

Oral allergy syndrome (OAS): symptoms of IgE-mediated hypersensitivity to foods

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Summary

Eighty highly atopic patients were selected for study because they had either atopic eczema (fifty cases) or atopic reactivity to foods, as judged by a positive skin-prick test (thirty cases). In all, sixty-five out of eighty subjects (81%) described symptoms of some kind provoked by foods, but correspondingly positive skin tests were found in only half of these, thirty-three out of eighty (41%). The symptoms experienced by thirty-one of the thirty-three patients with positive skin tests were immediate in onset (within 1 hr) and were at first confined to the upper gastrointestinal tract, the most frequent symptoms being oral irritation and throat tightness. In a proportion of these patients, further symptoms such as urticaria, asthma or anaphylaxis developed following the initial oral symptoms, which suggested the term 'oral allergy syndrome'. In the absence of the oral allergy, symptoms such as asthma, urticaria, migraine or eczema starting later than 1 hr after food were seldom associated with positive skin tests. In the oral allergy syndrome, the characteristic symptoms (strong association with positive skin tests and RAST, time of onset and sites at which symptoms are expressed) suggest a causative relationship between exposure to food antigens and specific IgE-induced release of mediators. In cases of food intolerance that lack a characteristic symptom pattern and a positive skin test or radio-allergo-sorbent test, it seems appropriate to consider non-IgE-mediated causes.

Introduction

The term 'food allergy' has been used to describe a wide variety of food-induced symptoms, and this has led to a conceptual confusion about the mechanisms involved. Symptoms that have at some time been attributed to 'food allergy' include asthma, eczema, angioedema, urticaria, anaphylaxis, rhinitis, nausea, vomiting, diarrhoea,

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migraine, serous otitis media, mood change, behaviour disorders such as hyperactivity and the sudden infant death syndrome (for review see [1,2]). 'Food allergic' symptoms that have an immediate onset (i.e. within 1 hr of ingesting the food) are often associated with positive skin-prick tests (SPT) or radio-allergo-sorbent tests (RAST) to the offending food [3]. The results of such tests correlate well with those of food challenge in children [4] and adults [5].

Those symptoms that have a late or delayed onset, such as asthma or eczema, are less easy to understand in terms of an IgE-mediated phenomenon and are less constantly associated with positive SPTs or RASTs [3,6]. Furthermore, the symptoms of migraine and behaviour disorders show no correlation whatsoever with positive tests for IgE antibody to the implicated food [7]. While 'food allergic' symptoms of the delayed type appear to be more frequent in atopic subjects, whether induced by food or not, the link with IgE-mediated disease is by association rather than direct evidence.

It was the purpose of this study to assess the frequency of food-induced symptoms in a highly atopic population (patients with atopic eczema) and in a separate group of patients attending an Allergy Clinic who had positive skin-prick tests to one or more foods. An attempt was made to delineate those symptoms that were significantly associated with evidence of IgE-mediated hypersensitivity as judged by a positive skin-prick test to the food concerned. The term 'food allergy' is used here solely to mean an immediate hypersensitivity reaction mediated by IgE, corresponding to food anaphylaxis as defined by the Committee on Adverse Reactions to Foods at the NIH [1].

Subjects and methods

Patients

(1) The Atopic Eczema group consisted of fifty patients attending the Dermatology Department who had been diagnosed as having atopic eczema from their skin lesions and, in most, a history of other atopic symptoms. Their mean age was 20 years, (range 4–41 years with thirteen < 14 years old, and comprised twenty-five males and twenty-five females.

(2) The Food-Reactive group consisted of thirty patients from those attending the Allergy Clinic, who were selected on the basis of records showing positive skin-prick tests to foods within the last 4 years. Their mean age was 25 years, (range 3–60 years) with six < 14 years old, and comprised twelve males and eighteen females.

History

A careful clinical history was taken from each patient for possible atopic symptoms, including asthma, hay fever, eczema, urticaria, angioedema or migraine, and for a family history of such symptoms. Patients were asked about symptoms provoked by foods and were directly asked about reactions to milk or dairy products, egg, fish, shellfish, nuts, peanuts, flour, apples, oranges, pears, strawberries, tomatoes, meats, colourings, flavourings or aspirin. Particular attention was paid to: (i) age of onset of symptoms; (ii) provoking factors recognized by the patient; (iii) provoking factors suggested by medical attendants or others and whether they were confirmed by the patient or not; (iv) the time between ingestion of food and the onset of symptoms; (v) the reliability of symptoms with each ingestion of an offending food, and (vi) whether an elimination diet had been successfully tried or not.

Table 1. Atopic and food induced symptoms, skin-prick tests and IgE levels in fifty patients with atopic eczema and thirty food reactive patients

	Atopic eczema		Food reactive	
	No.	(%)	No.	(%)
Eczema	50	(100)	20	(67)
Asthma	32	(64)	24	(80)
Hay fever	36	(72)	26	(87)
Urticaria	25	(50)	22	(73)
Migraine	10	(20)	14	(47)
Food symptoms*	35	(70)	30	(100)
Atopic family history	46	(92)	27	(90)
Positive SPT:				
—inhaling	43	(86)	26	(87)
—foods	20	(40)	20†	(67)
Total IgE(IU/ml)				
—Geometric mean	1350		620	
(log ₁₀ ± s.e.)	(3.13 ± 0.12)		(2.79 ± 0.17)	

* Symptoms of any kind recognized by the patient.

† At time of study (see text).

Skin-prick tests (SPT)

These were performed on the volar aspect of the forearm using allergen extracts (Bencard Ltd, Brentford, Middlesex) of common inhalants (mixed pollens, cat fur and house dust mite) and foods (milk, egg, cod, mixed nuts, crab, apple, orange) and, where possible, any others causing symptoms. Positive SPTs were weals 4 mm or greater in diameter than the controls.

Radio-allergo-sorbent test (RAST)

This was performed by Phadebas RAST (Pharmacia Ltd, Uppsala, Sweden) according to the manufacturer's instructions, except that horse serum was used as a diluent and all sera were diluted 1:10 or more, so that the test sample contained less than 2000 i.u./ml of IgE. RAST was done with inhalants (pollens, *D pteronyssinus* and cat fur) and foods (milk, egg, cod, crab, nut, wheat, tomato and orange).

Total IgE

This was measured by double-antibody radio-immunoassay as previously described [8].

Results

Comparison of atopic parameters in the Eczema and Food-Reactive groups

Both groups of patients were highly atopic and showed a similarly high incidence of an atopic family history, hay fever, asthma, positive skin-prick tests (SPT) to inhalant allergens, and elevated serum IgE levels (Table 1). By definition, the Eczema group all had eczema—a significantly higher incidence than in the Food-Reactive group

($P = < 0.001$) which, however, had a higher incidence of food-related symptoms ($P = < 0.001$) and positive SPT to foods ($P = 0.04$). Food symptoms, in this context and elsewhere, mean any symptoms recognized by the patient in relation to food. There was also a higher incidence of urticaria ($P = 0.07$) and migraine ($P = 0.02$) in the Food-Reactive group, compared with the Eczema group by the χ^2 test using Yates' correction. Only twenty of the thirty Food-Reactive patients still showed positive skin tests to foods when examined in this study. This was due to a loss of the skin test response in four patients, and because of a change in the definition of a positive skin test from 3 to 4 mm in the other six. Foods inducing 3 mm skin test responses were associated with symptoms in only one out of seventeen Eczema patients (for one out of twenty-one foods) and four out of twelve Food-Reactive patients (for four out of seventeen foods). Skin test responses of 4 mm or greater were much more likely to be associated with symptoms (Table 2).

The two patient groups, however, were strikingly similar, and for the purpose of examining food-related symptoms they were analysed together.

Skin test responses and RAST to foods

SPT and RAST results at the time the study was performed are shown in Tables 2 and 3, regardless of the type of symptoms provoked or whether ingestion of the food could still provoke symptoms. With animal food proteins these two tests of specific IgE antibody showed significantly more positive results in symptomatic than asymptomatic patients, and for both tests patients with symptoms to milk had the lowest frequency of positive results. In asymptomatic patients there was a low frequency of 'false positive' skin tests to foods except for crab. Despite their negative history, sensitivity to crab could not be ruled out because three of the asymptomatic patients could never recall having eaten crab or shellfish and the remainder seldom ate such food. Provocation

Table 2. Skin-prick test responses in patients with and without symptoms provoked by food

Food†	SPT in patients who are:			
	Symptomatic		Asymptomatic	
	+ ve/tot*	(%)	+ ve/tot*	(%)
Crab	4/5	(80)	6‡/48	(12)§
Cod	9/15	(60)	0/52	(0)¶¶
Egg	20/33	(61)	1/46	(2)¶¶
Milk	6/23	(26)	0/53	(0)**
Nuts	14/21	(67)	1/46	(2)¶¶
Wheat	—		—	
Orange	—		—	
Tomato	—		—†	

* Number with positive SPT/total number tested.

† Only one +ve response.

‡ Three patients did not recall eating crab or shellfish.

§ $P = < 0.01$; ¶¶ $P = < 0.0001$ and ** $P = < 0.0002$ comparing asymptomatic with symptomatic patients by χ^2 using Yates' correction.

Table 3. RAST results* in patients with and without symptoms provoked by foods

Food	Symptomatic		Asymptomatic	
	+ ve/tot	(%)	+ ve/tot	(%)
Crab	3/3	(100)	10†/40	(25)
Cod	3/4	(75)	4/41	(10)‡
Egg	9/12	(75)	5/33	(15)§
Milk	2/6	(33)	0/38	(0)¶¶
Nuts	4/9	(44)	12/36	(33)
Wheat	3/3	(100)	12/42	(29)
Tomato	1/5	(20)	8/40	(20)
Orange	0/3	(0)	12/42	(29)

* Excluding Class I reactions.

† One patient did not recall eating crab.

‡ $P = < 0.02$; § $P = < 0.0001$ and ¶¶ $P = 0.002$ comparing asymptomatic with symptomatic patients by the χ^2 test.

tests may have revealed sensitivity in some of these cases. The virtual absence of positive skin tests to wheat, tomato and orange raises the question as to whether these skin test solutions were effective, but we shall see later that symptoms to these foods differed from those seen towards foods giving positive skin tests.

RAST was performed on forty-five of the Eczema patients. There was a higher proportion of 'false positive' RASTs than SPTs among asymptomatic patients, and this was particularly marked with plant food allergens (most obvious in the case of nuts). Non-specific binding in the RAST can occur when test samples contain more than 2000 IU/ml of IgE [9]. Despite dilution of serum samples below this level of IgE, 'false positive' RASTs to plant allergens (wheat, nut, tomato or orange) occurred in eighteen out of twenty patients (90%) whose undiluted serum IgE was above 2000 IU/ml, as compared with two out of twenty-five of those whose serum IgE was below this level (8%). Furthermore, a positive RAST to wheat was always accompanied by a strongly positive RAST to grass pollen (mean class 3.4) and although a positive RAST to grass pollen (mean class 2.3) could occur with a negative RAST to wheat, the opposite was never seen.

Sequence of symptoms following oral irritation

Thirty-six of the eighty patients (45%) gave a history of oral symptoms in response to food ingestion that always preceded the onset of any accompanying symptoms such as asthma or nausea and vomiting (see Table 4). Half of these patients only experienced the initial oral symptoms, while the remaining eighteen patients (in addition to the initial oral symptoms) had experienced various combinations of nausea, abdominal discomfort, vomiting, asthma, urticaria, diarrhoea and anaphylaxis on at least one occasion. Urticaria usually affected the neck and upper chest, but it could occur anywhere on the body and, like angioedema, sometimes led to swelling of the eyes. The various symptoms are grouped together as the OAS because they occurred in a clear chronological order that is not indicated by any of the recognized terms in current use. The initial symptoms, usually described as a sensation of tingling in the lips or mouth followed by a feeling of tightness at the back of the throat, often occurred with small

amounts of the offending food, while the subsequent development of additional symptoms was reported to be likely to occur when greater quantities were ingested. The quantities of food involved varied according to the patient's sensitivity. Thus, a highly sensitive patient might describe the initial oral symptoms following ingestion of a trace of egg or a single peanut, while subsequent symptoms (Table 4) ensued from the inadvertent ingestion of part of a peanut-butter sandwich or of an egg flan.

Correlation between symptoms and skin tests

Table 5 shows the type of symptoms that patients associated with eating certain foods. The symptoms were classified as 'immediate' (occurring with 1 hr), 'late' (between 1 hr and 8 hr) and 'delayed' (later than 8 hr and usually between 16 hr and 48 hr). In Table 5, patients were only included if they were able to be skin tested against an appropriate food extract. Most patients with a history of oral symptoms or vomiting had positive skin tests of the food involved. Three of these patients with negative skin tests had already lost their hypersensitivity by the time the study was performed (Table 5) and other patients had avoided eating seven of the foods (which gave negative skin tests) for between 3 years and 13 years. If such patients were excluded from analysis then there was almost a complete association between positive skin tests and symptoms of OAS or vomiting induced by specific foods. Skin tests were negative, or infrequently positive, to foods involved in other types of immediate symptoms, and late or delayed symptoms excepting eczema. Six out of seven of the patients with eczema who had positive skin tests to foods known to aggravate their eczema also had symptoms of OAS towards the same foods. There was no significant difference in total IgE levels between patients with OAS (median: 1620 IU/ml or 3.21 ± 0.14 log mean₁₀ $\pm$ s.e.) and those without (725 IU/ml or 2.86 ± 0.13).

It is worth emphasizing that where solitary symptoms or urticaria, asthma, abdominal discomfort or nausea occurred without the initial oral symptoms, there was no positive correlation with skin tests (Table 5). Most patients had symptoms provoked by more than one food, and many patients had more than one class of

Table 4. The Oral Allergy Syndrome (OAS)

Onset after food	Initial symptoms	No. cases
Within 15 min*	Oral irritation	36
	Throat tightness	30
	Lip tightness/swelling	21
	Oral mucosal blebs	11
15-60 min	May proceed to:	
	Urticaria	8
	Conjunctivitis/orbital oedema	9
	Asthma	10
30-60 min	Anaphylaxis	3
	Abdominal pain	6
	Nausea and vomiting	10
	Rarely—diarrhoea	3
	—rhinitis	3

* Facial flushing may also occur.

Table 5. Symptoms provoked by food related to SPT responses

Symptoms	Positive SPT/number tested (%) per:			
	Patient		Food*	
Immediate				
OAS†	31/36‡	(86)	49/64§	(77)
Vomiting	2/3¶¶	(67)	2/3¶¶	(67)
Other**	0/16	(0)	0/21	(0)
Late††	2/10	(20)	2/13	(15)
Delayed				
Eczema‡‡	7/18	(39)	9/26	(35)
Other§§	0/5	(0)	0/5	(0)

* Many patients reacted to more than one food.

† Oral allergy syndrome (see Table 3).

‡ 31/34, § 49/59 and ¶¶ 2/2, excluding patients who were known to have lost their symptoms.

** Nausea (four cases), itching or urticaria (seven cases), asthma, diarrhoea, circumoral irritation, abdominal discomfort and earache (one case each).

†† Itching or urticaria (five cases), migraine (two cases), asthma, diarrhoea, colic (one case each).

‡‡ Six SPT positive patients with eczema had OAS to seven of the foods.

§§ Diarrhoea, migraine (one case each) and mood changes (three cases).

symptom. Symptoms were classified into the categories described in Table 5 with the oral allergy syndrome, including the initial oral symptoms, and subsequent symptoms (Table 4) all grouped together as one symptom complex. The OAS and vomiting formed one class of immediate symptoms and all the rest were grouped together as a second class of immediate symptoms. Thus, eighteen patients were asymptomatic and, of those with symptoms, thirty-one only had one class of immediate; three had two classes of immediate; two had immediate and late; thirteen had immediate and delayed; two had immediate, late and delayed; four had late; two had late and delayed; four had delayed, and one had two types of delayed symptoms. One of the patients with immediate, late and delayed symptoms also had two classes of immediate symptoms.

Shellfish, fish, nuts and eggs were mainly associated with the OAS and vomiting (72.5% of symptoms with these foods) while wheat, milk, tomatoes and oranges were mainly associated with other reactions (only 16% of symptoms were OAS or vomiting). In only six out of twenty-three patients with different classes of symptoms was the same food responsible for the separate symptoms. In each case this was due to an overlap between OAS and the subsequent development of eczema.

Age of onset of eczema, asthma, oral allergy and hay fever

Characteristically eczema began in the first year of life in most patients (fifty-three out of seventy and only three out of seventy began in adult life (20–40 years). Asthma and OAS arose at similar ages and, while accepting that symptoms may be underestimated

in small children, their incidence in the first year of life was estimated at 25% and 16%; from 2 to 12 years old, 57% and 65%; and later, 18% and 19%, respectively. Four cases of oral allergy began in adult life (22–40 years), and in three of these OAS was provoked by egg, which had been eaten without ill effect hitherto. No case of hay fever began in infancy but 55% began between the ages of 2 years and 12 years while the rest began later. The age at which late or delayed onset food-induced symptoms began was poorly recollected by many patients, but in those who were able to date the onset of their symptoms, 43% began between 2 years and 12 years and 57% began over 12 years of age.

Discussion

Hypersensitivity to foods was described in Cooke and Vander Veer's classical paper on human sensitization [10] in which symptoms of urticaria, angioedema or gastroenteritis were reported to occur in approximately 20% of subjects suffering from asthma or hay fever. This lead has not been followed by reliable information on the prevalence of immediate hypersensitivity to food, which is partly a problem of definition and partly due to a lack of reporting of a largely self-remediable condition. Symptoms that follow immediately after eating leave the sufferer in little doubt as to their cause, and the food that is identified is subsequently avoided. The help of a doctor is sought mainly when the sensitivity is very severe or when avoidance is difficult because it involves a common and ubiquitous food such as egg or milk. Indeed, the majority of eczema patients in this study had not mentioned their hypersensitivity symptoms to the dermatologist, even though some had suspected and discussed the possible role that food could play in exacerbating their eczema.

Certain types of food, like certain types of inhalant allergen, are more commonly implicated in provoking immediate hypersensitivity reactions. Cooke drew attention to the importance of fish and shellfish in this respect [10], and the importance of eggs and nuts has been realized subsequently [3,4,11,13]. Cow's milk has been recognized as an important food causing hypersensitivity in infants, usually expressed through vomiting and diarrhoea [14]. Children and adults differed in the reactions provoked by milk. In this study, four out of five children lost their immediate symptoms towards milk between 2 years and 3 years of age, but these were replaced by delayed symptoms of eczema or mood change. Whereas shellfish, fish, nuts and eggs commonly gave rise to immediate symptoms and showed positive skin-prick tests, milk was mainly associated with delayed symptoms and negative tests [3,12]. In contrast to milk, reactions to other food antigens have been shown to persist in most cases [14]. In seventeen out of twenty-one patients in this study, oral allergy symptoms that developed in childhood still occurred in adult life. In the remaining four patients, one had acquired tolerance to both fish and nuts, two tolerated egg but still developed OAS to fish and nuts, and one tolerated fish but not nuts.

Symptoms of immediate hypersensitivity to food differed in a number of ways from those of delayed onset. The former were reliably provoked by small quantities of food and were characteristically associated with oral allergic symptoms. Relatively larger quantities of food would still provoke the same symptoms but were reported to be followed by more severe symptoms such as asthma or anaphylaxis. Immediate reactions also correlated with positive skin tests [3,4,12,15] which were corroborated by histamine-release tests [12,16] and by RAST [13]. Thirty-three out of thirty-five

patients (94%) with OAS assessed their symptoms as being very reliably provoked by the offending food, and many patients with an oral allergic response had experienced symptoms after taking food that, without their knowledge, had been contaminated with the food to which they were hypersensitive. For these patients there was no question of elimination diets since they voluntarily avoided those foods that caused symptoms. Our skin-prick test data and RAST provide supporting evidence of an IgE-mediated reaction. Of the food extracts used, cod, egg, milk and nuts provided satisfactory materials for skin test purposes and seldom gave positive reactions in asymptomatic patients. The efficacy of tomato and orange as skin test extracts was uncertain, partly because they gave negative results but also because the symptoms they provoked (consisting of an immediate soreness on circumoral skin splashed by the fruit juices) were completely unlike those described for the OAS. Similar results to skin testing were obtained by RAST for milk, cod and egg, but RAST appears to be unreliable with plant allergens. Using sera that initially contained IgE levels greater than 2000 IU/ml, there was a very high number of positive tests in asymptomatic individuals. This may be due to non-specific cross-reactivity amongst certain plant carbohydrates [17].

On the other hand, it was a feature of delayed onset symptoms that they were not reliably provoked and usually required relatively large quantities of food. Here patients described the development of symptoms following the consumption of pints of milk or several eggs over a number of days. The symptoms did not include the initial oral symptoms of OAS, nor did they include anaphylaxis. They did not correlate with positive skin tests or histamine release, and the symptoms in this study consisted of eczema, mood changes, migraine and diarrhoea. Analysis of our data showed that only seven out of twenty (35%) of those suffering delayed symptoms assessed their symptoms as being reliably provoked, and only six out of fifteen (42%) thought that their symptoms had improved with an elimination diet. IgE-mediated reactions seem an improbable cause of these symptoms, and the delayed onset suggests a delayed rather than an immediate hypersensitivity mechanism. The finding that migration of leucocytes (a measure of cell-mediated immunity) from patients with delayed onset symptoms was inhibited in the presence of specific food extracts supports this view [18].

The process of eating exposes the buccal cavity, pharynx, oesophagus and stomach to food, while the nasopharynx and lungs may be exposed to much smaller quantities of aerosolized food—for example the inhalation of sulphur dioxide from food or wine containing metabisulphite [19]. Therefore, in patients sensitized with food-specific IgE antibody, one would expect hypersensitivity reactions to occur primarily in the upper gastrointestinal tract, and this accords with the symptoms described here as oral allergy. This does not imply that selected tissues become sensitized with food-specific IgE to the exclusion of others. There is indeed evidence of general sensitization, as indicated by the positive SPT found in most patients with the oral allergy syndrome, by the response to nasal challenge [5] and histamine release from blood leucocytes [16]. The rich mast cell and sensory innervation of the oropharynx, combined with a high food concentration in an undigested form, make this site the most likely to react in the presence of food-specific IgE sensitization. Larger amounts of allergenic food are required to provoke nausea and vomiting [5], and the direct effects on the gastric mucosa have been observed following intra-gastric provocation [20]. Absorption of intact allergen in any quantity can induce anaphylaxis and asthma as part of the OAS, but the occurrence of asthma in the absence of other evidence of anaphylaxis suggests

that there may be other mechanisms that can trigger a bronchial response. By recognizing the classical features of an IgE-mediated oral allergic response, we believe that the separate recognition and analysis of these other mechanisms will be facilitated.

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