**:359–361.
- NOVAK N, ALLAM JP, BIEBER T. Allergic hyperreactivity to microbial antigens – a trigger factor of the intrinsic form of atopic dermatitis? *J Allergy Clin Immunol* 2003;**112**:215–6.
- AKDIS CA, AKDIS M, SIMON D, DIBBERT B, WEBER M, GRATZL S, et al. Role of T cells and cytokines in the intrinsic form of atopic dermatitis. *Curr Probl Dermatol* 1999;**28**:37–44.
- OPPEL T, SCHULLER E, GUNTHER S, MODERER M, HARBERSTOK J, BIEBER T, et al. Phenotyping of epidermal dendritic cells allows differentiation between extrinsic and intrinsic forms of atopic dermatitis. *Br J Dermatol* 2000;**143**:1983–1988.
- NOVEMBRE E, CIANFERONI A, LOMBARDI E, BERNARDINI R, PUCCI N, VIERUCCI A. Natural history of 'intrinsic' atopic dermatitis. *Allergy* 2001;**56**:525–531.

13. NOVAK N, BIEBER T. Allergic and non-allergic forms of atopic diseases. *J Allergy Clin Immunol* 2003;**112**:252–262.
14. WUTHRICH B. Clinical aspects, epidemiology and prognosis of atopic dermatitis. *Ann Allergy Asthma Immunol* 1999;**83**:464–470.
15. ETAC STUDY GROUP. Allergic factors associated with the development of asthma and the influence of cetirizine in a double-blind, randomized, placebo-controlled trial: first results of ETAC. Early treatment of the atopic child. *Pediatr Allergy Immunol* 1998;**9**:116–122.
16. WUTHRICH B, SCHMID-GRENDELMEIER P. Natural course of AEDS. *Allergy* 2002;**57**:267–268.
17. SICHERER SH, SAMPSON HA. Food hypersensitivity and atopic dermatitis. Pathophysiology, epidemiology, diagnosis, and management. *J Allergy Clin Immunol* 1999;**104**:114–122.
18. GUILLET G, GUILLET MH. Natural history of sensitizations in atopic dermatitis. A 3-year follow-up in 250 children: food allergy and high risk of respiratory symptoms. *Arch Dermatol* 1992;**128**:187–192.
19. SAMPSON HA, BROADBENT KR, BERNHEISEL-BROADBENT J. Spontaneous release of histamine from basophils and histamine-releasing factor in patients with atopic dermatitis and food hypersensitivity. *N Engl J Med* 1989;**321**:228–232.
20. SAMPSON HA. Food allergy. Part I: Immunopathogenesis and clinical disorders. *J Allergy Clin Immunol* 1999;**103**:717–728.
21. TUFT L. Importance of inhalant allergens in atopic dermatitis. *J Invest Dermatol* 1949;**12**:211–219.
22. BRUIJINZEEL-KOOMEN CAFM, BRUIJINZEEL PLB. A role for IgE in patch test reactions to inhalant allergens in patients with atopic dermatitis. *Allergy* 1988;**43**:15–21.
23. REEKERS R, BUSCHE M, WITTMANN M, KAPP A, WERFEL T. Birch pollen-related foods trigger atopic dermatitis in patients with specific cutaneous T-cell responses to birch pollen antigens. *J Allergy Clin Immunol* 1999;**104**:466–472.
24. CLARK RA, ADINOFF AD. The relationship between positive aeroallergen patch test reactions and aeroallergen exacerbations of atopic dermatitis. *Clin Immunol Immunopathol* 1989;**53**:S132–S140.
25. TUPKER RA, DEMONCHY JG, COENRAADS PJ, HOMAN A, VAN DER MEER JB. Induction of atopic dermatitis by inhalation of housedust mite. *J Allergy Clin Immunol* 1996;**97**:1064–1070.
26. BECK HI, RORSGAARD J. Atopic dermatitis and housedust mite. *Br J Dermatol* 1989;**120**:245–251.
27. HARVING H, KORSGAARD J, DAHL R, BECK HI, BJERRING P. Housedust mites and atopic dermatitis: a case control study on the significance of housedust mites as etiologic allergens in atopic dermatitis. *Ann Allergy* 1990;**65**:25–31.
28. WANANUKUL S, HUIPRASERT P, PONGPRASIT P. Eczematous skin reaction from patch testing with aeroallergens in atopic children with and without dermatitis. *Pediatr Dermatol* 1993;**10**:209–213.
29. TUFT L, TUFT HS, HECK VM. Atopic dermatitis: role of the sweating mechanism. *J Invest Dermatol* 1950;**15**:333–337.
30. SCHMID-GRENDELMEIER P, FISCHER B, WUTHRICH B. IgE to *Malassezia furfur*: a serologic marker for the atopic eczema/dermatitis syndrome? *ACI Internat* 2002;**14**:140–142.
31. JONES S. Triggers of atopic dermatitis. *Immunol Allergy Clin N Am* 2002;**22**:55–72.
32. WESSELS MW, DOEKES G, VAN IEPEREN-VAN KIJK AG, KOERS WJ, YOUNG E. IgE antibodies to *Pityrosporum ovale* in atopic dermatitis. *Br J Dermatol* 1991;**125**:227–232.
33. LEUNG DYM, HAU P, STRICKLAND I, TRAVERS JB, NORRIS DA. The role of superantigens in human diseases: therapeutic implications for the treatment of skin diseases. *Br J Dermatol* 1998;**139**:S53:17–29.
34. LEUNG DYM, HARBECK R, BINA P, REISER RF, YANG E, NORRIS DA, et al. Presence of IgE antibodies to staphylococcal exotoxins on the skin of patients with atopic dermatitis. Evidence for a new group of allergens. *J Clin Invest* 1993;**92**:1374–1380.
35. BUNIKOWSKI R, MIELKE M, SKARABIS H, HERZ U, BERGMANN RL, WAHN U, et al. Prevalence and role of serum IgE antibodies to the *Staphylococcus aureus*-derived superantigens SEA and SEB in children with atopic dermatitis. *J Allergy Clin Immunol* 1999;**103**:119–124.
36. AKDIS CA, AKDIS M, SIMON D, DIBBERT B, WEBER M, GRATZL S, et al. T cells and T cell-derived cytokines as pathogenic factors on the nonallergic form of atopic dermatitis. *J Invest Dermatol* 1999;**113**:628–634.
37. VALENTA R, NATTER S, SEIBERLER S, WICHLAS S, MAURER D, HESS M, et al. Molecular characterization of an autoallergen Hom S₁, identified by serum IgE from atopic dermatitis patients. *J Invest Dermatol* 1998;**111**:1178–1183.
38. OCHS RL, MURO Y, SI Y, GE H, CHAN EK, TAN EM. Autoantibodies to DFS 70 kd/transcription coactivator P75 in atopic dermatitis and other conditions. *J Allergy Clin Immunol* 2000;**105**:1211–1220.
39. HANIFIN JM. Atopic dermatitis. *J Allergy Clin Immunol* 1984;**73**:211–222.
40. WAHLGREN CF, HAGERMARK O, BERGSTROM R. Patients perception of itch induced by histamine, 44/80, and wool fibers in atopic dermatitis. *Acta Derm Venereol (Stockh)* 1991;**71**:488–494.
41. STEIGER T, BORELLI S. Significance of climatic factors in the treatment of atopic eczema. In: RIZICKA, T, RING, J, PRZYBILLA, B, editors. *Handbook of Atopic Eczema*. Berlin: Springer Verlag, 1991:415–428.
42. HORNSTEIN OP, HEYER G. Responses of skin temperature to different thermic stimuli in atopic eczema. *Acta Derm Venereol (Stockh)* 1987;**144**:S149–152.
43. BENDER BG. Psychologic dysfunction associated with atopic dermatitis. *Immunol Allergy Clin N Am* 2002;**22**:43–52.
44. GIANETTI A, GIROLMONI G. Skin reactivity to neuropeptides in atopic dermatitis. *Br J Dermatol* 1989;**121**:681–688.
45. KEMMETT D, TIDMAN MJ. The influence of the menstrual cycle and pregnancy on atopic dermatitis. *Br J Dermatol* 1991;**125**:59–61.