

Immediate Contact Reactions to Cow's Milk and Egg in Atopic Children

ARNOLD P. ORANJE¹, ROLAND S. R. AARSEN², PAUL G. H. MULDER³ and GINEKE LIEFAARD⁴

¹Department of Dermatology and Venereology [Division of Paediatric Dermatology], ²Department of Paediatrics, ³Department of Epidemiology and Biostatistics, ⁴Department of Dietetics, Erasmus University and University Hospital Rotterdam/Dijkzigt-Sophia Children's Hospital, The Netherlands

Forty children (0–5 years old), presented with immediate contact urticaria, rash and often atopic dermatitis ($n = 34$). Redness or urticaria around the mouth appearing after consuming cow's milk or egg, were the major complaints in all. These symptoms suggested a food-induced immediate contact reaction, which can be immune-mediated or irritative. To re-induce this reaction, a skin provocation test, called SAFT, was performed. SAFT stands for Skin Application Food Test. This test is based on direct skin contact, during a maximum of 30 min with food in its 'ordinary consumptive state'. The SAFT can be regarded as a 'physiological' provocation patch test. If positive, contact urticaria develops most often within a few minutes. The results of SAFT and IgE RAST correlated significantly well. Total IgE values were not informative. The rapid onset of the SAFT reaction, induced by proteins, supported by RAST re-

sults, strongly indicates an immune-mediated mechanism. In 52% of the 34 patients with atopic dermatitis, dermatitis was exacerbated following food-to-skin contact. Immune-mediated contact reactions to foods play an important role in (dermal) food allergy. *Key words: Contact urticaria; Dermal food allergy; Atopic dermatitis.*

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A. P. Oranje, University Hospital Rotterdam/Sophia Children's Hospital, PO Box 70029, 3000 LL Rotterdam, The Netherlands.

The diagnosis of food allergy is a controversial issue. A reliable conclusion is often hampered by misleading histories from the parent(s) and psychological

Table I. Results of SAFT and RAST with cow's milk and egg white in 40 atopic children with immediate contact reactions.

All deter- minations (n=95)	SAFT+ RAST+	SAFT+ RAST-	SAFT- RAST+	SAFT- RAST-
Cow's milk or/ and egg allergic	+ 51	9	2	0
	- 0	0	7	26

RAST class ≥ 2 is considered positive. SAFT and RAST results correlated significantly with milk and/or egg allergy by Fisher's exact test ($p = 0.001$).

'pseudo' reactions. Most food-allergic reactions are IgE-mediated. However, for expression of symptoms, not only the immune mechanism is of importance, but also the target organ (1). The skin is often involved in the reaction pattern of food allergy; when predominating one can speak of dermal food allergy.

Minor reactions suggesting immediate contact reaction are pruritus, redness and urticaria around the mouth and on the hands. Immediate contact reaction is immune-mediated, irritative, or of unknown origin (2). Immune-mediated contact reaction is particularly common in young children with atopic dermatitis (AD) (3). Based on immediate contact urticaria, Oranje developed a provocation test system: SAFT (skin application food test) (4). Earlier, Salo et al. (5) had described an open application test in children with AD and milk allergy. We describe the results of the SAFT and the RAST in 40 atopic children. They presented with immediate contact reactions around the mouth after consuming milk, egg or sometimes other foods.

Table II. Comparison of height of scores of SAFT and RAST.

SAFT (classes)	RAST cow's milk and egg (classes)			
	0	1	2	≥ 3
0	18	8	7	2
1	0	0	0	0
2	2	3	12	14
3	1	3	9	16

Rank correlation coefficient (Spearman): $r_s = 0.58$, $p < 0.001$.

MATERIAL AND METHODS

Patients

Forty 0-5-year-old atopic children, with symptoms suggesting immediate contact reaction, were included. The female-male ratio was 11:29. They attended the Out-patient Department of the Division of Paediatric Dermatology during the period 1985-89. The children suffered from urticaria or less specific rashes. Of the 40, 34 suffered from atopic dermatitis, diagnosed according to the criteria of Rajka & Hanifin (6). Recent history and clinical observations suggested an immediate contact reaction or more generalized allergic reactions after food ingestion. The dietician verified the history extensively. Additional data were obtained by elimination and oral provocation tests with the suspected foods.

SAFT

Symptoms were imitated by a patch test, called SAFT (Skin Application Food Test). On a symptom-free part of the skin (most often the back 2×2 cm gauze patches impregnated with standardized amounts of foods or control liquid were fixed to the skin [0.8 ml saline (control), 0.8 ml pasteurized cow's milk and 1 slice (1 g) of boiled egg white]. From 10 min on, but often after a few minutes when positive, the patch sites were inspected. After a positive reaction, the test was stopped immediately. Otherwise the test ended after 30 min.

Tests were read as 0, 1+ redness (both negative), 2+ redness and edema (urticaria) within an standard area of 2×2 cm, 3+ the same but involving more than 2×2 cm (2+ and 3+ positive). Sometimes generalized urticaria occurred and the test was then interrupted immediately.

Oral challenge tests

Oral food challenges were performed in patients with disparities in SAFT, clinical signs and RAST. The oral provocations took place in the hospital under strict supervision and controlled conditions on the daycare ward. First the SAFT was repeated in all cases. After $2 \times$ negative SAFT, titrated oral provocations were performed with increasing amounts at one-hour intervals (5 ml, 10 ml, 20 ml and unrestricted amounts of cow's milk or 2, 4, 8 and 16 g of egg). All children remained in hospital for at least 7 h after oral provocation so that possible late reactions could be recorded. Only when the mother did not give a diet completely free of the suspected antigen, was food reintroduced at the Out-patient unit.

IgE test procedure

Total IgE was measured by a non-competitive immunoassay (Enzyme-Test IgE, Boehringer Mannheim, Almere, The Netherlands). The RAST was performed according to the manufacturer's instructions (Pharmacia, Uppsala, Sweden). RAST results were expressed as RAST classes.

Statistical analysis

Fisher's exact test (7) was used to correlate the positive scores of the SAFT and corresponding RAST, both with each other and with food allergy. Equality of the means of

the 'Total IgE' scores was tested with the Kruskal-Wallis 1-way ANOVA (non-parametric) test. For this calculation the patients were divided into three groups: 1) with negative SAFT's, 2) with positive SAFT's for egg and/or milk, and 3) multiple foods. The heights of the scores of SAFT and corresponding RAST were compared using the Spearman rank correlation test (7).

RESULTS

Clinical characteristics

All children were suffering from urticaria or rashes, in particular redness or urticarial rashes around the mouth and on the hands. Most children were younger than 2 years (75%) and 34 (85%) suffered from atopic dermatitis (AD). AD was exacerbated by foods in 52% of this subgroup. Of all the children, 15 (38%) were suffering from gastrointestinal problems and 9 (22%) from asthma.

SAFT and oral challenges with milk and egg

In 20 of the children, oral challenge was performed, but only when the SAFT was repeatedly negative, except in one case (see below). Seventeen times, 14 × milk and 3 × egg, the oral challenges proved negative. In all these cases the responsible food could be reintroduced without any problem.

In one child with a positive SAFT, three positive challenges were performed. Every time the child developed urticaria and oedema. In 2 cases (aged 3 and 4 yrs) SAFT became negative as the child grew older. At oral challenge, both developed erythema, sneezing, red eyes and tears, and swelling in the mouth. In both, the skin had been cleared from AD and skin dryness was rather evident.

SAFT and RAST

SAFT and RAST, with egg and milk and sometimes with other foods, e.g., peanut, were performed in all the children. The results of all the corresponding tests were compared (Table I). RAST as well as SAFT indicated most cases of IgE-mediated food allergy correctly (Fisher's exact test, $p = 0.001$). The height of the scores (Table II) also correlated significantly, for egg and milk separately, as well as for the combined results (Spearman rank correlation coefficient, $r_s = 0.58$, $p < 0.001$). Comparing SAFT and RAST, the RAST shows far more clinically irrelevant scores.

SAFT and total IgE

The mean of the distribution of IgE values increased significantly with increasing number of positive

SAFTs (Kruskal-Wallis 1-way ANOVA, $p < 0.005$). However, the mean age of the children also increased (leading to an increased mean Total IgE).

DISCUSSION

Immediate contact reactions around and in the mouth after consuming cow's milk or egg and sometimes other foods, are rather common in young atopic children with food allergy. Atopic dermatitis (AD) in young children is often complicated by acute urticarial flare-ups, partly on food to skin contact. These immune-mediated urticaria, induced by proteins, mostly occur a few minutes after contact with foods such as cow's milk, egg, peanut etc. (3). It is interesting that with fruits and vegetables, immediate contact reactions have also been reported in birch-allergic atopics by cross-reacting mechanisms (8).

The SAFT can be regarded as an imitation of these naturally occurring events. The rapid onset of the SAFT reaction, induced by proteins, supported by RAST results, strongly indicates an immune-mediated mechanism. Histamine-liberating and non-immune-mediated reactions are possible, however, but not with cow's milk and egg. A positive SAFT is explained by penetration of proteins that bind to specific IgE on mast cells, releasing histamine and other substances. The dermal vasculature can be damaged, giving rise to oedema. When entering the blood circulation, a generalized urticarial or systemic reaction may develop (2). In a few patients we observed generalized urticarial reactions or flare-ups of atopic dermatitis during the SAFT.

The SAFT is a variation of the 'rub-test', as described by Lahti & Maibach (2), and by Gronemeyer et al. (9). In the 'rub-test' the allergen is rubbed into the skin at the test site (9). In young children we do not have to rub the allergen into the skin, as illustrated by us and Salo et al. (5). The skin is more permeable than in older children and adults. Gronemeyer found a close correlation between the 'rub-test' and the IgE titre (RAST) (9). High anti-food IgE RAST class-scores often correspond to positive blind challenges, and thus with food allergy (10). In our study the SAFT and RAST results correlated statistically significant as well.

In our series, a food-induced aggravation of dermatitis was observed in 52% of the children with AD. The SAFT proved positive in all of them. The SAFT was false-negative in only 2 children (aged 3

and 4 years), as shown by positive oral challenge. IgE RAST class-scores were 2+ in both. In these 2 children, however, AD had cleared; 1–2 years before they had had a positive SAFT.

The diagnosis of food allergy is based mainly on double-blind placebo-controlled oral challenges (DBPCOC) (11). Like DBPCOC, the SAFT is not influenced by psychological factors. A positive IgE RAST indicates atopic immune response, but not always manifest allergy. Next to atopic immune response, a positive SAFT indicates releasability of the dermal mast cells. The organ involved, the releasability of mast cells, eosinophils and basophils determine the clinical expression of atopic disease (12). Recently Metcalfe pointed to the importance of the target organ in food allergy, suggesting different expressions of food allergy (1). The SAFT is only useful when the skin is the target organ. A positive SAFT means at least immediate food contact allergy of the skin and, of course, mouth ('oral allergy syndrome').

REFERENCES

1. Metcalfe DD. Diseases of food hypersensitivity. *N Engl J Med* 1989; 321: 255–257.
2. Lahti A, Maibach HI. Immediate contact reactions. *Immunology and Allergy Clin North America* 1989; 9: 3: 463–477.
3. Atherton DJ. Skin manifestations of food allergy. In: Hamburger RN, ed. *Food Intolerance in Infancy: Allergology, Immunology and Gastroenterology*. Los Angeles, New York: Raven Press, Ltd, 1989; 145–154.
4. Oranje AP. Skin provocation test (SAFT) based on contact urticaria: a marker of dermal food allergy. In: Vermeer J, ed. *Proceedings of Metabolic Disorders and Nutrition Related to the Skin*. Basel: Karger, 1990 [accepted for publ.].
5. Salo OP, Mäkinen-Kiljunen S, Juntunen K. Milk causes a rapid urticarial reaction on the skin of children with atopic dermatitis and milk allergy. *Acta Derm Venereol (Stockh)* 1986; 66: 438–442.
6. Rajka G. *Essential aspects of atopic dermatitis*. Berlin, Heidelberg: Springer-Verlag, 1989.
7. Siegel S. *Nonparametric statistics for the behavioural sciences*. New York: McGraw-Hill, 1956.
8. Hannuksela M, Lahti A. Immediate reactions to fruit and vegetables. *Contact Dermatitis* 1977; 3: 79–82.
9. Gronemeyer W, Fuchs E, Bandilla K. 'Reibtest' und RAST. *Z Hautkr* 1979; 54: 205–212.
10. Sampson HA, 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* 1984; 74: 26–33.
11. Burks AW, Mallory SB, Williams LW, et al. Atopic dermatitis: clinical relevance of food hypersensitivity reactions. *J Pediatr* 1988; 113: 447–451.
12. Marone G, Casolaro V, Ayala F, Melillo G, Condorelli M. Releasability in allergic disorders. In: Milillo G, Norman PhS, Marone G, eds. *Respiratory Allergy, Clin Immunology*. Toronto: BC Decker Inc, 1990; 2: 67–77.