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Management of the Patient with Multiple Food Allergies

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Abstract

Food allergies affect 6% of children and 3% to 4% of adults in the United States. Although several studies have examined the prevalence of food allergy, little information is available regarding the prevalence of multiple food allergies. Estimates of prevalence of people allergic to multiple foods is difficult to ascertain because those with allergy to one food may avoid additional foods for concerns related to cross-reactivity, positive tests, or prior reactions, or they may be reluctant to introduce foods known to be common allergens. Diagnosis relies on an accurate history and selective IgE testing. It is important to understand the limitations of the available tests and the role of cross-reactivity between allergens. Allergen avoidance and readily accessible emergency medications are the cornerstones of management. In addition, a multidisciplinary approach to management of individuals with multiple food allergies may be needed, as avoidance of several food groups can have nutritional, developmental, and psychosocial consequences.

Keywords

Multiple food allergy; IgE; Sensitization; Cross-reactivity; Diagnosis; Allergy management

Introduction

Almost 20% of individuals in the population believe they have adverse reactions to foods. However, not all these reactions are food allergies, as they are not immune mediated [1]. Population studies have found that food allergies affect 6% of children in the United States and 3% to 4% of adults, and the prevalence seems to have increased in recent decades. Although several studies have examined the prevalence of food allergy, few data regarding how many people suffer from multiple food allergies are available.

People who are allergic to one food may avoid additional foods for a variety of reasons, including history of food reactions, positive tests without prior history of ingestion or reaction, or general concern that certain foods are “common allergens.” Many foods share homologous proteins; thus IgE-mediated sensitization to one food can result in positive tests or clinical reactivity to related foods. Studies have estimated that at least one third of peanut allergic patients are also allergic to at least one tree nut [2]. Furthermore, homologous proteins can be shared between foods and pollens, and this cross-reactivity is not always clinically relevant. For example, individuals who have IgE positivity to grass pollens can have positive test results for wheat [3], and birch pollen allergic individuals can have positive test results for peanut and hazelnut [4,5]. Unfortunately, concerns about food

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allergy also have been reported to result in avoidance of foods despite no evidence of allergy [6].

Prevalence of Multiple Food Allergies

Data from published studies can provide estimates of multiple food allergy prevalence. In a study of food allergies in a highly atopic group of children (all of whom had atopic dermatitis and 50% of whom had concurrent asthma or allergic rhinitis), 57% of children reacted to two or three foods during double-blind, placebo-controlled food challenges [7]. Most children in this subset had positive skin prick tests (SPTs) to several foods, although only about one third of positive tests correlated with positive food challenges. However, few reacted to more than three foods. Five foods (egg, peanut, milk, wheat, and soy) accounted for about 60% of the positive clinical responses.

Another dataset that can provide insight into the prevalence of multiple food sensitization comes from the National Cooperative Inner City Asthma Study. More than 500 random serum samples were evaluated for specific IgE to six common food allergens (milk, egg, wheat, soy, peanut, and cod) [8]. Although having evidence of IgE-mediated sensitization to a food (specific IgE levels to foods >0.35 kU/L on ImmunoCAP [Phadia, Uppsala, Sweden]) does not necessarily imply true food allergy, this study found that 27% of children were sensitized to more than one of these foods. A subset of the group was found to have IgE levels that were more than 95% predictive for clinical reactivity to at least one of these foods. This group was considered to be highly likely to have a true food allergy, and within this group, nearly all (96%) had sensitization (>0.35 kU/L) to additional foods, and 25% were sensitized to all six foods tested. The main limitation of this retrospective study was that information regarding clinical reactivity to foods was not available; therefore, it is not known how many of these patients were truly allergic to more than one food.

A recent study examining the prevalence of multiple food allergies in a pediatric food allergy referral practice found that most (>70%) food allergic children were allergic to or were avoiding multiple foods [6]. On average, each person was avoiding three or four foods or food groups (ie, if a person was avoiding multiple tree nuts, he or she was counted as avoiding one food group) [6]. These children were generally very atopic, with 56% having atopic dermatitis, 47% with allergic rhinitis, and 38% having asthma. Thus, highly atopic children may be at greater risk for having allergies to multiple foods.

Diagnosis of Food Allergy

History and Physical Examination

Obtaining a detailed history is the first step in the diagnosis of food allergy. Information regarding timing of ingestion to the onset of symptoms, types of signs and symptoms, type and quantity of food that triggered the reaction, prior exposures to the triggering food or related foods, and association of additional factors such as exercise and concurrent medications is crucial for determining whether the reaction is due to an allergic reaction as opposed to an adverse reaction to food that is not IgE mediated or not immune mediated. Symptoms of immediate hypersensitivity generally occur within 2 h of ingestion and can involve the cutaneous (pruritus, urticaria, angioedema), gastrointestinal (oral pruritus, nausea, vomiting, diarrhea), respiratory (rhinorrhea, congestion, laryngeal edema, wheezing, shortness of breath), or cardiovascular systems (hypotension, syncope). The presence of symptoms with exposure to the triggering food and lack of symptoms with exclusion of the food is highly suggestive of allergy. A dietary history provides useful information in identifying the triggering food. For infants who are breast fed, the maternal diet history should be recorded, as food allergen exposures can occur through breast milk [9].

The physical examination can reveal other signs of atopy, such as atopic dermatitis, rhinitis, and asthma. In addition, evidence of growth failure, malnutrition, and signs of nonallergic disorders that would require additional evaluation may be identified.

Skin Prick Testing

If the history and physical examination are consistent with immediate food allergy, the diagnosis can be confirmed with SPT and/or serum IgE testing. SPT and serum IgE testing measure allergen-specific IgE and provide an indication of the likelihood of allergic reaction with exposure to the food allergen; however, the severity of reactions that occur is unpredictable.

SPT can provide rapid detection of IgE sensitization. It involves placement of glycerinated extracts on the skin along with negative (saline) and positive controls (hista-mine) and pricking with an appropriate needle to assess for IgE-mediated reactions. Food allergens that elicit wheal diameters at least 3 mm larger than the negative control are considered positive results. The SPT can provide rapid results with high sensitivity. The SPT has a high negative predictive value (>95%), with a negative skin test essentially excluding IgE-mediated food allergy. In contrast, the positive predictive value is less than 50%; thus, an isolated positive test is not definitive for food allergy [10]. In the context of a history suggestive for food allergy, a positive SPT can serve to confirm the diagnosis of food allergy, and larger SPT wheals have been correlated with increased likelihood of positive food challenge. It has been demonstrated that SPT wheals of at least 8 mm for milk or peanut and at least 7 mm for egg indicate a greater than 95% likelihood of clinical reactivity [11].

The limitations of this type of test include variability in SPT devices and interoperator variation in technique and interpretation of results. Also, commercial extracts are not standardized and can have variable protein content and potency. In addition, this test cannot be used if the patient is on chronic antihistamines. For pollen food allergy syndrome, skin testing with fresh fruits and vegetables is generally a better predictor of clinical reactivity when compared with commercial extracts because the proteins involved are particularly labile [12,13]. Of note, intradermal testing to foods has been associated with systemic reactions. Therefore, this is not recommended for the evaluation of food allergy [14].

Specific IgE Testing

Specific IgE testing is another diagnostic tool for food allergy. It is preferred for use in patients with dermatographism, severe skin disease, and those who cannot discontinue use of antihistamines. Higher levels of specific IgE indicate increased likelihood of allergic reaction with exposure. However, levels cannot predict the severity of allergic reactions. Similar to SPT, positive test results need to be taken in the context of history. As an example, a birth cohort study of 4-year-old children found that 42% of children sensitized to peanut reported clinical reactivity to peanut, and in fact, ten children with high IgE to peanut were clinically tolerant [15]. These results indicate that the presence of specific IgE is not definitive for clinical reactivity.

Similar to SPT, high IgE levels are correlated with increased likelihood of clinical reactivity. The ImmunoCAP is the only assay that has been systemically evaluated for its predictive value in food allergy. Predictive values for food-specific IgE levels have been published for the major food allergens [16–19]. Recent studies have compared the different commercially available IgE detection assays and found that the assays are not equivalent [20]. Differences in allergen-specific IgE levels can be due to a combination of technical differences between the assays and differing allergen sources. Therefore, it is important to note which assay is

being used when interpreting IgE results for the management of food allergies based on the published predictive values.

Another consideration in interpreting IgE results is that allergen extracts do contain multiple proteins, and cross-reactivities between homologous proteins can yield positive IgE results that may not be clinically relevant (Table 1) [21]. For example, Ara h 8 is a peanut protein that is a Bet v 1 homologue, so individuals with birch pollen allergens can demonstrate positive tests to peanut [4]. In fact, a recent study by Asarnoj et al. [22•] found that children sensitized to both peanut and birch were less likely to report clinical reactivity to peanut than children sensitized to peanut but not birch. The authors suggest that peanut allergy is less likely if IgE levels to birch pollen are higher than those to peanut. Within the legumes, a high rate of cross-sensitization exists, but clinical cross-reactivity is less common [23]. Similarly, although many children demonstrate cross-sensitization to multiple cereal grains, most react only to one grain [3]. In contrast, clinical cross-sensitization and reactivity to multiple species of fish or shellfish is more commonly observed [21]. Other cross-reactivities that should be noted include wheat and grass pollen [3], hazelnut and birch tree pollen [5], and shellfish and dust mite/cockroach [24].

The gold standard for the diagnosis of food allergy is a double-blind, placebo-controlled oral food challenge. Food challenges are conducted to determine the clinical relevance of positive tests, especially when the individual may be outgrowing his or her food allergy, or when mild positive results are associated with little or no exposure [25]. They should be performed in settings in which medical staff and equipment are readily available in case of anaphylaxis. SPT and food-specific IgE levels are used to determine when food challenges may be appropriate.

Novel Diagnostic Tests Under Investigation

Several novel diagnostic tests are currently being investigated for food allergy. These include component-resolved diagnosis, peptide microarrays, and basophil release assays. Because cross-reactivity to homologous proteins can yield positive test results in a clinically tolerant patient, determining which allergens are being bound can prevent misdiagnosis of allergies. A recent study reported the use of component-resolved diagnosis to distinguish between individuals who were clinically reactive to peanuts and those who were sensitized but clinically tolerant [26•]. The test assessed IgE binding to recombinant proteins of peanut (Ara h 1, 2, 3, and 8), grass (Phl p 1, 4, 5b, 7, and 12), and potentially cross-reactive components (Bet v 1, Pru p 3, and cross-reactive carbohydrate determinants). Peanut allergic individuals had high responses to Ara h 1, 2, and 3; however, peanut-sensitized but clinically tolerant individuals had high responses to grass allergens and cross-reactive carbohydrate determinants. Further analysis found that Ara h 2 was the most important component for accurate discrimination.

Identifying the location of IgE binding on an allergenic protein using peptide microarray immunoassay is also showing promise as a potential diagnostic tool [27]. Peanut epitope recognition has been shown to correlate with severity of peanut allergic reactions using peptide microarray immunoassay [28]. Similarly, peptide microarray results have been shown to correlate with clinical features of milk allergy. Milk allergic and tolerant patients demonstrated different epitope recognition patterns, with allergic patients having higher ratios of IgE to IgG_4 binding than those who were clinically tolerant to milk [29]. Recently, greater IgE epitope diversity and higher IgE binding affinity were found to be associated with clinical phenotypes and severity of milk allergy using peptide microarray [30]. The investigators analyzed serum from a clinical study investigating tolerance of heated milk in milk allergic individuals and found greater epitope diversity in the milk allergic group as compared with those who outgrew their milk allergy. IgE binding to higher numbers of milk

peptides was also associated with more severe allergic reactions during food challenge. Using a competitive peptide microarray assay, allergic patients were shown to have a combination of high- and low-affinity IgE binding, whereas heated milk tolerant individuals and those who had outgrown their milk allergy had primarily low-affinity IgE binding to milk peptides.

Another novel test that may complement current diagnostic tools is the basophil activation test. Ocmant et al. [31] reported that basophil activity was significantly higher in peanut and egg allergic individuals upon in vitro peanut and ovalbumin challenge compared with controls, whereas the majority of egg- or peanut-sensitized children failed to activate basophils in response to challenge. Another study investigated the role of the basophil activation test for milk allergy. Wanich et al. [32] found that basophil reactivity was strikingly distinct between individuals who tolerated heated milk and heated milk reactive individuals. As reactivity to heated milk has been associated with a higher risk of reactions requiring epinephrine, and heated milk tolerant individuals seem more likely outgrow their allergy [33•], basophil reactivity may be a useful tool in distinguishing between different phenotypes of milk allergy.

Additional studies are needed to determine the clinical utility of these novel tests. These tests have the potential of improving the diagnosis and management of food allergies, thus preventing unnecessary avoidance diets. Furthermore, they may help decrease the need for costly, time-consuming, and potentially life-threatening reactions with oral food challenges.

Management of Food Allergy

The keys to management of food allergies consist of education about food allergen avoidance and having emergency medication (eg, self-injectable epinephrine, antihistamines) readily available in case of allergic reactions. Patients are advised to examine all the ingredients of foods to be consumed. Fortunately, a labeling law is now in effect in the United States that facilitates this process [34]. The Food Allergen Labeling Consumer Protection Act requires that less complicated terminology be used to identify major food allergens in foods and dietary supplements. Food allergen avoidance involves not only reading ingredient labels but also requires vigilance for cross-contamination during food preparation and cooking. In fact, studies have indicated that severe reactions can occur inside and outside the home, and people often are not aware that the foods they are consuming contain the food allergens [35]. Additional education should be provided for management of food allergies in settings such as schools [36] and restaurants [37] because not everyone is educated about food allergies.

Although these preventive measures are generally effective, accidental exposures to food allergens can still occur. Therefore, it is necessary to prescribe self-injectable epinephrine and instruct the patient and his or her family on its use. Furthermore, education regarding the identification of allergic symptoms and a written individualized emergency plan that outlines when the epinephrine would be indicated should be provided. Emergency medication should be available at all times, as delayed administration has been associated with increased risk of fatal reactions [35].

Additional Management Challenges

Children with multiple food allergies may need multidisciplinary care because avoidance of several major allergens can have nutritional, oromotor, and social implications (Table 2). Food avoidance diets can result in vitamin and mineral deficiencies, protein calorie malnutrition, and poor growth [38,39]. In fact, Christie et al. [38] found that children with allergies to two or more foods were significantly shorter than those with allergy to one food,

based on height-for-age percentiles. The authors also found that more children with milk allergy or multiple food allergies consumed less-than-recommended amounts of calcium compared with children without milk allergy and/or only one food allergy. It is important to note that milk provides not only calcium and vitamin D but also protein and fat, so appropriate replacement for these should be considered. Furthermore, it is necessary to ensure that children with multiple food allergies are not limiting their diets beyond the foods to which they are allergic. Often, families with food allergic children may be concerned about introducing potentially cross-reactive foods or other major allergens (ie. peanuts, tree nuts, fish, and shellfish) and thus avoid these foods without testing or despite negative tests. Therefore, consultation with a dietician knowledgeable about food allergies can be beneficial for these children and their families.

If multiple food allergies are diagnosed in very young children, oromotor development can be affected. The development of mature oral motor skills occurs between birth and 24 months, which coincides with the time that most major food allergens are introduced. For children with food allergies who have repeated negative experiences associated with eating (ie, vomiting, hives, abdominal pain), it can be a frustrating experience to the child and the family and can result in altered feeding practices, including food refusal, food aversion (specific foods, textures), or coughing/gagging in some cases [40]. Delays in acquiring feeding skills or development of behavioral feeding problems may require the assistance of feeding specialists.

Because the major food allergens are ubiquitous in the diet, food allergic children often experience a significant negative impact on their quality of life. These children not only have a limited diet but also report limitations in social activities. Family members are also significantly impacted by food allergies. In a study assessing quality of life in families with a food allergic child, parents whose children had more than two food allergies were more affected than parents whose children had fewer allergies [41]. Within families, mothers reported more anxiety and decreases in psychological and physical quality of life than fathers [42]. For some patients and their families, the anxiety can lead to significant limitations in daily activities, and consultation with a psychologist/psychiatrist may be beneficial.

Children with asthma who have concurrent food allergies have higher asthma morbidity than non-food allergic asthmatics. Using a case-control design, Vogel et al. [43] examined medical records from 72 patients admitted to a pediatric intensive care unit for asthmatic exacerbation and compared them with two randomly selected groups of 108 patients admitted to a regular nursing floor for asthma and 108 ambulatory patients with asthma. The authors found that 13% of these children had reported food allergy in the medical records and that more than one third of these children were avoiding multiple foods. Children admitted to the pediatric intensive care unit (instead of the regular nursing unit) were 3.3 times more likely to have at least one food allergy. Furthermore, in a study examining food allergen sensitization in inner city children with asthma, results demonstrated that sensitization to more than one food was associated with increased hospitalizations [8].

Natural History of Food Allergy

The persistence of food allergy is variable and depends on the specific food allergen. Recent reports indicate that it is taking longer for children to outgrow their milk and egg allergies, with most developing tolerance in their teenage years rather than in early school age, as previously thought [44,45]. A risk factor for persistence of egg allergy is having allergy to other foods; however, having other food allergies was not predictive of milk allergy persistence. For peanut allergy, only 20% of children will develop tolerance [46], and 9% with tree nut allergy will outgrow their allergy [46,47].

Currently, there are no reliable predictors to determine when and in whom this will occur. Therefore, periodic follow-up SPT and/or serum-specific IgE levels can help determine when food challenges should be pursued. Using the published predictive values and monitoring the rate of decrease in food-specific IgE levels over time can provide indicators of when outgrowth might be occurring [48]. Recent studies also demonstrate that tolerance to heated forms of milk and egg may be associated with better prognosis [33•,49•].

Conclusions

Children who are avoiding multiple foods seem to constitute a significant fraction of the food allergic population. Recent developments in diagnostic tools can potentially distinguish between clinically relevant and irrelevant positive tests, thereby preventing overly restrictive diets. Because food avoidance can have a major impact on nutrition, development, and psychosocial well-being, it is important to make accurate diagnoses and ensure that management strategies involve a multidisciplinary approach.

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Table 1

Important cross-reactivities that can lead to positive tests

Peanut	Cross-reactive with birch tree pollen. Ara h 8 is a Bet v 1 homologue [4].
Hazelnut	Cross-reactive with birch tree pollen. Cor a 1 is a Bet v 1 homologue [5].
Wheat	Cross-reactive with grass pollen and with other cereal grains (but low clinical relevance) [3]
Shellfish	Cross-reactive with dust mites and cockroach due to tropomyosin [21]
Soy	Cross-reactive with peanut and other legumes [21] and with birch tree pollen (Gly m 4 is a Bet v 1 homologue; Gly m 3 is a profilin)

Table 2

Key points for the management of multiple food allergies

1	Allergen avoidance: ingredient label reading, cross-contamination issues, discuss strategies for food allergy management in schools, camps, during travel, etc.
2	Self-injectable epinephrine and emergency action plan always should be available
3	Dietary assessment to ensure appropriate intake of essential vitamins and nutrients
4	Developmental assessment, particularly for young children to ensure attainment of feeding skills
5	Address psychosocial concerns for the child and the family
6	Closely monitor asthma and other atopic conditions