

Review article

Epidemiology, clinical features, and immunology of the “intrinsic” (non-IgE-mediated) type of atopic dermatitis (constitutional dermatitis)

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Atopic dermatitis (AD) is a common, chronic relapsing, inflammatory skin disease, characterized by typically distributed eczematous skin lesions, dry skin, intense pruritus, and a wide variety of pathophysiologic aspects (1–4). The current knowledge of the genetic background and the immunopathogenesis of AD, as well as the role of environmental and other major provocation factors in this disorder, was recently reviewed in *Allergy* (3, 4). Thus, AD is a genetically determined, IgE-mediated, delayed-type hypersensitivity reaction of the skin (5, 6) that can be triggered by multiple factors, varying in their intensity in each individual patient and during different life phases (1–7).

The term “atopic dermatitis” was first proposed by Wise & Sulzberger in the 1930s, because of the close

association with other atopic diseases such as bronchial asthma (AB) and allergic rhinitis (AR) (8). The various other names, such as atopic eczema, intrinsic allergic dermatitis; neurodermitis constitutionalis, endogenous eczema, eczema flexurarum, Besnier’s prurigo, asthma-eczema, or hay fever-eczema, reflect the uncertainty in the understanding of the pathophysiology of this disease (9). The debate about the appropriate name is still going on, as all these definitions emphasize some aspects but may not cover all pathomechanisms or abnormalities. The revised nomenclature of allergic diseases, which appears in this issue of *Allergy*, proposes the term “constitutional dermatitis” for AD; however, in this review, the generally accepted term “AD” will still be used.

Abbreviations. AB: bronchial asthma (asthma bronchiale); EAB: extrinsic bronchial asthma; IAB: intrinsic bronchial asthma; AD: atopic dermatitis (constitutional eczema); EAD: extrinsic AD (IgE-mediated AD); IAD: intrinsic AD (non-IgE-mediated AD); APC: antigen-presenting cells; APT: atopy patch test; CLA: cutaneous lymphocyte-associated antigen; EDC: epidermal dendritic cells; LC: Langerhans cells.

Definition and diagnostic criteria of the intrinsic type of AD (IAD)

Although most patients with AD have high concentrations of total and allergen-specific serum IgE levels and positive skin prick and intracutaneous test reactions of the immediate type to common environmental aller-

gens, a subgroup of AD patients, both children and adults, suffer from a skin disease with features that clinically resemble the skin lesions and distribution pattern of AD, but that is not associated with sensitization to aero- or food allergens (3, 4, 7, 10–12). As the main clinical characteristic, these patients suffer from a “pure” type of AD, without previous or actual associated respiratory diseases (7, 11, 12). In analogy to the extrinsic and intrinsic types of asthma (13, 14), the term “intrinsic type of AD” (IAD) has been proposed as a counterpart to the term “extrinsic type of AD” (EAD) (11, 12, 15, 16) (Fig. 1). Other terms used are “nonallergic AD”, “nonatopic eczema”, or “nonatopic AD” (17). This subtype can be characterized by the following criteria:

- 1) clinical phenotype of AD, according to the criteria of Hanifin & Rajka (18)
- 2) absence of other atopic diseases such as allergic asthma and rhinoconjunctivitis (11, 12)
- 3) negative prick and/or intracutaneous skin tests for common inhalant and food allergens (11, 12, 19)
- 4) normal total serum IgE levels (according to the age classes) (10)

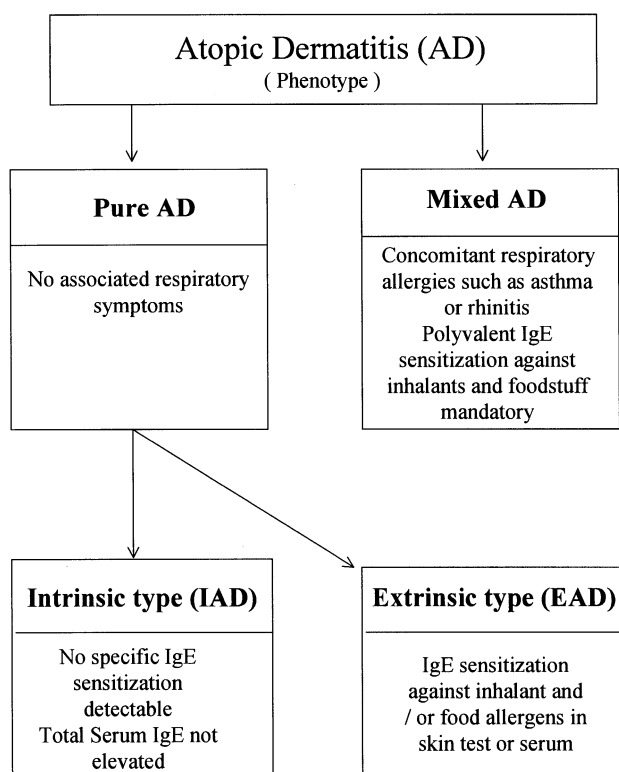


Figure 1. Classification of clinical phenotype “atopic dermatitis” (AD) into main types “pure” AD, without associated allergic respiratory diseases (ARD), and “mixed” type (AD with ARD). On basis of results of accurate allergologic investigation by means of skin tests and specific IgE determinations, “pure” AD can be subdivided into subtypes “extrinsic” (EAD) and “intrinsic” (IAD). Modified after Wüthrich (11, 12, 16).

- 5) no detectable specific IgE antibodies to common aero- and food allergens (e.g., Phadiatop, SX₁ RAST/CAP, and FX₅ RAST/CAP) (4, 7, 11, 12, 15–17).

In the following review, we emphasize various aspects of this particular subtype of AD. The distinction between the two types is not just academic. The clinician, the patient, and (in the case of children) the parents, respectively, have to know whether primary or secondary allergen-avoidance might be useful, as in EAD. In the case of IAD, a subsequent onset of respiratory diseases (“allergy march”) is quite improbable (19), and a long-term pharmacologic treatment with cetirizine, an H₁-histamine antagonist with anti-inflammatory properties, as a prevention of subsequent asthma, is not indicated (7, 20).

The epidemiology and clinical features of IAD

The frequency of patients presenting with IAD is quite variable, ranging from 16% (21) to over 25% in East German schoolchildren (22, 23), and up to 45% in a French study of children, the latter based on skin tests only (24). In our studies, we observed a frequency of IAD of up to 40% of all AD patients (7, 19, 25–28) (Table 1). A female predominance has been observed generally in AD, as well as in IAD, by several studies (27–29).

Patients with IAD tend to have a late onset of the disease, but otherwise family history and disease duration seem to be similar in IAD and EAD (15). The distribution and clinical features of the skin lesions do not differ either. A more frequent distribution in the head and neck area in IAD patients has been demonstrated by some studies, and this feature is also characteristic of AD associated with sensitization to fungi, mainly *Pityrosporum ovale* (30–33). Although rather improbable, sensitization to *P. ovale* might be missed, since *P. ovale* is not routinely included in skin prick tests and standardized extracts are not available.

Histologic differences have not been observed. The typical findings, such as epidermal spongiosis and a lymphocytic dermal infiltrate in acute-stage lesions, as well as acanthosis in chronic stages, are similar in both types of AD (15). The dermal cellular infiltrate in AD is dominated by T cells, but other cells such as eosinophils, mast cells, and antigen-presenting dendritic cells are also present.

Immunologic similarities and differences between EAD and IAD

Various immunologic parameters have been investigated in peripheral blood cells, as well as in biopsy samples of lesional skin or patch test reactions, in

Table 1. Frequency of IAD in various studies

Reference	No. of patients	Patients with IAD	Age (years)	Mean total serum IgE (kU/l)
Wüthrich et al. 1990 (25)	37	9 (24%)	14–60	62
Hochreutener 1991 (26)	40	15 (30%)	1–5	
Walker et al. 1993 (27)	25	5 (20%)	28 (17–56)	134 ± 39
Somos et al. 1993 (21)	58	11 (16%)		71.4
Kägi et al. 1994 (28)	33	14 (42%)	35.5 (19–55)	77.7 ± 88.6
Cabon et al. 1996 (24)	59	27 (45%)	5.2 (0–12)	89.3
Wedi et al. 1997 (46)	21	9 (43%)	39 ± 17	22.2
Wüthrich et al. 1999 (7)	93	17 (18%)	37	< 150
Schäfer et al. 1999 (23)*	2201	726 (25%)	5–14	76.7
Fabrizi et al. 1999 (29)	72	8 (11%)	36	n.g.
Akdis et al. 1999 (35)	1151	117 (10%)		< 200
Oppel et al. 2000 (64)	69	7 (10%)	Adults	76.7 ± 28.4

*Epidemiologic study in schoolchildren.

patients with EAD and IAD. Some of the main differences in the clinical and immunologic parameters are shown in Table 2.

T cells and B cells

Immunohistologically, the dermal infiltrate in AD mainly comprises CD4+ and CD8+ cells with a CD4/CD8 ratio similar to that in peripheral blood (17, 35). Numerous studies have shown the importance of activated CD4+ T cells in AD. Aeroallergens, food allergens, and superantigens are involved in the activation of T cells in AD (2, 3, 17, 34, 35). Numerous studies have shown the importance of activated CD4+ T cells in AD. Aeroallergens, food allergens, and superantigens are involved in the activation of T cells in AD (36, 37).

In IAD and EAD, different cytokine patterns of involved T cells have been observed in peripheral blood, as well as in lesional skin biopsies. A differential cytokine pattern in peripheral blood lymphocyte supernatants and skin was shown by

Kägi et al. (28). As a major difference, 19 EAD patients expressed elevated levels of IL-4 compared to 14 IAD patients. The low-affinity Fc receptor for IgE on B cells (CD23) shows increased expression in EAD (17, 27, 37). This surface molecule is upregulated by IL-4, IL-13, and IgE, and that may explain the lower expression in IAD (38, 39).

T-cell activation occurs in both types, as measurable by expression of soluble IL-2R+ and HLA-DR+ lymphocytes (28). Activated skin-homing T cells expressing the selective skin-homing receptor, the cutaneous lymphocyte-associated antigen (CLA), induce IgE mainly via IL-13, and prolong the eosinophil lifespan, mainly via IL-5 (17, 40). Most importantly, CLA expression in the skin of IAD and EAD variants does not show any difference (17).

In the skin, immunohistologic features correspond to a Th2 response (increased IL-4, IL-5, and IL-13 levels) in the acute stage, while chronic lesions show preferably a Th1-like pattern with increased levels of IL-12 and IFN- γ (41). Interestingly, IFN- γ , a key cytokine involved in the induction of T-cell-

Table 2. Various characteristics of IAD in comparison with EAD

	IAD	EAD	Reference
Skin manifestation	Similar	Similar	
Onset eczema	Later than EAD	Early (in childhood mostly)	(27–29, 64)
Sex	Slight female predominance	Slight male predominance	(27–29, 64)
Frequency	16–45% of AD-patients		
Total Serum IgE	< 150 kU/l	> 150 kU/l	Table 1
Specific IgE against common inhalant and food allergens	Negative	Positive	
Skin prick, intracutaneous tests with common inhalant and food allergens	Negative	Positive	
Eosinophilia	Mild-moderate	Mild-moderate	(27, 28)
Eosinophil survival	No difference from EAD		(35, 48)
ECP	No difference from EAD		(28)
T cells in peripheral blood	HLA-DR as in EAD		(27, 28)
Cytokines in peripheral blood	IL-5 levels as in EAD		(27)
	IL-4 levels low	IL-4 levels increased	(27)
B-cell activation	CD23 + B cells low	CD23 + B cells increased	(27, 28)
Epidermal dendritic cells	FcRI/Fc ϵ RII expression ratio < 0.5 (> 1.5 in EAD)	Ratio > 1.5	(64)
Cytokine derived from lesional skin	IL-5, IL-13 < EAD		(17)

mediated apoptosis in eczema, does not show any difference between IAD and EAD (42, 43), whereas a decreased capacity of skin T cells to generate IL-5 and IL-13 in IAD, compared to EAD, was demonstrated (17). Thus, T cells isolated from skin biopsies of EAD were able to induce a high IL-13-mediated IgE production in cocultured normal B cells, but not in IAD (35).

In conclusion, in AD, activated T cells predominate in the cell infiltrate of the skin. The two types of AD are reflected by their cytokine patterns: while IL-5 and IFN- γ are observed in rather similar amounts, IL-4 and mainly IL-13 are expressed in lower levels in IAD, especially in involved skin.

Eosinophils, mast cells, and basophils

Eosinophils are the hallmark of the late-stage inflammatory reaction in asthma and other allergic inflammations (43). In asthma and AD, eosinophils are recruited into the affected tissue to a much higher degree than in healthy individuals (44).

Prolonged eosinophil survival apparently plays a central role in the pathogenesis of asthma (45). This phenomenon has also been shown in AD (46). However, the role of eosinophils in AD is not clear (47, 48). Eosinophilic toxic granule proteins, as well as eosinophil-attractive chemokines such as eotaxin and its receptor, are increased in lesional skin (49, 50). As eosinophils are mainly effector cells, they may also act as immunoregulatory cells, and they seem to play an important role in the switch from a Th2-cytokine pattern in acute lesions of AD to a more Th1-like pattern in the chronic stage (51–53).

The number of blood eosinophils and serum ECP levels are elevated in both types of AD without differences between EAD and IAD (27, 28, 54). The survival times of eosinophils do not differ either (48).

Mast cells and basophils mediate the classical immediate-type hypersensitivity, triggered by allergen-induced cross-linking of specific IgE antibody bound to mast cells through high-affinity receptors. Except for acute urticarial reactions, this mechanism is not of major importance in the clinical manifestation of AD. Mast cells release a wide range of chemokines and cytokines that contribute to the recruitment and activation of other inflammatory cells, particularly eosinophils (55, 56). Differences in the numbers of mast cells in IAD and EAD have not been reported.

Antigen-presenting cells (APC)

The immune response to foreign proteins is strongly dependent on the efficiency of antigen uptake and presentation by antigen-presenting cells (APC). Langerhans cells (LC) and epidermal dendritic cells (EDC), as skin resident cells, play a crucial role in these

diseases (57). Dendritic cells, as well as APC, can be upregulated by various cytokines such as GM-CSF, which is overexpressed in AD (58).

The high-affinity receptor for IgE (Fc ϵ RI) has been demonstrated not only on mast cells and basophils, but also on LC and EDC (59, 60). An increased expression of the high-affinity receptor for IgE (Fc ϵ RI) on epidermal DC from the nonlesional and lesional skin of AD patients has been reported repeatedly (61, 62). The expression of Fc ϵ RI correlates with serum IgE level. It has been shown in animals that cross-linking of Fc ϵ RI substantially upregulates its own expression. The same observation was made in human patients treated with monoclonal anti-IgE antibodies (63). Oppel et al. found a lower expression of Fc ϵ RI on EDC in IAD patients than EAD patients (64). In EAD, the Fc ϵ RI/Fc ϵ RII expression ratio was above 1.5, in contrast to a ratio of 0.5 in IAD (62, 65). It is not yet clear whether the low levels of Fc ϵ RI found on EDC are a cause or a consequence of low local or serum IgE levels in IAD patients. However, it is known that Fc ϵ RI is upregulated in mast cells and basophils by the serum IgE concentrations (66). Regardless of the underlying mechanism, these findings underline the differences found in the inflammatory micromilieu between IAD and EAD.

The antagonizing effects of anti-IgE monoclonal antibody treatment in AB suggest that IgE-mediated antigen presentation plays a major role in Th2 cytokine production, lung eosinophilia, and bronchial late-phase responses (67, 68). Therefore, it will be very interesting to observe the effect of anti-IgE treatment in both types of AD.

The role of IgE in AD

The role of allergens and IgE-mediated reactions in AD remains controversial. Besides the presence of positive skin tests or specific IgE directed against inhalant or food allergens, it is known that skin contact or inhalation of these allergens may provoke flare-ups in AD patients (12, 69).

In allergy to house-dust mite it could be demonstrated that the avoidance of allergen exposure is effective in preventing exacerbation of AD (70, 71). In a recent study, Schäfer et al. demonstrated a significant correlation between disease severity and degree of sensitization to perennial indoor allergens such as *Dermatophagoides pteronyssinus* and cat epithelium (23). These authors also observed a higher rate of allergic sensitization to food and aeroallergens in children with severe AD than in those with mild or moderate AD. Moreover, sensitization to fungal allergens (*Malassezia furfur*) can also correlate with disease activity (72).

None of these studies allow conclusions on whether

atopic eczema precedes the development of allergic sensitization, or vice versa. The fact that AD usually develops very early in life, whereas allergen-specific antibodies usually appear later in infancy (73), seems to point to the first conclusion. Since most AD patients have a dry skin and a damaged skin barrier, this way of allergen penetration and sensitization may be of great importance. In a mice model, it was shown that primary sensitization to aeroallergens through the skin does indeed occur, followed by an allergen-specific IgE response (74). Compared to allergic AB and AR, where the role of IgE is evident, the influence in AD of immunologic mechanisms other than IgE-mediated ones, as well as nonimmunologic factors, seems much more prominent.

Genetic background and environment

Both environmental and genetic factors are thought to be important in the pathogenesis of AD. Twin studies strongly support the importance of inheritance (75, 76). Genes that are potential candidates include regions coding for atopy, AD, and IgE regulation, and have been reviewed in *Allergy* recently (4). These potential candidate genes are closely related to IgE synthesis such as areas coding for IL-4 and IL-13, their receptors, signal transduction pathways, and variants in the promoter area of these cytokines and the IgE susceptibility (77, 78).

On the assumption of identical genetics in the German population, recent epidemiologic studies comparing populations in the former West and East Germany point out the role of environmental factors in AD (79). The prevalence of AD in children was significantly higher in East than West Germany. However, the frequency of IgE-mediated sensitization to environmental allergens in AD-affected children was much higher in West Germany. Prospective studies involving large cohorts of patients will probably help to reveal the relevance of genetics and environment in AD, especially their roles in the two subtypes. So far, no data comparing the genetics of the two subtypes of AD are available.

Autoallergens and their role in the various types of AD

Already in the 1920s, it was reported that human skin dander can trigger immediate-type skin reactions in individuals with severe AD and to a lesser extent in patients with bronchial asthma (80, 81). The fact that human skin dander induces PBMC proliferation raises the hypothesis of autoimmune reactions in AD (82). Recently, the presence of autoantibodies against human proteins in sera from patients with AD has been reported (83–85). The molecular analysis of allergens has revealed striking similarities between environmental

allergens and human proteins. Five of these autoantigens representing cytoplasmic proteins in human keratinocytes have been cloned and designated Hom s 1 to Hom s 5 (84). IgE antibodies against Hom s 1 could be detected only in patients with AD, but not in patients with other skin diseases such as chronic urticaria and systemic lupus erythematosus, or in healthy control subjects. In addition, autoantibodies to another autoantigen, the dense fine speckles 70-kDa antigen (DFS 70), a nuclear protein, have recently been described in AD (85). DFS 70 autoantibodies have been found in 30% of patients with AD, but to a lesser extent also in patients with asthma or interstitial cystitis. The limitation of this study is that all analyses were done in sera, while skin samples have not yet been investigated for the expression of this antigen.

Although the autoallergens characterized until now are mainly intracellular proteins, they have also been detected in IgE immune complexes. This suggests that the release of these autoallergens from damaged tissues could trigger allergic responses. Autoantibodies of the IgE type have been found not only in patients with elevated total serum IgE levels but also in those with normal IgE (83). The severity and exacerbation of AD are correlated with IgE autoreactivity in some patients.

Autoallergens might also be relevant in patients with IAD. Because current routine allergologic tests such as skin tests or specific IgE measurement do not detect autoallergens, their identification might be missed. However, the immunologic differences found between EAD and IAD cannot be sufficiently explained by the presence of autoreacting antibodies instead of IgE directed against environmental allergens. In IgE-mediated reactions, one would expect a similar cytokine pattern irrespective of the allergen. Thus, further studies are needed to allow an insight into the immunologic processes involved in autoallergenicity in relation with IAD.

The atopy patch test – a new diagnostic tool in AD

It is possible to elicit eczematous skin reactions after epidermal application of aeroallergens or food allergens (69, 86). These so-called atopy patch tests (APT) are classical T-cell-mediated skin reactions (87, 88). The APT with the house-dust mite *D. pteronyssinus* is positive in up to 44% of AD patients, and shows high concordance with clinical history, skin prick test, and CAP-RAST (29). The APT is assumed to evaluate the clinical relevance of IgE-mediated sensitizations in AD patients. While some authors found an association with an air-exposed pattern of AD (69, 88, 89), others could not confirm this observation (90). Various investigations have shown the involvement of allergen-specific T cells in APT reactions or in food-responsive AD (37). AD patients with positive APT have higher surface

IgE-bearing CD1a+ cells in the dermis as well as in the epidermis than patients with negative APT (90). Interestingly, 3–5% of IAD patients show positive APT to inhalant or food allergens (89, 90). In another report, positive patch tests to *D. pteronyssinus* and various food allergens were found in 17 of 40 patients with IAD (29). Using APT as a model, further studies will help to elucidate the different tissue microenvironment in the two types of AD.

Comparison of the intrinsic types of AD and bronchial asthma

AD and AB belong to the atopic diseases and frequently occur together in the same patient. They represent inflammatory diseases with involvement of T helper cells (mostly Th2 type) and eosinophils. Two subtypes are distinguished in AB – an extrinsic (atopic) type (EAB) and an intrinsic (nonatopic) type (IAB) (13, 14, 91). In the intrinsic type of AB, patients present with negative skin tests, no specific IgE against common inhalant and food allergens, and a normal total serum IgE. The same features are taken to define IAD. The frequency of the intrinsic type of asthma is 10–30% and therefore is comparable to that of IAD (13, 14). IAB is also slightly more common in females. At the time of disease manifestation, patients with IAB are usually older than their extrinsic counterparts. Just as in IAD, IAB patients show an onset of symptoms later in life, often associated with a more severe clinical course (92, 93). In both AD and AB, the susceptibility to irritant or psychological stimuli is increased (94).

In a recent review, Humbert et al. pointed out that immunologic findings are rather similar in both the extrinsic and intrinsic types of asthma (14). No major differences can be observed in bronchial biopsies. Both types show marked eosinophil infiltration and enhanced expression of Th2-type cytokines (mainly IL-4, IL-5, and IL-13), CC chemokines, and IgE receptor (FcεRI). The main differences are seen in the peripheral blood, the extrinsic asthmatics showing higher total serum IgE

levels, with blood eosinophilia being more pronounced in the intrinsic type. The authors conclude that the local inflammatory processes might be the same in both types. They postulate that IgE production must be local rather than general in the intrinsic type. In contrast, in the two types of AD, as discussed before, it has been possible to detect local differences in cytokine expression and IgE production in lesional skin.

Conclusions

IAD is a variant of AD that fulfills the most commonly used diagnostic criteria for AD. These patients show normal total serum IgE levels, no specific IgE, and negative skin prick tests to environmental or food allergens. IAD is found in a relevant proportion of all AD patients at a frequency of 15–45%. Some studies revealed a slightly later onset than for EAD. In general, there is a female predominance in AD. Clinically, IAD cannot be separated from EAD.

Immunologic differences between IAD and EAD in cell and cytokine pattern can be located mainly in the affected skin, but also in peripheral blood. Differences in the capacity to produce IL-13 by skin T cells might be responsible for the variation of IgE production. The positive APT with IAD point to the importance of T-cell-mediated reactions. Differences of IgE regulation may be explained by a different genetic background in IAD and EAD patients, but also by varying exposure to environmental stimuli. However, an increased susceptibility of the skin to external and internal stimuli can be observed in the intrinsic type in the same manner as in the extrinsic type of AD.

Today, we see the intrinsic and extrinsic types of AD as two types of one disease with identical clinical features. They can be distinguished by different cytokine levels and cell activation that lead to an increased IgE production in EAD. The current explanations of this distinction are based on differences in genetics and/or environmental conditions.

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