

Food hypersensitivity in children: Clinical aspects and distribution of allergens

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The aims of this work were to investigate, in children and adolescents, the clinical aspects of food hypersensitivity and the distribution of allergens, in a prospective and descriptive study. Five hundred and forty-four pediatric cases from a series of 703 patients with food allergies, confirmed by food challenge, were studied. Their clinical characteristics and the distribution according to allergen were investigated. There was a family history of atopic disease in 70.5% of patients. Atopic dermatitis was the main symptom (275/544; 50.5% of patients), followed by urticaria and angio-edema (165/544; 30%). There was asthma in 8.6% of patients (47 children) and anaphylaxis in 4.5% (27 patients). The rarest signs were rhinitis ($n=2$; 0.3%), oral allergy syndrome ($n=8$; 1.4%), and gastrointestinal signs ($n=11$; 2%). Five allergens accounted for 78% of food hypersensitivity. These allergens were: eggs (36%), peanuts (24%), cow's milk (8%), mustard (6%), and cod (4%). Peanut was the most common allergen for children over the age of 3 yr. In this selected population, sensitivity of individuals to more than three foods was unusual (5%). Atopic dermatitis was the main symptom of food allergy in children. The symptoms changed over time, with respiratory disorders, oral allergy syndrome and ocular problems occurring later. Anaphylaxis also occurred mostly in older children. Five allergens were responsible for more than three-quarters of food allergies in children. However, the number of allergens implicated was higher for the group of children over the age of 6 yr than for younger children.

F. Rancé¹, G. Kanny², G. Dutau¹ and D. -A. Moneret-Vautrin²

¹Department of Respiratory and Allergic Diseases in Children and Adolescents, University Hospital Purpan, Toulouse cedex, France, ²Medecine Department D, 29 avenue De Lattre De Tassigny, University Hospital, Nancy cedex, France

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Dr F. Rancé, Department of Respiratory and Allergic Diseases in Children and Adolescents, University Hospital Purpan, Place du Dr Baylac, F-31059 Toulouse cedex, France
Tel.: + 33 5 61 77 75 52
Fax: + 33 5 61 77 77 31

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Food hypersensitivity involves a number of clinical signs which are associated with an allergic immune response that is dependent on immunoglobulin E (IgE) antibodies directed against food allergens (1). Food hypersensitivity has increased in prevalence over the last few years (2–4). This increase seems to be, in part, a result of improvements in screening and diagnosis, but also because of changes in dietary habits with introduction of new allergens and exposure to new products that may be allergenic.

The prevalence of food allergy and intolerance has been studied in a random sample of the Dutch adult population, using a questionnaire. The rate of proven allergy or intolerance was found to be 0.8% in the general population (5). The prevalence rate, after double-blind, placebo-controlled food challenge, was estimated to be

1.4% in UK subjects (6). These population-based data take account of the fact that allergies to foods are most prevalent in children, in particular preschool infants (7–10). We report on the French experience of food hypersensitivity in children and adolescents, and describe the clinical features and distribution according to age and allergen.

Materials and methods

Study population

A prospective study was performed at the medical centers of Toulouse and Nancy, France, involving 703 cases of food hypersensitivity in adults, children, and adolescents. We analyzed the results of food hypersensitivity in children and

adolescents, and the observations were validated using the proposals of the European group for the study of food allergies (3, 4, 11, 12). Sensitization was confirmed by positive skin-prick tests (SPT) and/or specific IgE. Observations were validated with one of the following criteria: a positive standardized food challenge, improvement after 6 months of avoidance of the suspected food, a history of unequivocal anaphylactic reaction, or a fruit or vegetable oral allergy syndrome in a subject with allergy to pollen. Food-induced anaphylaxis was defined as an immediate systemic reaction caused by immune response, and manifested by an abrupt onset of symptoms within minutes to hours of ingestion of a food (13–17). Anaphylaxis was recognized by a generalized reaction that included cutaneous, respiratory, cardiovascular, and gastrointestinal signs and symptoms. Oral allergy syndrome was defined as allergic symptoms occurring within 5–15 min after eating fruits or vegetables, localized to the oral mucosa as oral irritation, tongue swelling and itching, palatal itching, lip tightness or swelling (18, 19). The results were inserted into a computer database for analysis.

The study population consisted of 544 children (544 of 703 food hypersensitivity cases) – 344 boys and 200 girls, giving a gender ratio of 1.7 (M:F). Food hypersensitivity concerned children aged under 15 yr in three-quarters of the cases (77.4%), and 58.4% of the children were younger than 3 yr. Four groups were defined: group 1, 97 children aged between 1 month and 1 yr (17.8%); group 2, 221 children aged between 1 and 3 yr (40.6%); group 3, 123 children aged between 3 and 6 yr (22.6%); and group 4, 103 children aged between 6 and 15 yr (18.9%). The clinical symptoms and the food allergens implicated were studied for the total population and according to age and clinical signs.

Methods

Skin prick tests. Stallergenes (Fresnes, France) or Allerbio (Varennes en Argonne, France) or fresh extracts (France; 1:10 w/v) were used for SPTs. A drop of extract was placed on the skin of the inner forearm, and a lancet with a 1-mm tip (Dome Hollister-Stier, Slough, UK) was used to prick the skin through the drop. A clinical history of food allergy was followed by testing the following allergens: peanut, almond, banana, beef, carrot, chicken, cod, maize, egg white, egg yolk, garlic, hazelnut, cow's milk, peas, pork, potato, rye, crab, soybean, melon, tomato, tuna, walnut, wheat, celery, mustard, baker's yeast, orange pips, sesame, kiwi fruit,

prawn, apple, peach, vanilla, vanillin, and chocolate. Other foods were used for SPTs, as appropriate. The size of the wheal produced was compared in each case with that induced by histamine, and 10 mg/ml histamine base and/or 9% codeine if the test with histamine was negative. We excluded dermographic reactions with a negative control solution, 50% glycerosaline. Only wheals that were $\geq$ one-half of the average size of the positive control, and ≥ 3 mm, were scored as positive.

Serum IgE. A blood sample was taken for determination of specific IgE antibodies to the allergens used in the SPTs. We used immunoenzymatic methods to determine specific IgE antibodies (Cap-system; Pharmacia, Saint Quentin, Uvelines, France). A child was regarded as being sensitized to a particular allergen if the concentration of specific IgE antibodies was ≥ 1.50 IU/ml.

Food challenge. Labial food challenge (LFC) was performed as previously described (12). Briefly, allergen extracts were placed on the lower lip and left for 2 min. The result was read 30 min later. The five scores were: 1, smoothing of the lower lip; 2, erythema under the lip; 3, contiguous rash of the cheek and chin; 4, edema of the lip with rhinitis and conjunctivitis; 5, systemic reaction. A score of 3 or higher was considered positive. Children with negative LFC were investigated by single-blind, placebo-controlled food challenge. The methods used and the criteria for a positive result in an oral food challenge were as described elsewhere (3, 4, 20). The food suspected was eliminated from the diet for 2 weeks before testing. Between 0.1 and 10 g of lyophilized food was masked in stewed apples, and administered over 20 min. One challenge contained placebo, and the other contained the suspected food on the following day. All reactions were scored as to type, time of onset, severity, and duration. Symptoms included cutaneous symptoms (urticaria, edema), gastrointestinal symptoms (nausea, abdominal pain, vomiting, and diarrhea), respiratory symptoms (dyspnea, cough, wheezing), and upper airway symptoms (rhinitis, conjunctivitis, laryngeal edema). Only symptoms that developed within minutes to 2 h from the last dose of the food challenge were used for the diagnosis.

Table 1. Clinical symptoms of food hypersensitivity in 544 children aged from 1 month to 15 yr, with positive skin prick test and/or specific IgE and positive food challenge (%)

	0–1 yr	1–3 yr	3–6 yr	6–15 yr	Total
No. of patients (%)	97 (17.8)	221 (40.6)	123 (22.6)	103 (18.9)	544
Symptom					
Atopic dermatitis	76	141	42	16	275 (50.5)
Urticaria, angio-edema	15	56	50	44	165 (30.3)
Asthma	3	6	20	18	47 (8.6)
Anaphylaxis	2	6	5	14	27 (4.9)
Laryngeal edema	0	5	3	8	16 (4.2)
Gastrointestinal	1	6	3	1	11 (2)
Oral allergy syndrome	0	0	1	7	8 (1.4)
Conjunctivitis	0	0	2	0	2 (0.3)

Results

In this selected material, a family history of atopic disease was reported in 384 of the children (70.5%). Atopic dermatitis was the main symptom of food allergy (see Table 1 for details of the clinical signs recorded).

We analyzed the frequency of clinical signs as a function of age and found that atopic dermatitis was very common in children under the age of

Table 2. Frequency of food allergy to various foods in 544 children with positive prick tests and/or specific IgE and positive food challenge

Food	No. of patients	% (813 foodstuffs)
Egg	291	35.7
Peanut	192	23.6
Cow's milk	68	8.3
Mustard	49	6
Cod	35	4.3
Hazelnut	15	1.8
Kiwi fruit	13	1.5
Wheat	13	1.5
Shrimp	12	1.4
Beef	8	0.9
Pea	7	0.8
Lentil	7	0.8
Soya	7	0.8
Lupin flour	7	0.8
Sesame seed	5	0.6
Vanilla	4	0.5
Salmon	4	0.5
Walnut	4	0.5
Pork	3	0.3
Almond	3	0.3
Crab	3	0.3
Apple	3	0.3
Banana	3	0.3
Chicken	3	0.3
Goat's milk	3	0.3

Two cases of allergy were reported for each of the following foods: vanillin, pepper, fennel, mandarin, cherry, duck, trout, cashew nut, Brazil nut, garlic, celery, baker's yeast, and chickpea.

One case of allergy was reported for each of the following foods: rabbit, pig's kidney, whelk, sardine, scampi, coriander, avocado, peach, chestnut, fig, green pepper, squid, carrot, turkey, ewe's milk, snail, broad bean, green bean, angler fish, and melon.

Table 3. Frequency of the predominant foods implicated in food allergy according to age (544 children aged from 1 month to 15 yr with positive skin prick tests and/or specific IgE and positive food challenge)

Food	0–1 yr	1–3 yr	3–6 yr	6–15 yr	total
Egg	87	156	38	10	291
Peanut	21	84	50	37	192
Cow's milk	15	38	13	2	68
Mustard	1	15	16	17	49
Cod	0	10	11	14	35
Total	124	303	128	80	635

Other food allergens according to age (no. of patients) were: 0–1 yr: wheat (3), pork (2), beef (2), and 1 case for vanillin, pea, vanilla, chestnut, fig, soy, green pepper and banana; 1–3 yr: wheat (7), hazelnut (6), beef (5), kiwi fruit (3), shrimp (2), almond (2), trout (2), garlic (2), chicken (2), pea (2), lupin flour (2), vanilla (2) and 1 case for cashew nut, crab, banana, salmon, pork, lentil, soy and goat's milk; 3–6 yr: kiwi fruit (5), hazelnut (5), lentil (3), sesame seed (3), wheat (3), lupin flour (3), goat's milk (2), mandarin (2), shrimp (2), pea (2) and 1 case for rabbit, salmon, vanillin, vanilla, chickpea, soy, ewe's milk, baker's yeast, walnut and cashew nut; 6–15 yr: shrimp (8), kiwi fruit (5), hazelnut (5), soy (5), apple (3), lentil (3), pepper (3), cherry (2), fennel (2), crab (2), celery (2), salmon (2), pea (2), chicken (2), duck (2), lupin flour (2), walnut (2) and 1 case of pig's kidney, almond, coriander, avocado, sardine, banana, peach, scampi, whelk, pepper, beef, baker's yeast, Brazil nut, squid, carrot, turkey, snail, broad bean, green bean, angler fish, melon, chickpea, and sesame.

3 yr. The prevalence of atopic dermatitis was lower among older than younger children. In contrast, other clinical signs, such as laryngeal edema, angio-edema, asthma, and anaphylaxis, were more prevalent among older children. Anaphylactic reaction was reported for 51.8% of the children over the age of 6 yr. Oral allergy syndrome and conjunctivitis occurred only in older children.

Five food allergens were responsible for 78.1% of food allergies: egg, peanut, milk, mustard, and cod (Table 2). A wide variety of other food allergens also caused reactions (listed in Table 2).

We investigated which food allergens caused allergy in children of the various age groups. Peanut was the most common allergen in children over the age of 3 yr (Table 3). The number of allergens implicated was greater for children over the age of 6 yr than for younger children.

We assessed whether particular allergens were associated with particular clinical signs. All the

Table 4. Clinical symptoms, according to the five predominant food allergens, in 544 children with food allergy

Symptoms	Egg	Peanut	Milk	Mustard	Cod
Atopic dermatitis	204	89	34	21	8
Urticaria, angio-edema	61	61	18	21	17
Asthma	13	28	4	2	7
Anaphylaxis	8	9	5	1	2
Gastrointestinal	4	4	5	1	0
Oral allergy syndrome	0	1	0	1	1
Conjunctivitis	1	0	2	2	0
Total	291	192	68	49	35

Results are expressed as no. of patients.

Table 5. Multiple food hypersensitivity in 544 children with food allergy

	No. of patients	%
Two-food hypersensitivity	134	24.6
Three-food hypersensitivity	38	7.0
Four-food hypersensitivity	16	2.9
Five-food hypersensitivity	10	1.8

food allergens tested were involved in atopic dermatitis (Table 4). In cases of anaphylaxis, the foods well known to be allergens (including crustaceans) were frequent causes of anaphylaxis. In descending order of frequency, these were: peanut, egg, milk, cod, mustard, crustaceans (crab, shrimp, and scampi), sardine, hazelnut, cashew nut, and pig's kidney (Table 4).

Multiple food hypersensitivity was caused by three food allergens in 38 patients (7%), four allergens in 16 patients (2.9%), and five allergens in 10 patients (1.8%) (Table 5).

Discussion

Food allergy is commonest in children, particularly preschool infants. The estimated prevalence was 6–8% in children under the age of 2 yr and 1.5% in adults (21). Food allergy has been reported to occur mainly in atopic subjects (22); this was confirmed in our study. Our results showed that food allergy affects young children, with most cases reported in children under the age of 3 yr.

This study is a description of findings and symptoms in a selected population with food allergy. Some reactions were severe, involving respiratory and cardiovascular symptoms, as demonstrated by recent studies. Food-induced anaphylaxis and fatal food-induced anaphylaxis were described in children and adolescents. Cow's milk allergy has been implicated in several cases of death of suckling infants (23, 24). Sampson et al. reported seven cases of near-fatal anaphylaxis of which one was caused by peanuts, two by cow's milk, and six owing to ingestion of other foods. Three of these six deaths followed consumption of peanuts outside the home (16). Similarly, four of the seven deaths caused by food allergy reported by Yunginger et al. were caused by eating peanuts (17). Indeed, most deaths from food allergy are caused by peanut or hazelnut. The severity of peanut allergy is clear from this and other recent studies (25), in which peanut was the principal cause of anaphylaxis.

Skin reactions include atopic dermatitis urticaria and angio-edema. Atopic dermatitis is particularly common in children (26–28).

However, it is difficult to demonstrate an association between atopic dermatitis and food allergy (28). Atopic dermatitis was the most common symptom in our series of allergic children. Respiratory symptoms such as asthma and rhinitis were less common. However, asthma is a severity factor, reported in the most severe forms of food allergy (16, 17). The other common symptoms were gastrointestinal, including nausea, vomiting, diarrhea, and abdominal pain (29).

Oral allergy syndrome appears to be a manifestation of adult food allergy (30). Other clinical signs, such as food-associated exercise-induced anaphylaxis, were not reported in our study (31, 32).

The prevalence of allergy to individual foods clearly varies with the dietary practices of different populations. Peanut and tree nuts caused most episodes of food allergy in the USA and the UK (25). Fish allergy is common in Spain and Portugal (33, 34). Seafood and milk are reported in food-induced anaphylaxis from Italy (35). Our study found an increasing peanut and mustard allergy in France. The increasing allergy to mustard has been reported in other studies (36). A larger number of food allergens affect older than younger children. These observations suggest that a list of usual food allergen tests could be standardized according to age. The list must be based on the best available test, placebo-controlled food challenge, or a report of a reaction with the typical features of an IgE-mediated anaphylactic reaction. Double-blind, placebo-controlled food challenge (DBPCFC) studies in children and adults have shown that a shortlist of eight foods account for 90% of IgE-mediated allergic reactions: cow's milk, egg, peanut, soya, wheat, fish, crustacea, and seeds (sesame, cottonseed) (4, 27). If the age of the children is taken into account, as in our study, it is clear that peanut is the principal food allergen affecting children over the age of 3 yr. Our study also reveals the emergence of new allergens in children, such as sesame seeds (37). There has also been an increase in the frequency of allergy to some allergens, such as lentils, peas (25, 34), and leguminous species from the same botanical family as peanut.

Conclusion

In the very young age group, the predominant manifestation of food allergy is atopic dermatitis. It is difficult to prove a link between a food allergy and atopic dermatitis. Isaulori & Turjanmaa used a combination of patch tests and prick tests with foodstuffs to study food

allergy in patients with eczema (38). The results of such tests may be of value for identifying the cause of eczema and for designing avoidance diets.

The symptoms change and worsen with age. In particular, respiratory, oral allergy syndrome, and ocular symptoms are more common in older children. Anaphylaxis is also a symptom associated with older children and adults.

Five food allergens: egg, peanut, milk, mustard, and fish, were responsible for symptoms in $\approx 78\%$ of patients. Peanut was the predominant allergen in children over the age of 3 yr. A greater number of allergens caused symptoms in children over the age of 6 yr, and this older age group presents a pattern similar to that in adults. Sensitivity of individuals to more than three foods was unusual (5%).

The diagnosis of food allergy is difficult because of its clinical diversity. Food challenge should be carried out for the diagnosis of food allergy so that studies can be standardized. This should improve both diagnosis and treatment.

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