

Original article

Low prevalence of the intrinsic form of atopic dermatitis among adult patients

Background: Atopic dermatitis (AD) is a chronic inflammatory skin disease commonly associated with respiratory allergies such as rhinitis and asthma, and a high serum level of IgE. In contrast to the 'classic' IgE-mediated allergic (extrinsic) form of AD, approximately 20% of the patients are reported to show normal IgE levels, lack of sensitizations towards environmental allergens, and absence of associated respiratory allergies. Accordingly, these patients are assigned to a nonallergic (intrinsic) form of the disease.

Objectives: In order to define these two forms of AD more closely, 259 adult patients with AD were investigated.

Results: After a thorough diagnostic workup there were 18 patients (6.9%), who fulfilled the criteria of intrinsic AD. After follow-up, four additional patients had developed respiratory allergies or IgE-mediated sensitizations resulting in an overall proportion for intrinsic AD of 5.4%.

Conclusions: Based on these figures the nature and relevance of the intrinsic form of AD deserves further evaluation.

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Atopic dermatitis (AD) is a chronic inflammatory skin disease, most often affecting children and adolescents with an age-related prevalence of about 10% in the industrialized populations. Recently, the distinction of an extrinsic (allergic) and an intrinsic (nonallergic) etiology, a classification well established in asthma, has been introduced in the concept of AD (1, 2). Several authors have considered intrinsic atopic dermatitis (iAD) to be a distinct disease entity with a unique immunological pathogenesis (3–5).

There is still an ongoing debate about the classification of AD. Accordingly, the nomenclature varies between the different concepts of AD, as reflected in designations like intrinsic/extrinsic AD, eczema/dermatitis syndrome (AEDS) (6), but also 'atopiform dermatitis' (7).

In order to reassess the prevalence and associated factors of these different forms, 259 adult patients with AD were investigated and classified according to established 'extrinsic' criteria.

Materials and methods

A diagnosis of AD according to the criteria of Hanifin and Rajka (8) was made in 259 adult patients (male : female = 77 : 182, age 20–75 years, median age 32 years) attending the dermatological outpatient ward between 1992 and 2001. According to established criteria (2), the intrinsic form of AD was defined by low total serum IgE serum levels (< 200 kU/l), the absence of associated respiratory diseases, and a lack of allergen specific serum IgE antibodies and

negative skin prick tests (SPT) for common allergens. Both forms (intrinsic and extrinsic AD) were compared regarding clinical features and personal history. Disease severity was determined by SCORAD (9). In patients assigned to the intrinsic form, repeated follow-up investigations were performed during an average time period of 7.5 years (2–16 years) to achieve data about the course of intrinsic AD.

The concentration of total IgE and specific IgE-antibodies were measured by CAP-FEIA and RIA commercial kits, respectively, according to manufacturers instructions (Pharmacia, Freiburg, Germany). The range of antibodies tested varied, but a minimal set of antibodies (*Dermatophagoides pteronissinus* and *D. farinae*, cat dander, birch pollen, grass pollen, apple, and nut) was tested in all patients. All assay measurements were performed in duplicate.

Results

Out of the 259 patients, 83 (32%) showed low IgE-levels (< 200 kU/l). Thirty-two of these (39%) suffered from allergic rhinitis and/or asthma. Among the remaining 51 patients, however, we could detect specific sensitization by IgE-antibodies in serum or by SPT in 33 individuals. According to these selection criteria, 18 patients (6.9%) belonged to intrinsic form of AD (Fig. 1). Only two of these patients were male (11%) as opposed to 75 (31%) in the group of patients with eAD.

As shown in Table 1, patients with iAD had a significantly higher age of onset, and a lower severity of the disease as shown by a significantly lower SCORAD

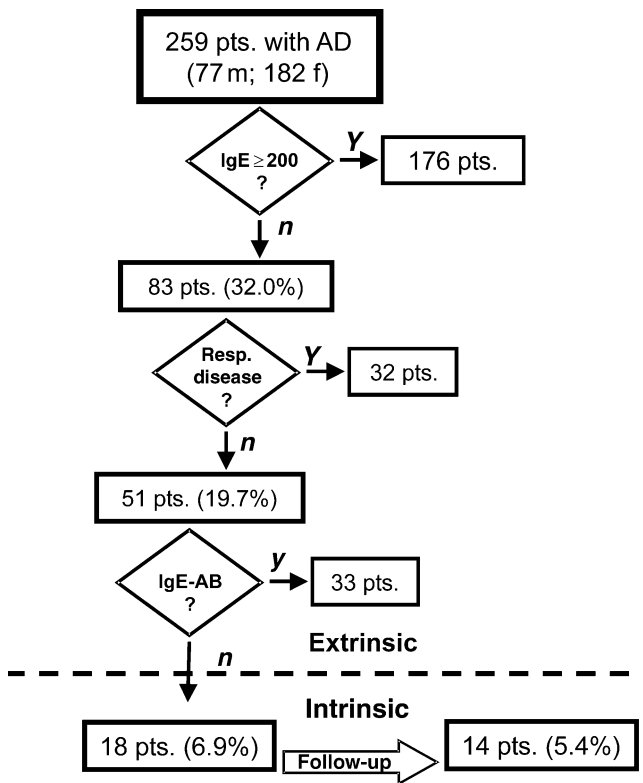


Figure 1. Pts, patients; AD, atopic dermatitis according to Hanifin/Rajka; N, no; Y, yes; m, male; f, female; IgE, serum level of IgE; resp. disease, respiratory diseases including allergic rhinitis and allergic asthma; IgE-AB, specific IgE sensitization demonstrated by skin test or *in vitro* serum test. During follow-up, four additional patients developed allergic respiratory disease or specific IgE.

Table 1. Characteristics of patients with atopic dermatitis

	Extrinsic (n = 241)	Intrinsic (n = 18)	P
Patients [n]			
Male	75	2	
Female	166	16	n.s.
Age [years], median (range)	32 (20–75)	32 (23–60)	n.s.
SCORAD, median (range)	54 (15–89)	27 (23–60)	<0.001
Age of onset [years], median (range)	3 (0–48)	15 (0–58)	<0.05
Positive family history, n (%)			
Atopic dermatitis	64 (27)	1 (6)	<0.05
Allergic asthma	27 (11)	0 (0)	n.s.
Allergic rhinitis	68 (28)	5 (28)	n.s.

Clinical characteristics of 259 patients with atopic dermatitis (AD) according to Hanifin/Rajka. Intrinsic AD was defined by serum IgE levels <200 kU/l, absence of respiratory allergies, and lack of specific IgE antibodies in serum and/or positive skin prick test. P denotes significance of differences between both groups (chi² test or Mann–Whitney test, as appropriate). n.s., not significant.

value. The clinical appearance was otherwise similar in both groups, in particular flexural eczema in 88% vs 91% face and neck in 82% vs 90%, and hand eczema in 22% vs

17% in the intrinsic compared with the extrinsic patients, respectively. Remarkably, a prurigo (Besnier) pattern was only observed in 11% of patients with the extrinsic form, but none in the intrinsic group (*P* = 0.2; chi²).

Less often, patients with iAD had a positive family history for atopic diseases when compared with patients with the extrinsic form. In particular, this applied to the presence of allergic asthma and AD in first degree relatives, while allergic rhinitis showed similar prevalences in family history.

A follow-up examination of patients with the intrinsic form took place after a median follow-up time of 7.5 years. Eleven out of 18 patients still suffered from chronic eczematous skin problems at follow-up. IgE levels remained <200 kU/l in all follow-up investigations, but four out of the 18 patients with intrinsic AD had developed respiratory allergies, resulting in a 5.4% rate of iAD among the whole study population (*n* = 259) (Table 2).

Discussion

In our study only 6.9% of the patients fulfilled the criteria of intrinsic AD at the time of initial evaluation. After follow-up, this rate even dropped down to 5.4%. This rate appears to be extremely low in comparison with the data from the literature.

Reasons for this discrepancy may be related to the inhomogeneity of patient groups, especially regarding age of patients and severity of disease. However, the high prevalence of 45% of patients presenting with intrinsic AD, as cited in several articles (2–4) does not reflect the actual results of the respective study by Cabon et al. (10). These authors evaluated delayed contact reactions to aeroallergens in children with AD, and discussed their relevance in the context of prick testing, contact allergen patch testing, and specific IgE. Although ‘intrinsic’ and ‘extrinsic’ forms of AD were evaluated separately, the study did not claim to investigate the prevalence of iAD.

Among all studies investigating the prevalence of iAD, only Schäfer et al. (11) are reporting data from a large population-based sample. However, the high prevalences for iAD of 49.6–63.5% found in this study are solely based on SPT of selected allergens and do not take into account other allergens, personal history, or total IgE values.

Several other studies provide hospital-based prevalence rates ranging from 10% to 42% (1, 4, 5, 12–15) using more or less stringent criteria. Most of these studies give no precise definition of their sampling methods, leaving the possibility of selection bias.

In general, the prevalence rates given by these studies tended to be higher in younger individuals when compared with adults. It might well be that in very young children, a transient form of eczema exists for which the relatively high percentage of 15–45% iAD might be true.

Table 2. Characteristics of patients with intrinsic AD

Pat. No.	Sex M/F	Age (years)	Age of onset (years)	IgE (kU/l)	SCORAD	Extent L/G	Localization of eczema				Eczema		Rhinitis		Family history for atopy	
							Flexural	Hands	Face/neck	ED	Parents	Sibs	Parents	Sibs	Asthma	Sibs
1	M	33	20	13	13	L	Yes	Yes	Yes	No	No	No	No	Yes	No	No
2	F	37	24	2	16	L	No	No	Yes	No	No	Yes	No	No	No	No
3	F	33	2	87	21	L	No	No	Yes	No	No	No	No	No	No	No
4	F	37	10	13	22	L	Yes	No	Yes	No	No	No	No	No	No	No
5	F	60	58	3	22	L	Yes	No	No	No	No	No	No	No	No	No
6	F	31	23	23	24	L	Yes	No	Yes	No	No	No	No	No	No	No
7	F	27	6	61	26	L	Yes	No	No	No	No	No	No	No	No	No
8	F	28	0	25	27	L	Yes	No	Yes	No	No	No	No	No	No	No
9	F	29	0	3	27	L	Yes	Yes	No	No	No	No	No	No	No	No
10	F	23	20	11	28	L	Yes	No	Yes	No	No	No	No	Yes	No	No
11	F	26	0	37	28	L	Yes	Yes	Yes	No	No	No	No	No	No	No
12	F	23	1	120	30	L	Yes	No	Yes	No	No	No	No	Yes	No	No
13	F	35	28	9	40	G	Yes	No	Yes	No	No	No	No	No	No	No
14	F	57	53	37	48	G	No	No	No	Yes	No	No	No	No	No	No
15	F	25	2	12	53	L	Yes	No	Yes	No	No	No	No	Yes	No	No
16	M	58	50	53	59	L	Yes	No	Yes	No	No	No	No	No	No	No
17	F	33	29	50	67	L	Yes	Yes	Yes	No	No	No	No	No	No	No
18	F	23	3	75	69	G	Yes	No	Yes	No	No	No	Yes	No	No	No

Clinical characteristics of the 18 patients fulfilling the criteria for intrinsic atopic dermatitis (AD). At follow-up, four of them (Nos 3, 8, 9, 16) had developed allergic respiratory diseases.

Age, age at first visit; Extent, extension of affected areas at first visit; L, localized; G, generalized; ED, erythrodermic.

In fact, we and others have shown that many cases of this so-called 'eczema infantum' may spontaneously resolve and not develop into typical AD (16). It might also be that some forms of iAD are triggered by sensitization to completely different antigens, e.g. microbials (17), but proof for such a correlation is lacking.

Novembre et al. (18) investigated the persistence of AD and the development of respiratory allergic diseases in a group of 111 children seen at the ages of 2 and 11 years according to SPT at those ages. On re-evaluation 9 years later, more than half of patients who were SPT-negative at baseline became positive at follow-up. Therefore, we have to consider the delayed appearance of respiratory allergies in infants with AD. This 'atopic march' is in line with our results, as four out of 18 patients of the intrinsic group had developed respiratory allergies at follow-up and this further reduced the prevalence of this form.

A recent study focused on atopy patch testing (APT) with house dust mites in adult male patients with intrinsic and extrinsic AD (12). Basically, the concept of APT reactions resembles the model of extrinsic AD with FcεRI+CD1a+ epidermal cells elucidating an eczematous reaction which is driven by an environmental antigen (19, 20). Interestingly, in contrast to what would have been expected, APT positivity turned out to be more frequent in iAD (66.6%) than in eAD (47.4%) (12).

In fact, positive APT results in patients with intrinsic AD have previously been described and these patients were reported to be sensitive to worsening of their skin condition after exposure to the respective allergens (14).

All together our and other findings suggest that patients suffering from 'intrinsic' AD may rather represent the 'milder edge' of an overlapping spectrum of clinical phenotypes in AD. Disease severity, IgE level, and the association with respiratory allergies appear to be closely correlated (1, 21). Therefore, the prevalence of eAD might be higher among patients with a high SCORAD. In addition, the later age of onset of the intrinsic form also corresponds to a milder form of eczema. Concerning the family history for atopic diseases, the prevalence of AD was significantly higher among relatives of the extrinsic than among relatives of the intrinsic form. Interestingly this was not seen for allergic rhinitis, suggesting that genetic heterogeneity may contribute to the phenotypic features of iAD. As in other studies, we found a much higher prevalence of iAD in females when compared with males, the reasons for this effect being completely unknown.

In conclusion, the apparently low prevalence of 'pure' intrinsic AD among adults, and so far conflicting immunological findings suggest that the concept of intrinsic vs extrinsic AD might need further critical evaluation.

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