

Diagnosis of IgE-mediated food allergy among Swiss children with atopic dermatitis

Eigenmann PA, Calza A-M. Diagnosis of IgE-mediated food allergy among Swiss children with atopic dermatitis.
Pediatr Allergy Immunol 2000; 11: 95–100. © Munksgaard, 2000

Diagnosis of food allergy in children with atopic dermatitis (AD) relies on a good knowledge of the prevalence of the disease and of the foods most frequently involved. Our objective was to define these characteristics in a population of Swiss children with AD. Patients referred to a pediatric allergist or a dermatologist for AD were routinely tested by skin-prick test (SPT) to seven common food allergens (milk, egg, peanut, wheat, soy, fish, and nuts), and to all other foods suspected by history. Patients with positive SPTs were further evaluated for specific serum immunoglobulin E (IgE) antibodies (by using the CAP System FEIA[®]). CAP values were interpreted following previously published predictive values for clinical reactivity. Patients with inconclusive results (between the 95% negative predictive value [NPV] and the 95% positive predictive value [PPV]) were challenged with the suspected food. A total of 74 children with AD were screened for food allergies. Negative SPTs excluded the diagnosis in 30 subjects. Nineteen patients were diagnosed by histories suggestive of recent anaphylactic reactions to foods and/or CAP values above the 95% PPV. Forty-three food challenges (35 open challenges and eight double-blind, placebo-controlled in children with persistent lesions of AD despite aggressive topical skin treatment) were performed in patients with positive SPTs but with inconclusive CAP values. Six patients were diagnosed as positive to 15 foods. Challenges were not performed to high-allergenic foods in young children (under 12 months of age for egg and fish, and under 3 years of age for peanuts and nuts). Altogether, 33.8% (25 of 74) of the AD patients were diagnosed with food allergy. The prevalence of food allergy was 27% (seven of 25) in the group referred to the dermatologist for primary care of AD. The foods most frequently incriminated were egg, milk, and peanuts. The prevalence of food allergy in our population was comparable to that in other westernized countries, suggesting an incidence of food allergy in approximately one-third of children with persistent lesions of AD. Together with milk and eggs, peanuts were most frequently involved in allergic reactions.

**Philippe A. Eigenmann^{1,2} and
Anne-Marie Calza³**

¹Department of Pediatrics and Division of Immunology and Allergy, ²Department of Medicine and ³Department of Dermatology, University of Geneva School of Medicine, Geneva, Switzerland

Key words: food hypersensitivity; atopic dermatitis; IgE-mediated; diagnosis; prevalence; peanut; milk; egg

Philippe A. Eigenmann, MD, Allergy Unit, University Hospital of Geneva, 24 rue Micheli-du-Crest, 1211 Geneva 14, Switzerland
Tel.: +41-22-372 9417
Fax: +41-22-372 9369
E-mail: Philippe.Eigenmann@hcuge.ch

Accepted 12 January 2000

The role of food allergy in the pathogenesis of atopic dermatitis (AD) lesions is still debated, although compelling evidence links both conditions in a subset of children with AD (1–6). However, owing to frequent skin flares and to a high number of clinically non-relevant positive tests in routine diagnostic procedures, the diagnosis of food allergy in AD patients can be difficult to establish. For accurate diagnosis, the

prevalence of the disease and the most allergenic foods in a given population should be defined. The most frequent food allergens (peanuts, egg, milk, wheat, soy, fish) have been determined in different studies involving both American and European children (2,7–10). A prevalence of 33–60% has been found (2,8,9,11). However, most of these results were obtained in patients referred to allergy clinics for diagnosis of food

allergy, and might yield figures above the 'true' prevalence. In children seen primarily for AD at an allergy or a dermatology clinic, Burks et al. found positive skin-prick tests (SPTs) in 61%, but diagnosed food allergy by challenge in only 33% of the patients (12).

Recently, we conducted a study involving children recruited exclusively at a primary care clinic for AD (in order to avoid a selection bias for food allergy) (8). The prevalence of food allergy was 37%, and clinical sensitivities most frequently diagnosed in this North American population were to peanut, egg, and milk. These results may not be applicable to other populations. The current study was conducted, following a similar design, in Swiss children with AD. A standardized diagnostic protocol with routine SPTs to the most common foods, measurement of food-specific immunoglobulin E (IgE) antibodies, and standardized food challenges, was established. The results of these diagnostic procedures are reported.

Patients and methods

Patients

All consecutive new patients seen at the pediatric allergy or pediatric dermatology clinic, and diagnosed with AD according to the criteria of Hanifin & Rajka (13), were eligible for participation in the study. Patients with occasional but recurrent lesions and requiring less than one course of topical corticosteroid treatment per month were diagnosed with mild AD; those having persistent lesions but requiring topical corticosteroids less than three times a month with moderate AD; and those with persistent lesions involving more than three areas and requiring topical corticosteroids at least once a week were diagnosed with severe AD. The corticosteroid used was mometasone (potency class 3), and the

duration of a treatment course was 3–7 days. In addition, patients were using an ointment for skin hydration on a daily basis. The study was examined and approved by the Institutional Review Boards of the Department of Pediatrics.

Methods

Diagnostic procedures were conducted following the protocol outlined in Fig. 1. The initial visit to the allergist included routine SPTs with commercial food extracts to egg white, peanut, soy, cod fish, and hazelnut [1 : 3 w/v] (Stallergène, Antony, France), to cow's milk and wheat [5000 protein nitrogen units (PNU)/ml] (Allergopharma, Reinbeck, Germany), as well as to any other food suspected by history. A recent study revealed that screening by SPTs to these seven foods identifies 99% of AD patients with food allergy (7). SPTs were interpreted as positive when the mean diameter was ≥ 3 mm (14,15). In patients with positive SPTs, levels of food-specific IgE antibodies to the suspected food were measured by using the CAP System FEIATM (Pharmacia Diagnostics, Uppsala, Sweden) and interpreted according to predictive values established previously (Table 1) (16). When a CAP value was found above the 95% positive predictive value (PPV), food allergy was diagnosed without further investigations. Results below the 95% negative predictive value (NPV) were considered as highly unlikely for food allergy. In patients with CAP values above the 95% NPV and below the 95% PPV, the diagnosis was confirmed by a food challenge. Positive SPTs to foods to which the predictive value of CAPs was not established were further evaluated by food challenges, unless the patient had a suggestive history of a recent anaphylactic reaction consisting of definite urticarial lesions on two or more locations, and/or digestive and respiratory symp-

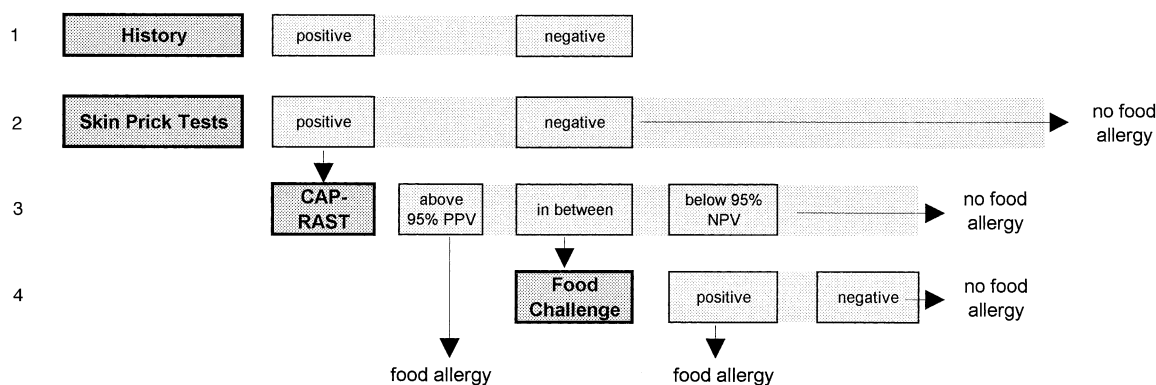


Fig. 1. Protocol for the diagnosis of food allergy in children with atopic dermatitis. NPV, negative predictive value; PPV, positive predictive value.

Table 1. Positive predictive CAP values (PPV) and negative predictive CAP values (NPV) to specific foods in the diagnosis of food allergy (95% PPV or 95% NPV unless specified otherwise)

Food	NPV	PPV
Milk	0.8	32
Egg	0.6 (90% NPV)	6
Peanut	<0.35 (85% NPV)	15
Wheat	5	>100 (75% PPV)
Fish	0.9	20
Soy	2	65 (50% PPV)

All CAP values are expressed in IU/ml.

Table adapted from Sampson & Ho (16).

toms, and/or shock temporally linked to the ingestion of the food.

Food challenges were performed as previously described and supervised by a physician trained in this procedure (8,17). Briefly, the suspected foods were removed from the diet at least 3–4 weeks prior to the challenges. Patients whose lesions of AD could be cleared by topical skin treatment were evaluated by an open oral food challenge protocol. Intravenous access was obtained, and emergency medications were available at the bedside. The food was given in graduated portions, over 60–80 min, up to a total corresponding to 10 g of dehydrated food. In patients with persistent skin lesions, the diagnosis was established by double-blind, placebo-controlled food challenge (DBPCFC), as previously described (17). Challenges were prepared and randomized by a dietician not directly involved with the procedures. The food or the placebo was camouflaged either in an infant formula or a juice. The two challenges were administered at least 4 h apart, and all symptoms were recorded. Negative challenges were confirmed by open feedings with the quantity of the test food normally consumed in a meal. Exclusion criteria for food challenges were a history of a severe anaphylactic reaction, or an age below that

considered at risk for introduction of allergenic foods (in our clinic: egg and fish, 12 months; peanuts and nuts, 36 months).

Results

Patients

A total of 74 consecutive patients were enrolled in this study (42 male, 32 female; median age 2.5 years: range 6 months to 16.3 years). Thirty-four were diagnosed with mild, 33 with moderate, and seven with severe AD.

Diagnosis by history

Suggestive histories for allergic reactions (worsening of AD, urticaria, and/or anaphylaxis) were obtained in 22 patients (29.7%) to a total of 44 foods. A diagnosis of food allergy based on a recent episode of an anaphylactic reaction was established in 14 patients to the following foods: fish, n=4; nuts, n=3; milk and peanut, n=2; mango, peaches, sesame, wheat, rye, and oat, n=1 (Table 2). In the patients with reactions to milk, peanut, fish, and wheat, CAP results were all positive but with food-specific IgE antibody levels below the 95% PPV. Owing to the severity of the initial reactions, a food challenge was contra-indicated. CAP tests with predictive values were not available for any other foods, but the history was suggestive for one or several anaphylactic reactions (in the presence or absence of eczema flares imputable to the food).

Screening by SPT

Initial screening by SPT identified 85 positive tests in 44 children (59.5%). SPTs were found to be positive most commonly to: eggs, n=26; peanuts, n=16; milk, n=14; wheat, n=5; soy, n=4; fish and nuts, n=3. No diagnosis of food allergy was based only on a positive SPT. Thirty

Table 2. Number of allergies to specific foods diagnosed by history alone (recent history of an anaphylactic reaction with a CAP value below the 95% positive predictive value [PPV]), by CAP alone (value above the 95% PPV in absence of a known previous ingestion of the food), by CAP and history, and by food challenges

Food	Diagnosed by history	Diagnosed by CAP only	Diagnosed by history and by CAP	Diagnosed by challenge	Total number of diagnoses to the food
Milk	2	0	3	6/8	11
Egg	0	9	2	1/2	12
Peanut	2	1	7	0/1	10
Wheat	1	0	0	3/5	4
Fish	4	0	2	1/1	7
Soy	0	0	0	1/3	1
Nuts	3	NA	NA	0	3
Others	5	NA	NA	3/23	8

NA, not applicable.

(40.5%) patients had negative SPTs. Fifty-nine negative SPTs in 21 patients were correlated with CAP results to verify their accuracy. In 48 SPTs, the corresponding CAP results were also negative, confirming the initial screening result. However, five negative SPTs to milk, two to wheat and peanuts, and one to soy and eggs, corresponded to CAP values between the 95% NPV and the 95% PPV. None of these patients were found to be allergic to the food.

Diagnosis by CAP

Children with positive SPTs were further evaluated by CAP. Values to 10 foods in nine patients, without previously known exposure, were found above the 95% PPV (egg $n=9$, peanut $n=1$) (Table 2). Owing to the high risk of a positive reaction ($>95\%$), these patients were not challenged. Ten patients with a suggestive history of a recent anaphylactic reaction and a CAP value above the 95% PPV were diagnosed as allergic to 14 foods (peanuts, $n=7$; milk, $n=3$; egg and fish, $n=2$). One patient with a history of possible skin flares of AD attributable to milk had a CAP value to milk above the 95% PPV. CAP results between the 95% NPV and the 95% PPV were further evaluated by standardized food challenge procedures, unless the patient was either eating the food without any allergic reaction, or was younger than the age of introduction of the food.

Diagnosis by challenge

Thirty-five open food challenges were administered to 11 patients without current lesions of AD, and eight DBPCFCs to six patients with a high skin reactivity and/or concomitant AD lesions (Table 2). Fifteen challenges were positive in six patients (10 open challenges and five DBPCFCs) with following symptoms: cutaneous (hives and/or erythematous pruritic lesions) $n=14$; respiratory (wheezing, cough and/or rhinitis) $n=4$; gastrointestinal (abdominal pain, vomiting and/or diarrhea) $n=3$. All symptoms were observed within 2 h after the completion of the challenge, except for an erythematous pruritic rash after 6 h in a child positive to wheat. The positive DBPCFCs were to: milk, $n=3$ and wheat, $n=2$; and the open challenges to: milk, $n=3$, barley, $n=2$, and oat, soy, fish, wheat, and eggs, $n=1$. None of the patients reacted to the placebo challenge. Further food challenges with negative results were to: chicken, turkey, pork, lamb, potato, tomato, peas, pears, apples, banana, corn, peanut, and rye.

Altogether, the diagnosis of food allergy by history and/or SPT was suspected for a total of 110 foods in 44 children. Twenty-five children with AD were diagnosed as allergic to 56 foods. The number of food-allergic patients classified by the diagnostic criteria are listed in Table 3. The prevalence of the disease was 33.8% (25 of 74) in the whole study population, and 28% (seven of 25) in patients recruited at the dermatology clinic (primarily referred for AD). Twelve patients were allergic to one food, seven to two foods, and six to three or more foods. Patients with severe AD had a high prevalence of food allergy (five of seven), while this proportion was lower in patients with moderate (12 of 33) and mild (eight of 34) AD.

Discussion

Diagnostic procedures for food allergy in children with AD should rely on a good knowledge of the prevalence and the most allergenic foods in a specific population. However, relatively few patient populations have been studied in detail. In the studies by Sampson et al., patients were mostly allergic to egg, milk, and peanuts, and had moderate and severe AD (2,18). More recently, a prevalence of food allergy of 37% was reported by the same authors, in a group of patients primarily referred to a dermatologist for AD (8). A similar proportion (33%) was found earlier by Burks et al. in a population of children, with AD, predominantly allergic to egg, milk, and peanuts (12). Further studies from the same group of investigators identified seven foods (milk, egg, peanut, soy, wheat, fish, and cashew) responsible for 89% of the positive diagnostic challenges (7).

In the UK, Atherton et al. identified skin reactions in 70% of 20 children with AD (11). Diagnostic exclusion diets in this study were only to egg and milk, and therefore may not have detected other food sensitivities. Guillet & Guillet found egg, milk, shellfish, cornstarch, peanut, fish, and soybean allergies in French children diagnosed with moderate or severe AD (19). More recently, a group from Spain found egg and fish sensitizations in 65% of children with AD (9). Niggemann et al. from Germany recently reviewed 387 DPCFCs to milk, egg, and wheat (10). Eighty-one per cent of these patients had a positive challenge, mostly to egg (70% of positive challenges). Other potential allergenic foods were, however, not evaluated. In all these studies, egg and milk allergies were common; however, other food sensitivities were mostly population specific. Furthermore, the prevalence data obtained cannot be extrapolated to other popula-

Table 3. No. of patients diagnosed as food allergic by specific diagnostic procedures

Classification	No. of patients
History of an anaphylactic reaction	6
CAP above 95% PPV	4
CAP above 95% PPV+ history	9
Food challenges	6
Total	25

Individual patients are classified under the most reliable diagnostic procedure performed. Patients listed under 'diagnosed by food challenges' might have other foods diagnosed by CAP and/or history, and patients listed under 'diagnosed by CAP and history' might have other allergies diagnosed by history alone. PPV, positive predictive value.

tions, owing to a recruitment selection bias for food allergy in most studies.

The general prevalence of food allergy in our patients was 33.8%. However, some were directly referred to the allergy clinic for suspicion of food allergy, which also resulted in a selection bias and a potential overestimation of the prevalence of food allergy. When considering only the patients recruited through the dermatology clinic (referred for primary care of their AD), the prevalence of the disease was slightly lower (28%). This number might reflect an accurate prevalence, with minimal selection bias, as the patients were self-referrals or referred to the dermatologist by primary care pediatricians for evaluation of AD, and not food allergy. In the current study, AD lesions were less severe, possibly explaining the slightly lower prevalence (28% vs. 37%), than found in the previous study using the same criteria for patient recruitment (8). Furthermore, a few patients who may have been food allergic (CAP values between the 95% NPV and the 95% PPV) were not challenged owing to their young age (less than 12 months old for eggs and fish, and less than 3 years for nuts and peanuts).

Thirty children (40.5%) had negative SPTs and/or CAP values at the initial screening, and 10 (13.5%) had a history of a recent anaphylactic reaction and/or CAP values highly suggestive for food allergy. These 40 patients (54.1%) did not require further investigations to confirm or reject the diagnosis of food allergy. However, patients diagnosed with food allergy on the basis of a strongly positive CAP result required follow-up food challenges to determine persistence or loss of sensitivity. Fifteen patients (20.3%) had one or several positive SPTs, but were not diagnosed as food allergic. This group is at risk of false diagnosis and may benefit from further investigations with food challenges. In general, SPT and CAP results correlated. However, SPTs to milk were negative in five patients with a positive CAP

result. None of these patients was found to be milk allergic. Fresh milk can be used for SPT to slightly increase the sensitivity of the test, and a potentially false-negative test should be correlated to a milk-specific CAP. A total of 43 food challenges were performed in 13 children with inconclusive screening test results. Twenty-eight (65.1%) were negative and 15 were positive in six patients. All other patients either tolerated the food or were below the age of introduction of the food and were not challenged at this time.

Our data might be extrapolated to other populations only after considering several caveats. First, the panel of foods recommended for use in screening tests corresponds to those most frequently diagnosed in food-allergic children living in westernized countries. Different feeding habits in early childhood might lead to other sensitizations, requiring re-evaluation of this list. Sensitivity of SPTs may also vary and be lower for certain foods (15). A patient with a negative SPT, but a suggestive history, should be further evaluated, and SPTs should only be performed by physicians familiar with this procedure and its interpretation. A serologic screening test for IgE antibodies specific to common foods might be a useful alternative. Second, the CAP values predictive for food allergy were established in a definite population of children with AD and food allergy (16). Positive or negative predictive values might vary with age or with total IgE antibody levels. They should be utilized as indicative numbers, and critically re-evaluated according to the history and the age of the patient. Finally, open challenges might be utilized safely in a subset of patients (8), but DBPCFCs remain the 'gold standard' for the diagnosis of food allergy. Open challenges with a negative outcome provide a predictive accuracy similar to DBPCFCs, while positive outcomes must be interpreted with caution, especially in children with allergies to multiple foods. If any doubt exists, a DBPCFC should follow an open challenge. In any child with an equivocal result at any stage of this diagnostic protocol, a physician familiar with the diagnosis of food allergy should be consulted for appropriate advice.

In summary, the prevalence of food allergy in our population of Swiss children with AD is comparable with others in Europe or North America. Egg and milk sensitivity was diagnosed most frequently. However, peanut allergy was as common in our population, possibly because children have peanut proteins introduced early to their diet (e.g. in the form of peanut butter). Therefore, all children with AD who are eval-

uated for food allergy should be routinely screened for peanut sensitivity. The diagnosis of food allergy could be established or excluded by SPT and/or by CAP in half of our patients. Standardized food challenge was an adequate diagnostic procedure for all other subjects. Allergy to most, but not all, foods is usually outgrown. Follow-up challenges will therefore be necessary in most allergic children.

Acknowledgments

This study was supported in part by grants from the Swiss National Research Foundation (32-44502.95 and 32-47118.96). We thank Drs Sampson and Sicherer for helpful discussions.

References

1. SAMPSON HA, JOLIE PL. Increased plasma histamine concentrations after food challenges in children with atopic dermatitis. *N Engl J Med* 1984; 311: 372–6.
2. SAMPSON HA, McCASKILL CC. Food hypersensitivity and atopic dermatitis: evaluation of 113 patients. *J Pediatr* 1985; 107: 669–75.
3. SAMPSON HA, SCANLON SM. Natural history of food hypersensitivity in children with atopic dermatitis. *J Pediatr* 1989; 115: 23–7.
4. CHARLESWORTH EN, KAGEY-SOBOTKA A, NORMAN PS, LICHTENSTEIN LM, SAMPSON HA. Cutaneous late-phase response in food-allergic children and adolescents with atopic dermatitis. *Clin Exp Allergy* 1993; 23: 391–7.
5. LEVER R, MACDONALD C, WAUGH P, AITCHISON T. Randomized controlled trial of advices on an egg exclusion diet in young children with atopic eczema and sensitivity to eggs. *Pediatr Allergy Immunol* 1998; 9: 13–9.
6. BRUIJNZEEL-KOONEN C, ORTOLANI C, AAS K, et al. Adverse reactions to food. European Academy of Allergology and Clinical Immunology Subcommittee. *Allergy* 1995; 50: 623–35.
7. BURKS AW, JAMES JM, HIEGEL A, et al. Atopic dermatitis and food hypersensitivity reactions. *J Pediatr* 1998; 132: 132–6.
8. EIGENMANN PA, SICHERER SH, BORKOWSKI TA, COHEN BA, SAMPSON HA. Prevalence of IgE-mediated food allergy among children with atopic dermatitis. *Pediatrics* 1998; 101: e8.
9. RESANO A, CRESPO E, FERNANDEZ BENITEZ M, SANZ ML, OEHLING A. Atopic dermatitis and food allergy. *J Invest Allergol Clin Immunol* 1998; 8: 271–6.
10. NIGGEMANN B, SIELAFF B, BEYER K, BINDER C, WAHN U. Outcome of double-blind, placebo-controlled food challenge tests in 107 children with atopic dermatitis. *Clin Exp Allergy* 1999; 29: 91–6.
11. ATHERTON DJ, SEWELL M, SOOTHILL JF, WELLS RS, CHILVERS CED. A double-blind controlled crossover trial of an antigen-avoidance diet in atopic eczema. *Lancet* 1978; i: 401–3.
12. BURKS AW, MALLORY SB, WILLIAMS LW, SHIRRELL MA. Atopic dermatitis: clinical relevance of food hypersensitivity reactions. *J Pediatr* 1988; 113: 447–51.
13. HANIFIN JM, RAJKA G. Diagnostic features of atopic dermatitis. *Acta Derm Venereol (Suppl)(Stockh)* 1980; 92: 44–7.
14. BOCK SA, BUCKLEY J, HOLST A, MAY CD. Proper use of skin tests with food extracts in diagnosis of hypersensitivity to food in children. *Clin Allergy* 1977; 7: 375–83.
15. EIGENMANN PA, SAMPSON HA. Interpreting skin prick tests in the evaluation of food allergy in children. *Pediatr Allergy Immunol* 1998; 9: 186–91.
16. SAMPSON HA, Ho DG. Relationship between food-specific IgE concentrations and the risk of positive food challenges in children and adolescents. *J Allergy Clin Immunol* 1997; 100: 444–51.
17. BOCK SA, SAMPSON HA, ATKINS FM, et al. Double-blind, placebo-controlled food challenge (DBPCFC) as an office procedure: a manual. *J Allergy Clin Immunol* 1988; 82: 986–97.
18. EIGENMANN PA, SAMPSON HA. An update on food hypersensitivity. *Fund Clin Immunol* 1994; 2: 121–33.
19. GUILLET G, GUILLET MH. Natural history of sensitizations in atopic dermatitis. *Arch Dermatol* 1992; 128: 187–92.