

The Natural History of Sensitizations to Food and Aeroallergens in Atopic Dermatitis: A 4-Year Follow-Up

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Abstract: The natural history of atopic dermatitis (AD) is variable. Generally the dermatitis disappears during the first years of life, but it is often followed by the appearance of allergic respiratory diseases (ARDs). Our aim was to establish the risk factors for developing an ARD in children with AD. We followed up for 4 years 78 children (51 boys, 27 girls) with mild (26%), moderate (48%), and severe (26%) AD (clinical score proposed by Rajka and Langeland). In all the patients IgE serum levels were checked and skin prick tests (SPTs) were performed at the first examination. The SPTs were repeated in 68 children at the end of the study. The children with severe AD had significantly higher IgE serum levels than those with mild or moderate AD. SPTs at the first observation were positive in 47% of cases, mostly in patients with severe AD, with a prevalence of food allergens, particularly in younger patients. At the second observation, SPTs were positive in 65% of cases, including 100% of children with severe AD. Inhalants were the most common allergens. An ARD appeared in 38% of all patients: in 75% of those with severe AD and in 54% of those with a positive first SPT. Allergic screening should be carried out at an early age, especially in severe AD, since SPT positivity to food allergens, associated with severe clinical AD symptoms and a high IgE serum level, identifies those children ages 0–3 years at high risk of development of ARD.

Atopic dermatitis (AD) is the most common childhood dermatitis. It generally starts in infancy and has a variable prognosis: it may be long lasting (1,2), but in most patients it disappears during the first years of life (3). Several factors suggest a role for IgE-mediated hypersensitivity in AD: about two-thirds of children have a positive family history for atopic disease (4); serum IgE

level is increased in more than 50% of children with AD (5); most children have skin prick tests (SPTs) and/or radioallergosorbent tests (RASTs) positive for food or aeroallergens (5,6), and more than 50% develop allergic respiratory diseases (ARDs), that is, asthma and/or rhinoconjunctivitis (6–8).

The aim of our study was to investigate changes in

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SPTs for food and inhalant allergens in a group of children with AD followed up for at least 4 years and to correlate these data with the appearance of an ARD.

METHODS

Patients

A group of 78 children affected by AD, whose diagnosis was made on the basis of Hanifin and Rajka's criteria (9), was followed up for a period of at least 4 years. The children (51 boys and 27 girls) were 2 months–3 years of age (mean age 14 months) at the time of the first examination. Mean age of onset of AD was 6 months (range 1 month–2 years) and no child had any ARD.

During the study, lasting at least 4 years, a clinical evaluation was performed using the clinical score proposed by Rajka and Langeland in 1989 (10), considering the intensity, extent, and course of lesions. The intensity of skin lesions was measured by the itch level (mild, moderate, severe); the extent was measured as the affected percentage of the total body surface (less than 18%, 18–54%, more than 54%); the course was evaluated in relation to the length of the remission period (more than 3 months of remission in 1 year, less than 3 months, persistent course). Each parameter was evaluated on a scale of 1 to 3 and the final score was obtained by summing the scores of the three parameters. Patients with a total score of 8–9 were considered to have severe AD, while those with a total score of 3–4 were considered to have mild AD; those with a total score of 5–7 were considered to have moderate AD.

All patients were treated according to the severity of their disease with antihistamines, emollient ointments, and topical steroids. In addition, we suggested delaying introduction of the most allergenic foods in children less than 1 year of age or a dietary restriction in the other patients, following the procedure proposed in the Consensus Conference by the Italian Allergologic and Immunologic Pediatric Group (11).

Laboratory Studies

IgE serum levels (PRIST, Pharmacia, Sweden) were checked in all 78 children at the first examination and compared with normal control values (12). SPTs were performed in all patients at the first examination and were repeated in 68 children at the end of the study. The battery included various food allergens (Bayropharm DHS, Italy) (cow's milk, chicken's eggs, cereals, fruits, fish, legumes, tomato) and inhalant allergens (grass pollen, *D. pteronyssinus*, *D. farinae*, cat and dog dander). Molds and other antigens were used to assess potential hypersensitivity in the second SPT.

Positivity was evaluated by comparing the wheal of the allergen with that of the histamine, as previously described (11). Food or inhalant allergens eliciting a mean wheal diameter of 3 mm or more than the negative control were considered positive.

Statistical Analysis

The data obtained were elaborated through DBIII (Aston Tate) and SPSS/Pc (SPSS Inc – Microsoft); chi-squared test with Yates correction and Fisher's exact test were used.

RESULTS

A family history positive for atopy was present in 35 of our 78 children (45%). We diagnosed mild AD in 20 children (26%), moderate AD in 38 (48%), and severe AD in 20 (26%).

At the time of the first examination, IgE total serum level was increased in 26 patients (33%): 14 of 58 with mild–moderate AD (mild and moderate AD were considered together since the mean IgE values of the two groups were similar) and 12 of 20 with severe AD. This difference is statistically significant ($p < 0.0033$).

The SPTs performed at the first examination were positive to one or more allergens in 37 of 78 (47%) and negative in 41 of 78 children (53%). Of the 20 patients with mild AD, 7 (35%) showed positive SPT, while 13 (65%) showed negative SPT. Of the 38 patients with moderate AD, 17 (45%) showed positive SPT, while 21 (55%) showed negative SPT. Of the 20 children with severe AD, 13 (65%) showed positivity to one or more SPTs and only 7 (35%) showed SPT negativity. This difference is statistically significant ($p < 0.035$) (Table 1). The SPTs performed at the first examination showed positivity only to foods in 23 patients (66%), while only 12 patients, 11 of whom were children over 12 months of age, showed positivity also to inhalants. The positive SPTs at the first examination are reported in Table 2.

After 4 years of follow-up, 68 patients repeated the SPT, of whom 19 had severe AD, 33 moderate AD, and 16 mild AD. At the second examination, SPTs were positive in 44 of 68 (65%) and negative in 24 of 68 cases (35%). The positive SPTs at the second examination are reported in Table 2 and compared with the positive SPTs of the first examination.

At the second examination none of the patients with severe AD had a negative SPT (Table 1). In contrast, in the patients with mild or moderate AD, we observed that only about one-third of patients (10 of 28) negative at the first SPT became positive at the second SPT.

After the 4 years of follow-up we clinically reexamined all 78 patients. In 69 of them (88.5%) a marked

TABLE 1. Correlation Between AD Clinical Score and Skin Prick Test at First and Second Examination

Clinical Score	First Examination					Second Examination				
	Food	Prick Positive		Prick Negative	Total Cases	Food	Prick Positive		Prick Negative	Total Cases
		Inhalants ± Foods	Total				Inhalants ± Foods	Total		
Mild	4 (57%)	3 (43%)	7 (35%)	13 (65%)	20	1 (17%)	5 (83%)	6** (37%)	10** (63%)	16
Moderate	10 (59%)	7 (41%)	17* (45%)	21* (55%)	38	2 (10%)	17 (90%)	19** (58%)	14** (42%)	33
Severe	9 (70%)	4 (30%)	13* (65%)	7* (35%)	20	—	19 (100%)	19** (100%)	—**	19
Total	23 (62%)	14 (38%)	37 (47%)	41 (53%)	78	3	44 (65%)	44 (65%)	24 (35%)	68

*p < 0.035, **p < 0.001.

TABLE 2. Positive Skin Prick Tests at the First and Second Examination

	First Examination (78 Cases)		Second Examination (68 Cases)	
	N	%	N	%
Food allergens				
Chicken's egg	28	76	10	23
Cow's milk	6	22	5	11
Legumes	4	11	6	14
Fish	2	5	1	2
Cereals	2	5	4	9
Tomato	1	3	4	9
Fruits	—	—	2	4
Aeroallergens				
Grass pollen	6	16	29	66
House dust mite	6	16	22	50
Cat	1	3	10	23
Alternaria	ND	ND	13	29
Ragweed	ND	ND	6	14
Dog	ND	ND	3	7
Horse dander	ND	ND	1	2
Positive for at least one of the above allergens	37	47	44	65
Negative	41	53	24	35

Some children have multiple positivity tests.
ND = not done.

improvement or a complete resolution of AD was seen; in 53 of these 69 patients AD had been mild or moderate, whereas in the remaining 16 patients AD had been severe. No change in AD severity was seen in 9 patients (11.5%), 5 of whom had had mild-moderate AD and 4 severe AD.

At this evaluation an ARD was noted in 30 children (38%), rhinoconjunctivitis in 9, and asthma in 21; in 7 of these 30 patients AD had completely disappeared when an ARD started. Of the 30 patients in whom an ARD developed, 14 belonged to the group of patients with a high IgE level. The correlation between the AD clinical score and the appearance of an ARD is summarized in Table 3.

TABLE 3. Appearance of ARD and Correlation to AD clinical score after a 4-year follow-up and skin prick test at the first examination

Severity of the Disease	Evolution the ARD	Allergen Positivity at First Skin Prick Test
Mild (20 cases*)	3 (15%)*	1 (inhalants)
Moderate (38 cases*)	12 (32%)*	5 inhalants 2 foods
Severe (20 cases*)	15 (75%)*	3 inhalants 9 foods

*p < 0.005.

First Skin Prick Tests	Evolution of ARD
Positive (37 cases*)	20 (54%)*
Negative (41 cases*)	10 (24%)*

*p < 0.014.

DISCUSSION

The development of atopic disease is now considered to be the result of a complex interaction between genetic (determinant tendency to atopy) and environmental factors, but the role of allergens in the pathogenesis of AD has only been demonstrated in slightly more than 50% of cases (13). In fact, the existence of the so-called non-atopic or intrinsic form of AD has been postulated as being characterized by a negative personal and family history of atopy, normal serum IgE level, absence of specific IgE, and negative SPT (14). Recent studies indicate that in some patients with AD, contact of the skin with environmental inhalant allergens mediates an allergen-specific immune response through Langerhans' cells (4).

AD is often followed by the appearance of an ARD, especially asthma. In a preliminary retrospective study we observed that aeroallergen-positive SPTs may be predictive of the development of an ARD (15). In addition, previous studies demonstrated a relationship between food allergy in early infancy and a more severe prognosis of AD, as well as the subsequent development of one or more ARDs (16,17). In our prospective study we fol-

lowed 78 children with AD to evaluate the predictivity of the SPT and other factors (IgE serum levels, severity of AD) for the appearance of ARD.

At the beginning of the study we used the very simple clinical score proposed by Rajka and Langeland, and we did not change it after the proposal of the SCORAD index in 1993 (18) so that the evaluation of our cases could remain uniform. We have now adopted the SCORAD index, and in some of the patients from this study we compared these two clinical scores without finding any difference in the attribution of a patient to the group with mild, moderate, or severe AD.

Several clinical and laboratory data were collected and the statistical elaboration showed some interesting results: In the first 3 years of life the children with severe AD had significantly higher IgE serum levels than children with mild-moderate AD. In the literature, serum IgE levels have been found to be elevated in approximately 50–80% of children with AD and some authors think this can be correlated with the severity of the disease (19,20), while in other studies AD severity did not correlate with IgE serum level (21).

Among the patients with positive SPT at the first examination (47%), positivity to food allergens was found in 80%, and particularly in the younger patients (94% for children less than 1 year old). SPT positivity to inhalant allergens was very low in patients less than 1 year of age in our study (only one case). In the literature we found food IgE antibodies to be most common in infancy, while IgE antibodies to aeroallergens began to be more apparent at 18 months of age (22). In our study IgE antibodies to aeroallergens could already be observed through a positive SPT from the age of 12 months. In addition, in a recent study, Nickel et al (23) found that the prevalence of IgE antibodies to indoor and outdoor allergens in a large group of children increased markedly with age, and particularly at the age of 3 years.

In our prospective study, SPT positivity to chicken's egg represents the most common food allergen and also the most common allergen in patients 0–3 years of age. In fact, 28 of the 29 patients with SPT positive to foods had positivity to chicken's egg (Table 2).

We performed a second SPT at the end of 4 years follow-up in 68 children. At that time SPT appeared positive for at least one allergen in 65% of cases; grass pollen and house dust mite were the most common allergens found (Table 2). Sensitization to food allergens was found in 48% of patients, and in the group of patients with mild-moderate AD, 19% of patients with SPT positivity at the first examination (4 of 21 cases) had negative results at the second SPT. None of these patients had shown positivity to inhalant allergens at the first SPT and all were free of symptoms of AD. In our

opinion two hypotheses could justify this evolution of SPT:

Food allergen avoidance reverses sensitization caused by these particular food allergens.

The positivity to food allergen SPT observed in the first years of life is usually transitory and disappears when the food becomes tolerated (15,24,25).

We were surprised to find a sensitization to SPT and particularly to aeroallergens in 100% of our children with AD scored as severe in the first 3 years of life (Table 1). These data suggest that patients with severe AD, although negative to SPT and having low values of IgE in the first months of life, all eventually became positive to allergens, in particular to inhalants. In our opinion therefore, a correct diagnosis of nonatopic or intrinsic AD is not possible during the first years of life.

A clinical follow-up of at least 4 years was carried out in all our patients. It showed AD persisted unchanged in nine patients; a complete remission of AD occurred in 24.5% of patients and a marked improvement occurred in 64%. These percentages of remission appeared similar in patients with severe, mild, or moderate AD and are comparable to those observed by Linna et al. (8). Other studies show lower percentages of remission (26).

The occurrence of an ARD in patients with AD is high (8,15) and this is confirmed in our study (Table 3). Severity of AD in the first years of life appears a very good predictive factor for the subsequent development of an ARD. In our study, food allergen avoidance did not seem to protect predisposed children from development of an ARD later in life (23,27). Some authors emphasize that bronchial hyperresponsiveness also is present in atopic patients without a history of asthma (28–30).

In conclusion, this study highlights the role of SPT in the management of AD. SPT is a well-established method, inexpensive, relatively painless, and is easy to use, even on patients in the first months of life (31). The determination of food allergen and aeroallergen sensitization should be carried out at an early age, especially in severe AD, as skin test positivity to aeroallergens could be predictive of the appearance of ARD (16), while in our study the chicken's egg positivity was not predictive.

The natural history of AD demonstrated that food sensitization is related to the severity of AD and occurs before aeroallergen sensitization, which develops after the first year of life. The chronologic sequence of AD and ARD could be predicted. The risk of developing asthma has been estimated to be about 35% (with a range from 10% to 50% according to the severity) (3). Our data show that SPT positivity to food allergens, associated with severe clinical AD symptoms and with a high IgE serum level, identifies children 0–3 years of age as being at high risk for development of ARD. This finding may

be useful in order to take appropriate preventive measures for respiratory allergies. Early treatment of high-risk AD with environmental prophylaxis and/or pharmacologic treatment should be proposed.

REFERENCES

1. Van Hecke E, Leys G. Evolution of atopic dermatitis. *Dermatologica* 1981;163:370-375.
2. Musgrove K, Morgan JK. Infantile eczema. A long term follow-up study. *Br J Dermatol* 1976;95:113-115.
3. Queille-Roussel C, Raynaud F, Saurat JH. A prospective computerized study of 500 cases of atopic dermatitis in childhood. *Acta Derm Venereol (Stockh)* 1985;114:87-92.
4. Halbert AR, Weston WL, Morelli JG. Atopic dermatitis: Is it an allergic disease? *J Am Acad Dermatol* 1995;33:1008-1018.
5. Monafo V, Ferrari G, Colivicchi M, et al. Implicazioni cliniche della sensibilizzazione ad inalanti nella dermatite atopica. *Minerva Pediatr* 1992;44:205-209.
6. Lammintausta K, Kalimo K, Raitala R, et al. Prognosis of atopic dermatitis. A prospective study in early adulthood. *Int J Dermatol* 1991;30:563-568.
7. Rysted I. Long term follow-up in atopic dermatitis. *Acta Derm Venereol (Stockh)* 1985;114:117-120.
8. Linna O, Kokkonen J, Lahtela P, et al. Ten-year prognosis for generalized infantile eczema. *Acta Pediatr* 1992;81:1013-1016.
9. Hanjfin JM, Rajka G. Diagnostic features of atopic dermatitis. *Acta Derm Venereol (Stockh)* 1980;92:44-47.
10. Rajka G, Langeland T. Grading of the severity of atopic dermatitis. *Acta Derm Venereol (Stockh)* 1989;144:13-14.
11. Vierucci A, Caffarelli E, Galli C, et al. La dermatite atopica nell'infanzia: approccio diagnostico e terapeutico. *Riv Immunol Allergol Ped* 1991;1:4-19.
12. Desmons F, Breuillard F, Drain JP. Taux d'IgE seriques dans l'eczema atopique de l'enfant. *Pediatric* 1976;4:337-347.
13. Sampson HA. Atopic dermatitis. *Ann Allergy* 1992;69:469-481.
14. Wuthrich B. Atopic dermatitis flare provoked by inhalant allergens. *Dermatologica* 1989;178:51-53.
15. Ricci G, Patrizi A, Specchia F, et al. Predictivity of prick test and RAST-positive reactions for inhaled allergens in children with atopic dermatitis for the appearance of respiratory allergic disease. *Pharmacol Skin* 1991;4:177-178.
16. 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.
17. Zeiger RS, Heller S. The development and prediction of atopy in high-risk children: follow-up at age seven years in a prospective randomized study of combined maternal and infant food allergen avoidance. *J Allergy Clin Immunol* 1995;95:1179-1190.
18. European Task Force on Atopic Dermatitis. Severity scoring of atopic dermatitis: the SCORAD index. *Dermatology* 1993;186:23-31.
19. Johnson E, Irons J, Patterson R, et al. Serum IgE concentration in atopic dermatitis. *J Allergy Clin Immunol* 1974;54:94-99.
20. Stone SP, Gleich GJ, Muller SA. Atopic dermatitis and IgE relationship between changes in IgE levels and severity of disease. *Arch Dermatol* 1976;112:1254.
21. Rothe MJ, Grant-Kels JM. Atopic dermatitis: an update. *J Am Acad Dermatol* 1996;35:1-13.
22. Sigurs N, Hattevig G, Kjellman B, et al. Appearance of atopic disease in relation to serum IgE antibodies in children followed up from birth for 4-15 years. *J Allergy Clin Immunol* 1994;94:757-763.
23. Nickel R, Kulig M, Forster J, et al. Sensitization to hen's egg at the age of twelve months is predictive for allergic sensitization to common indoor and outdoor allergens at the age of three years. *J Allergy Clin Immunol* 1997;99:613-617.
24. Zeiger RS. Atopy in infancy and early childhood: natural history and role of skin testing. *J Allergy Clin Immunol* 1985;75:633-639.
25. Host A. Adverse reactions to foods: epidemiology and risk factors. *Pediatr Allergy Immunol* 1995;6(suppl):20-28.
26. Wuthrich B. Epidemiology and natural history of atopic dermatitis. Gottingen, Germany: ACI International, 1996.
27. Zeiger RS. Breast-feeding and dietary avoidance. In: De Weck A, Sampson HA, eds. *Intestinal immunology and food allergy*. New York: Raven Press, 1995:203-222.
28. Salob ST, Atherton DJ. Prevalence of respiratory symptoms in children with atopic dermatitis attending pediatric dermatology clinics. *Pediatrics* 1993;91:8-12.
29. Salob ST, Lavery A, Atherton DJ. Bronchial hyperresponsiveness in children with atopic dermatitis. *Pediatrics* 1993;91:13-16.
30. Novembre E, Pucci N, Brizzi I, et al. Storia naturale della dermatite atopica nel bambino. *Eur J Pediatr Dermatol* 1998;8:145-148.
31. Berardesca E, Gabba P, Nume A, et al. Objective prick test evaluation: non-invasive techniques. *Acta Derm Venereol (Stockh)* 1992;72:261-263.