

Reliability of tests for specific IgE to food in atopic dermatitis^{*}

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The pathogenesis of AD is poorly understood, and studies exist which demonstrate the role of a genetic predisposition and environmental factors (4, 12, 20, 30). However, a relationship between food allergy and AD is indicated by a great deal of data, from which we can draw some conclusions (4, 17, 23): positive family history for atopic diseases are reported in most AD children; AD children frequently develop other atopic diseases; elevated serum IgE levels and positive immediate skin and radioallergosorbent (RAST) tests to dietary antigens are frequently positive in AD children; specific foods are able to provoke AD in some children; elimination diets are effective in the treatment in some AD children; manipulation of the diet in early infancy may affect the subsequent incidence of AD.

However, the pediatrician treating a child with AD often experiences several difficulties in detecting the offending food(s). Clinical history (CH), skin test (SPT), RAST, elimination diets and food challenges have been reported to be able only partially elucidate the problem (4, 11, 19, 26). In this paper we report our experience in diagnosing food allergy in children with AD.

MATERIAL AND METHODS

Children

Patients ranging in age from 0 to 5 y (median 4.6) referred for evaluation of AD were studied.

All subjects fulfilled the criteria of Hanifin & Lobitz (16) for the diagnosis of AD. On the basis of the area of the skin involved, AD was classified as mild, moderate, or severe (24).

Historical data

A detailed clinical history with particular attention to the possibility that foods may induce or aggravate AD was obtained. The parents also were questioned to determine the presence of other atopic disorders and the presence of allergic disease in other family members.

Skin testing

Glycerinated extracts (1/20 w:v) of the 9 more important foods (egg, milk, peanut, tomato, wheat, potato, rice, codfish and soybean) and the most common inhalant substances (*D. pteronyssinus*, grass pollen, *Parietaria officinalis*, *Artemisia vulgaris*, olive, cat dander, *Alternaria tenuis*) were selected for this study (Bayropharm, Milan).

Prick testing was performed by placing a drop of extract on the forearm and lifting the skin with a suture needle introduced through the drop of extract. Histamine (1 mg/ml) and glycerinated saline were used as positive and negative controls, respectively.

All skin tests were applied and evaluated after 15-20 min by the same pediatrician. Antigens eliciting a wheal ≥ 3 mm than control were considered positive (8).

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Table 1

Frequency of cutipositives to foods and/or inhalants according to age, in children with atopic dermatitis

Positive to:	Age 0-2 y (n = 26)	Age 3-8 y (n = 68)	Age > 9 y (n = 18)	P
Foods	14 (53.8%)	23 (33.8%)	1 (5.6%)	0.03455
Foods and inhalants	2 (7.9%)	21 (30.8%)	9 (50.1%)	0.01931
Inhalants	1 (3.8%)	7 (10.3%)	2 (10.2%)	n.s.
Negative	9 (34.6%)	17 (25%)	6 (33.3%)	n.s.

Laboratory evaluation

The laboratory evaluation included a measurement of total IgE (PRIST®, Pharmacia, Uppsala) in 112 subjects and specific IgE to some foods in 51 (RAST®, Pharmacia, Uppsala).

Serum samples for IgE determination were frozen at -20°C until tested. RAST results were recorded as a score ranging from 0 to 4, based upon four Pharmacia reference standards (PRU/ml), as described in the RAST package insert. Positive RAST = RAST PRU/ml; class 2 or more (> 6% of the total activity bound).

Food challenges

Fifty-nine challenges were performed in 35 children. Only 4 foods were considered (milk, egg, peanut and tomato). Food challenges were performed on the basis of a positive SPT and/or a suggestive history of food allergy. Children with histories of severe reactions (anaphylaxis, severe immediate cutaneous or respiratory manifestations) were excluded from the study. On the basis of SPT and CH, parents were instructed to eliminate up to 6 suspected food allergens from the child's diet for 1-2 weeks and to discontinue drugs (antihistamines for at least 7 days, β_2 -agonists for 24 h, topical steroids for 4-5 days, oral steroids for 10-14 days).

DBFC were performed by mixing the dehydrated food (Lofarma Allergeni, Milano) in 20-50 ml of water or soymilk with cherry or apricot syrup to mask the taste, similar to that described by Sampson et al. (24). Up to 8 g of dehydrated food were given in a 1-h period.

Two challenges separated by at least 4 h were administered each day, one containing the suspected food antigen and the other containing a placebo.

If the challenge was negative, the patient was allowed to continue the ingestion of the food in a quantity normally adequate to age. Symptoms resulting from positive food challenges were recorded in relation to severity, time-course and duration.

Statistics

The results of the DBFC were considered the "gold standard" for determining sensitivity, specificity and indices of predictive accuracy of skin testing and RAST. The sensitivity of RAST was calculated by dividing the number of positive DBFC correctly identified by RAST by the total number of positive DBFC; while the specificity was calculated by dividing the number of negative food challenges correctly identified by the total number of negative food challenges.

Positive predictive accuracy was calculated by dividing the number of positive food challenges correctly identified by the allergy test (i.e. SPT or RAST) by the total number of positive allergy test results.

The negative predictive accuracy was determined in a similar manner by dividing the number of negative food challenges correctly identified by the total number of negative allergy test results. Chi-square test was used to compare frequencies.

RESULTS

Seventy-two out of 112 (64.2%) children with AD had positive SPT to one or more food

antigen(s). In 38 AD children (33.9%) SPT were positive to food antigens alone, whereas in 34 (30.3%) positive SPT to food were associated with positivity to inhalant antigens.

When SPT results in AD children were considered according to age (Table 1), older AD children showed a significant decrease in positivity to foods alone, and a significant increase in positivity to both foods and inhalants. No statistically significant difference was observed in the proportion of AD patients SPT positive to inhalants alone, or SPT negative to both food and inhalant antigens. In Table 2, results of SPTs to inhalants are reported according to age.

Abnormally increased IgE levels (i.e. above 2 SD from the mean for age in a general pediatric population (31)) were observed in 58 out of 112 (51.7%) children with AD. The frequency of abnormally increased IgE levels significantly ($P = 0.0497$) increased with the severity of the disease, since they were observed in 17 out of 44 (38.6%) mild AD, in 24 out of 43 (55.8%) moderate AD, and in 17 out of 25 (68%) severe AD.

The frequency of positive SPT and RAST to nine food antigens is reported in Table 3.

A significant positive CH for five food antigens was reported in 79 cases. Concordance between a positive CH and SPT or RAST is reported in Table 4. Concordance between a negative CH and SPT or RAST is reported in Table 5. Fifty-nine DBFC were performed in 35 children; 34 positive food challenges were observed [milk 15/23 (65.2%), egg 12/18

(66.6%), tomato 2/9 (22.2%), peanut 5/9 (55.5%)] in 24 children (Table 6).

Symptoms induced by DBFC were cutaneous in 27/35 positive challenges (79.4%), gastrointestinal in 10 (29.6%) and respiratory in 5 (14.7%). Sensitivity, specificity and predictive indices of SPT and RAST, calculated on the basis of food challenges results, are reported in Table 7.

DISCUSSION

The purpose of this study was to investigate the significance and reliability of SPT and laboratory tests in the diagnosis of AD.

It is well known that most children with AD have positive SPT and RAST to various dietary and environmental allergens, but the usefulness of these tests in detecting the true offending food is controversial (5, 14, 24, 25). The frequency of positive skin tests to foods found in children with AD is significantly higher than that observed in a general pediatric population (12). When SPT response to food and inhalant antigens were compared in different ages, most children initially were found to be positive only to foods, but subsequently presented sensitivity to inhalants. The frequency of subjects with constantly negative SPT did not change. This pattern of sensitization is quite different from that of atopic respiratory diseases which occur later in childhood.

The development of sensitization to inhalants in children with AD progresses with age. Of

Table 2

Frequency of cutipositives to inhalants, according to age, in children with atopic dermatitis

Allergen	Age 0-2 y (n = 26)	Age 3-8 y (n = 68)	Age 9 y (n = 18)
<i>Dermatophagoides</i>	1 (3.8%)	14 (20.5%)	6 (33.3%)
Grass pollen	1 (3.8%)	15 (22.0%)	4 (22.2%)
<i>Parietaria officinalis</i>	1 (3.8%)	3 (4.4%)	3 (16.6%)
<i>Artemisia vulgaris</i>	0	6 (8.8%)	2 (11.1%)
Cat dander	0	4 (5.8%)	8 (44.4%)
<i>Alternaria tenuis</i>	0	3 (4.4%)	2 (11.1%)
Olive	0	3 (4.4%)	4 (22.2%)

Table 3

Frequency of positive skin tests and RAST in 112 children with atopic dermatitis

Food antigen	Positive SPT n (%)	Positive RAST n (%)
Egg	48 (42.8)	38 (33.9)
Milk	28 (25.0)	30 (26.7)
Peanut	21 (18.7)	20 (17.8)
Potato	19 (16.9)	17 (15.1)
Wheat	13 (11.6)	27 (24.1)
Tomato	11 (9.8)	18 (16)
Rice	11 (9.8)	33 (29.4)
Cod	9 (8.03)	13 (11.6)
Soy	4 (3.5)	24 (21.4)

Table 4

Concordance between positive clinical history and skin tests or RAST

Positive clinical history for:	Concordance with	
	SPT	RAST
Cod (<i>n</i> = 6)	4 (66.6%)	4 (66.6%)
Egg (<i>n</i> = 15)	9 (60.0%)	8 (53.3%)
Tomato (<i>n</i> = 10)	3 (30.0%)	1 (10.0%)
Milk (<i>n</i> = 33)	4 (12.1%)	10 (30.3%)
Peanut (<i>n</i> = 15)	8 (53.3%)	8 (53.3%)

particular interest is the elevated frequency (44%) fo sensitization to cat dander in children 9 y of age. The potential importance of non-food environmental allergens, such as mites, pollens and animal dander, in aggravating the AD has been reported (5). Adinoff et al. (3) were able to induce delayed response (with a patch-test) in a group of subjects with AD. Skin inflammation might be the first step allowing increased allergen penetration, presentation to the immunoreactive cells, and development of sensitivity. Therefore, if foods have relevance mostly in the initial establishment of AD, its continued aggravation may result from the passage of intact soluble infant antigens through the inflamed skin.

It has been demonstrated that the total IgE concentration roughly correlates with severity of AD (21) with a significant difference in IgE levels between mild and severe AD.

Sampson (27, 28) reported a significant decrease in total IgE and improvement in clinical status in AD children who complied with an appropriate long-lasting elimination diet. This did not happen in patients who failed to comply or who had no demonstrable reactions to various DBFC. It seems, therefore, that a link does exist between IgE response, diet and severity of disease, but as previously outlined, the significance of specific IgE antibodies to foods in AD is controversial.

IgE to egg and milk and foods are often detected in children with AD by SPT or RAST. SPT and RAST identify about the same frequency of positive subjects for egg, milk, peanut, potato, tomato and codfish, while for other

Table 5

Concordance between negative clinical history and skin tests or RAST

Negative clinical history for:	Concordance with	
	SPT	RAST
Cod (<i>n</i> = 106)	98 (92.4%)	80 (75.4%)
Egg (<i>n</i> = 97)	40 (41.2%)	63 (64.9%)
Tomato (<i>n</i> = 102)	93 (91.1%)	82 (80.3%)
Milk (<i>n</i> = 79)	58 (73.4%)	52 (65.8%)
Peanut (<i>n</i> = 97)	77 (79.3%)	77 (79.3%)

foods, such as wheat, rice and soybean, RAST shows a higher sensitivity. These discordant results may be due to variables both in SPT (quality of extracts, etc.) and in RAST (high levels of IgE with non-specific binding, etc.) (14).

The predictive value of SPT and RAST depends largely upon the criteria used for the diagnosis of food-induced AD. Most of the earlier studies were based on CH for diagnosis of food allergy and the concordance found with SPT and/or RAST was variable in relation to the type of CH (unequivocal, convincing, possible, doubtful) and to the type of symptoms (immediate or delayed) (2, 9, 10, 29, 32).

In the present study concordance between positive (possible) clinical history and positive SPT or RAST is good (50-60%) for codfish and egg, and poor (10-30%) for milk and tomato, whereas negative concordance was generally good (from 70 to 100%) for all foods except milk and egg.

Table 6

Results of food challenges performed in 35 children with AD

Antigen challenge	Positive challenges <i>n</i> (%)	Negative challenges <i>n</i> (%)	Total
Milk	15 (65.2)	8 (34.7)	23
Egg	12 (66.6)	6 (33.3)	18
Tomato	2 (22.2)	7 (77.7)	9
Peanut	5 (55.5)	4 (44.4)	9
Total	34 (57.6)	25 (42.3)	59

Table 7

Sensitivity, specificity, and predictive indices for 4 food antigens in children with atopic dermatitis

		SPT	RAST
Milk	s	0.28	0.35
	f	0.80	0.77
	v	0.66	0.71
	g	0.44	0.50
Egg	s	1	0.62
	f	0.25	0.33
	v	0.60	0.71
	g	0.75	0.50
Tomato	s	1	0.14
	f	0.66	0.50
	v	0.40	0.33
	g	1	0.25
Peanut	s	1	0.25
	f	0.50	1
	v	0.83	0.33
	g	0.50	0.25

s = sensitivity; f = specificity; v = positive predictive accuracy; g = negative predictive accuracy.

It is apparent that the considerable variability in these values may lead to erroneous conclusions. As a consequence, some researchers (8, 24, 25, 26, 17) proposed to consider DBFC as the “gold standard” in the diagnosis of food-dependent AD. In a study by Aas & Johansson (1), concordance between RAST and single blind challenge to fish was 93 %, with a sensitivity of 91 % and a specificity of 94 %. Sampson & Albergo (25), compared the results of SPT, RAST and DBFC for eight common antigens in 40 children with AD.

The food challenge was considered the gold standard for the diagnosis of food hypersensitivity; 23 children experienced a positive (cutaneous, gastrointestinal or respiratory symptoms) challenge. Sensitivity, specificity and predictive accuracy of SPT and RAST were found to be comparable, with no advantage of RAST alone or in combination with SPT in the evaluation of food hypersensitivity in children with AD. They concluded that SPT and RAST were a very useful means of excluding the presence of immediate hypersensitivity, but were only a sug-

gestive indicator for identifying food allergy, which requires more definitive procedures to be assessed. The role of DBFC in the diagnosis of food allergy was studied in adults by Bernstein et al. (7) who found a correlation with a positive SPT in only 4/13 subjects and by Atkins et al. (6), who found a higher correlation (9/10 subjects with positive DBFC had positive SPT).

In adults with AD, Pelikan (22) found a 34 % concordance between positive DBFC and positive RAST in 58 patients, and 76 % negative concordance in 21 subjects, concluding that the overall correlation between DBFC and RAST was not significant. In another study, Sampson et al. (27) performed a total of 514 DBFC in 160 patients aged 3 mo to 24 years (median age 5.3 y). Selection of DBFC was based on SPT or RAST results and/or a strongly suggestive history of food hypersensitivity. A total of 180/514 food challenges was interpreted as positive (cutaneous responses 79 %, gastrointestinal symptoms 43 % and respiratory symptoms 28 %). The most frequent offending foods were egg (38 %), peanut (24 %), milk (11 %), fish (7 %), soybean (5 %) and wheat (4 %). In the present study comparable results were observed, since about 60 % positive DBFC were found in children with AD, egg and milk being the most important foods (Table 6). Evaluating sensitivity, specificity and predictive indices for 4 food antigens and considering DBFC as “gold standard” we found that SPT is more sensitive than RAST for egg, peanut and tomato, while specificity is comparable.

However, when considering the positive predictive accuracy (i.e. how likely a patient is to have clinical food hypersensitivity if the test is positive) and the negative predictive accuracy (i.e. how likely a patient is to have no hypersensitivity if the test is negative) we were unable to confirm the excellent data of Sampson (25). In fact, both positive and negative predictive accuracy were variable (from 33 to 83 % and from 25 to 100 %, respectively). This means that neither SPT nor RAST were useful to confirm or exclude clinical food allergy. This possibly depends on some factors (14) that can interfere with SPT (type of antigen, stability, antigen purification) or with RAST (non-specific bind-

ing effect in sera having high level of IgE, presence of specific IgG, efficiency of binding, cross-reactions). Season and the releasability of mast cells at the moment of the test have to be considered. Again, some food reactions require the simultaneous presence of another stress factor such as ingestion of other substances (drugs, additives), infections, or exercise (15).

The importance of the challenging dose must also be stressed. The amount of substance normally used for the challenge (up to 8–10 g dehydrated food) may be not large enough or not repeated often enough (13). It is possible to speculate that complete tolerance to food is reached after a long period of partial dose-dependent tolerance.

Support for this view comes from an experiment in 10 milk-intolerant children with AD. After 1 year of a milk-free diet, we performed a DBFC with milk, and 5 subjects appeared initially to tolerate the usual challenging dose (100 ml), but after 7–14 days of free diet, children relapsed. They presented a gradual improvement when the milk was stopped (Vierucci et al., unpublished data). It follows, therefore, that in the period of partial tolerance it is never completely possible to disprove food hypersensitivity even when a single DBFC is negative.

According to all these considerations we think that the term of “gold standard” is inappropriate also for DBFC.

In conclusion, neither the CH nor SPT, nor the laboratory tests, nor the challenge test are individually reliable in diagnosing food-dependent AD. They can serve only to strengthen the diagnosis when they completely or partially agree.

REFERENCES

1. Aas, K. & Johansson, S. G. O.: RAST in the *in vitro* diagnosis of multiple reagenic allergy. *J. Allergy Clin. Immunol.* **48**, 134–142, 1971.
2. Aas, K. & Lundkvist, U.: The radioallergosorbent test with purified allergen from codfish. *Clin. Allergy* **3**, 255–261, 1973.
3. Adinoff, A. D., Tellez, P. & Clark, R. A. F.: Atopic dermatitis and aero-allergen contact sensitivity. *J. Allergy Clin. Immunol.* **54**, 736–742, 1988.
4. Atherton, D. J.: Allergy and atopic eczema. *Clin. Exp. Dermatol.* **6**, 317–325, 1981.
5. Atherton, D. J.: Diet and atopic eczema. *Clin. Allergy* **18**, 215–228, 1988.
6. Atkins, F. M., Steimberg, S. S. & Metcalfe, D. D.: Evaluation of immediate adverse reaction to foods in adult patients. *J. Allergy Clin. Immunol.* **75**, 348–355, 1985.
7. Bernstein, M., Day, J. H. & Welsh, A.: Double blind food challenge in the diagnosis of food sensitivity in the adult. *J. Allergy Clin. Immunol.* **70**, 205–210, 1982.
8. Bock, S. A., Buckley, J., Holst, A. & May, C. D.: Proper use of skin test with food extracts in diagnosis of hypersensitivity to food in children. *Clin. Allergy* **7**, 375–379, 1977.
9. Chua, Y. Y., Bremmer, K., Lobet, J. L., Kokubu, H. L. & Collins-Williams, C.: Diagnosis of food allergy by radioallergosorbent-test. *J. Allergy Clin. Immunol.* **58**, 477–482, 1976.
10. Danneus, S., Johansson, S. G. O., Foucard, T. & Ohman, S.: Clinical and immunological aspects of food allergy. *Acta Paediatr. Scand.* **66**, 31–37, 1977.
11. De Martino, M., Novembre, E. & Vierucci, A.: IgE-mediated food allergy. A critical review of controversial points. *Folia Allergol. Immunol. Clin.* **35**, 21–36, 1988.
12. De Martino, M., Donzelli, G. P., Galli, L., et al.: Allergia alimentare nel nato pretermine. *Riv. Ital. Ped.* **14** (suppl.) 92, 1988.
13. Ford, R. P. K., Hill, D. J. & Hosking, C. S.: Cow's milk hypersensitivity: Immediate and delayed onset clinical patterns. *Arch. Dis. Child.* **58**, 856–862, 1983.
14. Freed, D. L. F.: Laboratory diagnosis of food intolerance. In: Brostoff, J. & Challacombe, S. J. (eds.): *Food allergy and intolerance*, pp. 873–897. Bailliere Tindall, London, 1987.
15. Fries, J. F.: Food allergy: current concerns. *Ann. Allergy* **46**, 260–268, 1981.
16. Hanifin, J. M. & Lobitz, W. C.: Newer concepts of atopic dermatitis. *Arch. Dermatol.* **113**, 663–670, 1977.
17. Hanifin, J. M.: Epidemiology of atopic dermatitis. *Monogr. Allergy* **2**, 77–131, 1987.
18. Mantle, J. & Pepys, J.: Asthma among Tristan de Cunha islanders. *Clin. Allergy* **4**, 161–169, 1974.
19. Metcalfe, D. D.: Diagnostic procedures for immunologically-mediated food sensitivity. *Nutr. Rev.* **42**, 92–97, 1984.
20. Mihm, M. C., Soter, N. A., Dvorak, H. F. & Austen, K. F.: The structure of normal skin and morphology of atopic eczema. *J. Invest. Dermatol.* **67**, 305–309, 1976.
21. Ohman, S. & Johansson, S. G. O.: Immunoglobulins in atopic dermatitis with special reference to IgE. *Acta Derm. Venereol. (Stockh.)* **54**, 193–202, 1974.
22. Pelikan, Z.: RAST and PRIST in patients with adverse reactions to foods. *J. Allergy Clin. Immunol.* **82**, 188, 1988.
23. Pike, M. & Atherton, D. J.: Atopic eczema. In: Brostoff, J. & Challacombe, S. J. (eds.): *Food allergy and intolerance*, pp. 583–603. Bailliere Tindall, London, 1987.
24. Sampson, H. A.: Role of immediate food hypersensitivity in the pathogenesis of atopic dermatitis. *J. Allergy Clin. Immunol.* **71**, 473–480, 1983.

25. Sampson, H. A. & Albergo, R.: Comparison of results of skin tests, RAST and double-blind, placebo controlled food challenges in children with atopic dermatitis. *J. Allergy Clin. Immunol.* 74, 26-33, 1984.
26. Sampson, H. A. & McCaskill, C. C.: Food hypersensitivity and atopic dermatitis: evaluation of 113 patients. *J. Pediatr.* 107, 669-675, 1985.
27. Sampson, H. A.: IgE mediated food intolerance. *J. Allergy Clin. Immunol.* 81, 495-504, 1988.
28. Sampson, H. A.: The role of food allergy and mediator release in atopic dermatitis. *J. Allergy Clin. Immunol.* 81, 635-645, 1988.
29. Schur, S., Hyde, J. S. & Wypych, J. I.: Egg white sensitivity and atopic eczema. *J. Allergy Clin. Immunol.* 54, 174-179, 1974.
30. Vickers, C. H. F.: The natural history of atopic eczema. *Acta Derm. Venereol. (Stockh.)* 92, 113-115, 1980.
31. Vierucci, A., De Martino, M., Rossi, M. E., et al.: Raised IgE levels in β -thalassemia: correlation with splenectomy and hepatitis B virus infection. *Clin. Exp. Immunol.* 58, 199-205, 1984.
32. Wraith, D. S., Merret, J., Roth, A., Yman, L. & Merret, T. S.: Recognition of food allergic patients and their allergens by RAST. *Clin. Allergy* 9, 25-36, 1979.

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