

Clinical Features of Food Allergy

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INTRODUCTION

Atopic (IgE-associated) diseases have become increasingly prevalent over the past 30 years (1) and it should not be surprising that susceptible (atopic) individuals have developed allergies to food proteins. Food allergy may be a species “cost” paid by unfortunate individuals for the possession of a robust adaptive immune system and the broad diversity of the diet tolerated by the majority (more than 95%) of the human population. Allergic reactions to food can be disabling, even fatal. Even the prospect of exposure to food allergens causes considerable psychological morbidity and social isolation in affected individuals and their families (2). This anxiety is heightened further by the facts that the point prevalence of food allergies is highest in the age group about which families worry most—preschool children—and that no effective treatments are currently available (3). Parental anxiety and the necessary dietary exclusions can inhibit significantly the normal socialization of the child. Inaccurate information and the inadequate availability of expert advice often compound the anxiety. Management strategies are useful and

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when appropriately applied have been reported to decrease exposure and reaction rates (4).

True food allergy must be differentiated from intolerance and other hypersensitivity reactions and from other adverse reactions to foods (5). Allergic responses are, by definition, specific, adaptive immune responses. Food allergic reactions usually have a stereotypical presentation within an individual whichever immune mechanism is implicated, either associated with allergen-specific IgE and/or allergen specific Th2 cell populations (6). Allergen-specific IgE is only expressed under the influence of Th2 help but T-cell mediated responses can be independent of IgE, with undetectable or absent allergen-specific IgE and negative SPT. Both mechanisms can cause clinical symptoms at different times after a single exposure. The classic example of this is an egg-allergic child showing urticaria and angioedema (IgE-associated) within minutes of exposure to egg and later, within 24 hr, having an exacerbation of eczema (T-cell mediated).

GENES

Atopy (the tendency to develop allergic diseases) is a polygenic disorder. Associations have been identified between particular genotypes and polymorphism of relevant genes to individual food allergies (7, 8), but it is not possible at present to determine if these associations are causal. Atopy is a familial disorder, and allergies to particular foods are more common in the relatives of affected individuals than in other families. Peanut allergy is found in 7% of siblings of peanut allergic subjects (9). In monozygotic twin pairs there is 64% concordance for peanut allergy, but in dizygotic twin pairs the concordance rate of 6.8% is similar to the 7% rate in nontwin siblings (10). This striking similarity of prevalence of peanut allergy in dizygotic twins and nontwin siblings suggests the high concordance in monozygotic twins is due to genetic factors per se rather than identical in utero environment such as exposure to circulating allergens (11).

ENVIRONMENT

Even allowing for confounding factors such as study design, patient selection, referral patterns, and reporting bias, there are significant differences between countries in the relative frequencies of foods causing allergic reactions. These differences must surely reflect different dietary practices and lifestyles between countries.

Countries with an Americanized diet report the major allergens, as proven by double-blind food challenge (DBFC) studies, to be those shown in Table 1 (12).

TABLE 1 The “big 8” Foods that Cause Most Cases of IgE-Mediated Food-related Allergic Reactions (12)

Cows' milk	Fish
Egg	Shellfish
Peanut	Soya
Tree nuts	Wheat

Of a series of 96 anaphylactic reactions in Italian children in the community, as opposed to during formal challenges, 54 were due to foods (in order of frequency): fish, cows' milk, nuts, hen's egg, fruit, and cereals (13). In Central Europe allergies to hazelnut and celeriac are common (14), possibly related to sequence homology with the locally dominant inhalant allergens, birch and mugwort. French centers report an intermediate picture with a prevalence of peanut allergy similar to that in Britain and the US (15) but a relatively high rate of mustard allergy (16), although comparable studies of mustard allergy have not been conducted in other countries. Sesame seed allergy is seen frequently in Israel (17) and Australia (18), but only rarely in Britain (authors' personal observations). Food-related allergic reactions in Singaporean children are more commonly due to crustacea or a local delicacy—bird's nest soup—than to egg or milk (19). Buckwheat allergy is well recognized in Japanese and Korean children (20), whereas peanut allergy is rare (K.S. Park, personal communication).

The international differences act as examples of environmental influences on allergic disease. Within a country the differing prevalence of individual food allergies in different age groups and ethnic groups reflects a different effect of environment: how and when allergens are introduced to the human diet (21). Hens' egg and cows' milk are two of the staple foods for infants in developed or westernized countries. Wheat is a common weaning food. Soya is an almost ubiquitous ingredient in prepared foods. Peanut has been a common snack food for finger-feeding toddlers. These foods constitute the major allergens for infants (22, 23) and preschool children (24) in Europe and North America. In contrast, tree nuts, fish, and shellfish are not common foods in the first year of life, due to fears of inhalation of nut fragments or fish bones. The onset of tree nut allergy is, therefore, considerably later than that of peanut allergy (25). Allergy to fish and shellfish also are more common in older children and adults.

The introduction of new foods may eventually lead to clinical sensitivity to the introduced food, for example, cashew (26) and kiwi (27). The potential exists for clinical reactivity to a exotic fruit that is very rare in Europe to date—the nan gai fruit (*Canarium indicum*) wheal is being introduced to the European diet (28, 29). Ongoing studies in Eastern Europe suggest that sensitization to peanut was unknown until

recently, but it is now relatively more common (E. Sikorska, personal communication).

DIAGNOSING FOOD ALLERGY

A history of adverse reactions to food is not adequately sensitive or specific for a conclusive diagnosis of food allergy. *In vivo* and *in vitro* tests can support or refute the clinical suspicion. The key test is the formal food challenge, which as a gold standard needs to be double-blind, with placebo control. In young children, open or single-blind challenges are adequate, and negative double-blind challenges should be followed by an open challenge (30).

In unselected series there is a high chance of a false-positive history, refuted by a negative challenge. Bock (31) showed in a series of 480 children followed to the age of 3 years that about 33% reported reactions to a relatively broad range of foods but only 30% of the positive parental reports could be confirmed by a food challenge (31). It is notable that apart from citrus drinks (to which intolerance is common in young children), the other foods implicated were all recognized as common allergens such as egg, milk, and peanut. In a population survey of 1500 Dutch adults, only 12 of 37 food challenges were positive (32). Young et al. estimated that only 1 in 10 reports of food intolerance, including allergic reactions, could be supported by a positive challenge (33).

There are exceptions to the requirement for a food challenge. A severe and typical reaction after an unequivocal exposure to a known allergen does not require proof by a diagnostic food challenge. It is justifiable, in other, less clear-cut situations, to expose a subject to the small risk of a significant reaction during challenge—up to 10% of challenge induced reactions are severe (34)—but the benefit of a possible negative challenge is considerable and usually outweighs the risks. Some single allergen studies with case finding rather than population screening design have reported higher rates of sensitivity and specificity of 85% or more (25, 35).

Standardized skin prick testing or measurement of allergen-specific IgE-levels are very reproducible and are clinically useful. Their sensitivity and specificity depend on the prevalence in the population of sensitization to the allergens being tested. For example, the tests are more useful in a population of children referred to a specialist clinic for evaluation of food allergy than in community screening of unselected adults. Current reports suggest a change in the frequency of food challenge tests based on analyses of SPT and specific IgE results from series of double-blind food challenges. Values of SPT and specific IgE are being used to predict if a proposed food challenge would be positive (30, 36–39).

There are three caveats to this approach. First, the studies were performed in highly selected populations of children referred to national centers so the

results may not be applicable in less selected populations. This remains to be studied. Second, although negative challenges are reportedly unlikely if the IgE levels are “high” (whichever way they are measured), positive challenges can occur in subjects with very low-level positive or even negative results (Figure 1). A high result means a challenge might be positive but a low result does not mean a challenge must be negative. Third, a diagnostic challenge may be indicated to determine if an allergy has resolved despite significant levels of allergen-specific IgE, or to determine clinical severity in a subject with positive IgE-based tests but no history of exposure.

Dynamic tests of cellular function such as patch testing or *in vitro* stimulation assays of T-cells or basophils are not part of the routine work-up of a food allergic child. Such tests have been promoted as useful and specific in subjects with nonimmediate reactions to specific food, egg, or milk (Table 2) where an essential role for specific IgE is not suspected (40–42).

CLINICAL SEVERITY OF FOOD ALLERGY

There is a wide spectrum of severity of allergic disease, ranging from minor urticaria to fatal anaphylaxis. There appears to be an association between severe allergic reactions and the presence of asthma (43–45). Foods accounted for 36% of cases of anaphylaxis in a 5-year survey of a population in Minnesota, USA (46), and for more than 50% of anaphylactic reactions in the community referred to a regional immunology clinic in Manchester, UK (47).

In all series of anaphylactic reactions to foods, a range of foods have been implicated but it is clear that peanut and tree nuts stand out as the chief causes of severe and fatal allergic reactions. Pumphrey (48) reported that foods caused 37/70 (53%) fatal episodes of anaphylaxis that were not associated with medical care and that peanut or tree nuts caused 25 (67%) of the 37 food-related deaths (48). Bock *et al.* (45) reported that peanut and tree nuts caused all the deaths in 21 American subjects for which full data are available, whereas in a second group with less complete data 9/11 reactions were probably due to peanut or tree nuts, 1 to milk and 1 to fish (45). The increased risk attributed to a pre-existing diagnosis of asthma is important because more than 50% of peanut allergic subjects have asthma (44). Poor control of asthma in food allergic subjects has been implicated as an additional risk (43).

Some medical and nonmedical circumstances that can contribute to the severity of an allergic reaction to foods are shown in Tables 3 and 4.

ALLERGEN DOSE

The dose of allergen appears to be critical to the severity of an allergic reaction that the exposure elicits. In reactions due to mechanisms other than



FIGURE 1 A positive double-blind food challenge in a young woman showing lip and facial swelling with a typical nettle rash (called urticaria) and conjunctivitis. She had a peanut challenge because of a combination of an equivocal history of reactivity to peanut, a peanut SPT wheal of 6 mm (36), and serum level of peanut specific IgE of 1.3 KU_A/L (37).

TABLE 2 Findings in Clinical Tests of Allergic Responses to a Single Allergen can vary According to the Disease Mechanism (40–42)

Symptoms	Skin prick test	Serum-specific IgE	T-cell studies
Immediate <1 hr	++++	++++	+
Intermediate 2–6 hr	++	++	++
Delayed 8–24 hr	+/-	+/-	++++

those associated with IgE, small amounts of allergen can be tolerated, whereas larger amounts cause increasing symptom severity. Most of the recent focus on allergen doses has been directed toward peanut allergy due to its prevalence and severity. It is likely, however, that the principles outlined apply to other persistent allergies such as fish and shellfish and tree nut allergy. Tree nut allergies appear to differ from peanut allergy only in prevalence and age of onset but are equally severe for those affected (25).

IgE-associated reactions can be initiated by tiny doses, with reactions reported in oral DBFCs at doses of peanut extract of 1–2 mg (50). It has been difficult to assess the risk of severe reactions in subjects who have had only minor reactions or whose reactions have been to a “non-ingestion” contact,

TABLE 3 Intrinsic Human Factors that Contribute to Reaction Severity (49)

1. *Medical features*
 - Age
 - Asthma
 - Cardiovascular disease
 - Medication, beta blockers
 - Angiotensin converting enzyme-inhibitors
 - Nonsteroidal anti-inflammatory drugs
2. *Allergic history*
 - Target organ
 - Severity of previous reaction
3. *Decision making*
 - Anticipating and minimizing exposure to allergen
 - Awareness of family, friends, and colleagues
 - Alcohol consumed with meal containing allergen
 - Carrying rescue medication
 - Exercise
 - Using rescue medication

TABLE 4 Extrinsic Human and Non-Human Factors that Contribute to Reaction Severity (49)

Exposure	Response of others
Location: home or non-home	Accuracy of information given to subject about ingredients
Dose of allergen	Recognition of reaction
	Using rescue medication
	Seeking additional help

such as touching a piece of egg or peanut butter. Mild symptoms on such non-ingestion contact with peanut can be followed by more severe symptoms on subsequent oral exposure (51). Symptoms can progress from one severity category to another (44), and many deaths due to food allergy occur in subjects who previously have not experienced severe reactions (45, 48). In contrast, most subjects allergic to milk or egg do not progress to worse symptoms on subsequent exposure to similar doses of the allergen and most do not require epinephrine rescue strategies or training.

TREATMENT OF FOOD ALLERGY

Successful parenteral immunotherapy has been reported for food allergies using traditional protein-based solutions. Parenteral immunotherapy with peanut extract has been shown to increase tolerance of peanut in challenges, but the side effects are unacceptable (52, 53). Oral immunotherapy for food allergens is advocated by some European groups but is not practiced widely elsewhere (54). DNA-based immunization strategies have prevented sensitization in animal models (55, 56) but have not so far been shown to modulate existing allergic disease (reviewed in Reference 57). DNA-based immunization with food proteins also has caused sensitization rather than tolerance induction in some mouse strains (58), thus its applicability to humans (in whom anaphylaxis may be mediated by different mechanisms) is not assured.

In the absence of tolerable disease-modifying treatments, the management of food allergies is restricted to disease control: the establishment of a nutritionally complete diet that excludes only the relevant allergenic foods and the provision of medications to be used after inadvertent allergen exposure. The many aspects of dietary management, response to allergen exposure, and administration of rescue medication are daunting for parents and nonspecialist physicians alike. Strategies for the community management of allergic diseases are discussed elsewhere (4, 59–62).

EXCLUSION DIETS

Supervised exclusion diets and allergen reintroduction can be simultaneously part of both the diagnostic and therapeutic processes. This is particularly true for frequently consumed foods such as milk, egg, and soya where chronic (daily or more frequent) consumption may mean there is no obvious link between exposure and symptoms. For other sporadic allergens, such as peanut or shellfish, subjects or their parents can make a clear connection between exposure and adverse reaction and a correct diagnosis is easily made.

Food allergic subjects deserve to have as broad a dietary repertoire as is compatible with maintaining their safety and security from accidental exposure to allergen. Children must grow and therefore they require adequate nutrition. Children also must learn to participate in social situations in which food is consumed. Food allergic subjects are often excluded from social situations like camp or birthday parties due to inadequate confidence or information on the part of the food provider, rather than because of a documented risk. In many cases the parent of the food allergic subject does not allow social interactions when they are not in control of the food provided. Children can become isolated and stigmatized unless help is available to families from physicians, nurses, and dietitians, giving them a degree of added control over their lives.

Exclusion diets can be difficult and monotonous. They may involve all members of the family excluding a food, particularly if there is a high risk of severe reaction on exposure of the susceptible family member. In all other situations exclusion diets should be confined to the affected family member only. Professional dietetic advice is critical to prevent exclusion diets being overly restrictive or being used for too long. A good example of inappropriate advice regarding allergen avoidance is the apparently frequent, but inaccurate, advice given to peanut allergic subjects to avoid other legumes. Peanut is a legume but significant legume allergy is not common in peanut allergic people (63, 64) and avoidance of a legume is only considered for peanut allergic subjects if there is a history of reactivity to that legume.

The issue is different for peanut allergic subjects who must avoid exposure to most tree nuts. About 33% of peanut allergic children and 50% peanut allergic adult subjects are sensitized (have a positive SPT but no history of clinical reactivity) or are actually allergic to one or more tree nut (9, 25, 65). It can be difficult to distinguish between shelled peanuts or tree nuts and they can be used as substitutes for one another in prepared foods (66). For these reasons peanut allergic subjects must avoid tree nuts unless they are absolutely satisfied on two counts. One, they must be absolutely certain that they have tolerated that *specific* nut before and two, the nut they are going to eat cannot be confused with *and* has not been in physical

contact with a nut they cannot tolerate. For example, one safely eats a Brazil nut shelled in his or her presence but refuses to eat a Brazil nut picked out of a bowl of mixed nuts.

SUBSTITUTION DIETS

Many foods can be avoided or excluded without any adverse nutritional consequences. Foods eaten sporadically, such as peanuts or shellfish, are good examples. It is a more significant step to advise removal of a staple food, which may be eaten many times a day by unaffected individuals. Milk is the best example of a common, staple food to which allergy is common (67). Hydrolyzed preparations of milk proteins are effective in the management of milk allergic infants, though selecting the right milk can be difficult due to the variable contribution of whey or casein proteins to the clinical presentation (68). Several different preparations are available, including extensively hydrolyzed milks and amino acid preparations. The use of such milks as primary prophylaxis for allergic diseases is beyond the scope of this article but is reviewed elsewhere (67).

Milk becomes a less important part of the diet as a child grows and many older children and adults grow well and have minimal restrictions on their lifestyle by simply avoiding milk rather than using a substitute. Soya-based formula preparations are an acceptable alternative to cows' milk and can be consumed on a long-term basis by milk allergic subjects. There is no role for milk of other animals in the treatment of cow's milk allergy, as *in vitro* cross reactivity and clinical reactivity are too common (1, 69–71).

Many food allergies resolve with time and a good prognosis can be given to families of affected children. Egg and milk allergy usually resolve—or at least improve—in the preschool years. It is therefore usually possible to reintroduce egg to the diet either after a careful reintroduction at home (if the clinical history suggests benign reactions) or after a negative formal food challenge. There is no role for community-based food challenges in cases of peanut allergy in general or with other foods if there is a history of anaphylaxis (12, 30).

There has not been a documented death of a child under 10 years of age in Britain due to nut allergy since 1992 (48), although such reports continue to appear from North America (45). It is not clear if this represents adequate allergen avoidance by British families despite the risk of severe disease being present or rather that food allergy in childhood is usually benign, compared with the severe reactions suffered by adolescents and adults. The holistic management of children and adults with food allergy can be a challenge to physicians unfamiliar with the issues involved. These issues range from assessment of coexisting medical conditions, impacts of a diagnosis on the mental and social well-being of families, and the day-to-day protection of affected individuals from exposure to allergen. Physicians are hampered by

the lack of reliable *prognostic* tests and must rely upon the careful taking of a clinical history of reactions suffered to date and the rather blunt tool of a diagnostic food challenge.

Food challenge will remain the cornerstone of clinical practice for many years to come, although the refinement of indications for challenge and the different ways to perform food challenges will continue to exercise physicians and other professionals who deal with the complex problem of food allergy. Industry and governments must strive to ensure that food allergic subjects are given reasonable and understandable warnings about foods that may represent a risk of allergen exposure. In the absence of any curative treatment, physicians must remain cautious in the advice given to subjects and their families and they must ensure that their patients are as ready as possible to react appropriately to the allergen exposures that are unfortunately so predictable.

CONCLUSIONS

Only 1 in 10 adult cases of reactions to foods can be confirmed by challenge but this "hard core" of 2% of all adults constitutes a significant health problem in the 21st century. Preschool children have the highest prevalence of food allergy, but most have a good prognosis. The immunological and molecular characterization of both patients and allergens should soon lead to the identification of effective treatment strategies. Without such treatments, food allergic subjects bear a considerable burden of anxiety and uncertainty because avoidance of exposure to allergens is very difficult.

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