DIAGNOSTIC ISSUES IN FOOD ALLERGY

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SUMMARY

Adverse reactions to food (food hypersensitivity) may either be immunological (food allergy) or non-immunological (non-allergic food hypersensitivity or intolerance). Undiagnosed food allergy may result in fatal anaphylaxis, especially in children and adolescents with asthma. Skin prick tests, measurement of allergen-specific IgE levels and food challenges are well-established, evidence-based diagnostic tests. However, inappropriate testing and misinterpretation of test results may lead to misdiagnosis of food allergy resulting in unnecessary anxiety, dietary restriction and effects on growth and development, especially in children. This review summarizes the diagnostic issues in food allergy and explains the rationale for systematic evaluation of suspected food hypersensitivity.

Key words: Food hypersensitivity, food challenge, radioallergosorbent test, skin tests

INTRODUCTION

Adverse reactions to food (food hypersensitivity) may either be immunological (food allergy) or non-immunological (non-allergic food hypersensitivity or intolerance).[1] The spectrum of food allergy (FA) include immunoglobulin E (IgE)-mediated (e.g. urticaria, angioedema, anaphylaxis), mixed IgE and non-IgE mediated (e.g. atopic dermatitis/eczema syndrome [AEDS], asthma and allergic eosinophilic gastrointestinal disorders), and non-IgE mediated mechanisms (e.g. gluten-sensitive enteropathy [celiac disease] and food-sensitive enteropathies in infancy).[2] Adverse reactions to food additives (e.g. preservatives, colourants, gums, flavour-enhancers and sweeteners) are classified as non-allergic food hypersensitivity reactions/intolerance as the mechanism is non-immunological or unknown.

Epidemiology of FA

FA in childhood is probably more common than in adults, with prevalence reported as 6% to 8% of infants in the first year of life compared to 1% to 2% in adults. Common food allergens in childhood are cow's milk, egg, peanut, fish, shellfish and wheat. The incidence of cow's milk allergy in early childhood is estimated to be 2% to 3% in the first year of life, egg allergy 2.4% at 2 years of age and prevalence of peanut allergy 0.5% to 0.6% at 4 years of age. FA in childhood is usually transient, being one of the first manifestations of the "atopic march", with children "outgrowing" FA and AEDS as they develop asthma and allergic rhinitis. The majority of food allergic children (about 85%) lose their sensitivity to most allergenic foods (egg, milk, wheat, and soya) within the first 3 to 5 years of life, as demonstrated in children with AEDS. Recently, even resolution of peanut allergy, previously thought to be persistent, has been reported in about 20% of peanut-allergic children younger than 2 years who achieve tolerance by school age.[3] FA in children will probably persist if it has not resolved by 5 to 7 years of age, and especially so if it has not resolved by 12 years of age.

In contrast, FA in adults usually persists. Causative foods have not been identified through specifically designed community-based studies although peanuts, fish, shellfish, tree nuts are commonly reported in various case series and surveys. In addition, FA to fruit and vegetables ("pollen-fruit syndrome") are relatively common in adults due to cross-sensitivity between highly conserved homologous proteins present in grass and tree pollen, and fruit and vegetables in adults with seasonal allergic rhinitis or asthma.[4]

The true prevalence of FA in children and adults in Singapore is unknown. A population-based questionnaire survey of 6,404 Singapore children aged 5 to 12 years estimated the prevalence to be 4 to 5%. The actual figure may be lower as questionnaire surveys tend to overestimate the true prevalence. The most common food allergens were bird nest (27%), crustaceans (24%), egg and cow's milk (11%).[5] FA was found to comprise 49.3% of 73 cases of anaphylaxis seen in our adult clinical immunology/allergy clinic in Singapore over a four and a half year period. Shellfish (crustaceans), molluscs (limpet) and bird nest were the most common allergens.[6] In contrast to western studies, peanuts and tree nuts are not a common cause of FA in both local children and adults. The reason for this is unknown, although differences in dietary patterns, food preparation, ethnicity and genetic differences may contribute to this.

Clinical features

The clinical manifestations of FA are summarized in Table 1.[7] About 35% of children with moderate to severe AEDS have food-sensitive eczema.[8] Although food-induced respiratory reactions may occur as one of the clinical manifestations of anaphylaxis and has been reported in 6% of children with asthma,[9] FA as a cause of rhinitis/asthma is uncommon, with the exception of occupational asthma related to inhaled food allergens (e.g. Baker's asthma).[10] There is also little evidence to date that migraine, irritable bowel syndrome, attention deficit hyperactivity disorder, chronic fatigue syndrome and autoimmune diseases are due to food hypersensitivity.[11]

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Table 1. Signs and symptoms of FA in various target organs

Skin	Urticaria/ angioedema Flushing Erythematous pruritic rash Atopic dermatitis
Gastrointestinal tract	Pruritus and/or swelling of the lips, tongue, or oral mucosa Nausea Abdominal cramping or colic Vomiting or reflux Diarrhoea Nasal congestion
Respiratory tract	Rhinorrhoea Pruritis/ sneezing Laryngeal oedema, staccato cough, and/or dysphonia Wheezing/ repetitive cough Hypotension/ shock
Cardiovascular	Dizziness Cramping back pain (uterine contraction)
Other	Feeling of "impending doom"

Adapted from [7]

Evidence-based diagnostic tests

IgE-mediated FA is diagnosed based on a combination of history, physical examination and demonstration of food-specific IgE to the suspected food, either with skin prick tests (SPT) and/or measurement of specific IgE levels.

The temporal relationship between symptom onset and clinical manifestations, and details of the types of food ingested are crucial in the clinical evaluation of FA. Locally where our diet may comprise a variety of multicultural cuisines, evaluation of the putative food allergen can prove challenging especially when FA occurs following a restaurant meal or buffet. Occasionally, communication between the clinical immunologist/allergist and food establishments is necessary in order to establish the causative food allergen.

SPT using commercially available glycerinated food extracts are frequently used to evaluate IgE-mediated FA. In cases where the food allergen is not available in the form of extracts, prick-to-prick test using the fresh food (especially fresh fruit) is used. Allergens eliciting a mean wheal diameter of ³ 3 mm more than the negative control in the presence of a positive histamine control are considered positive tests. A positive SPT indicates a possibility that the patient has symptomatic reactivity to the specific food (overall positive predictive accuracy is <50%), whereas a negative test confirms the absence of IgE-mediated FA (negative predictive accuracy >95%).

SPT to cow's milk and egg are routinely offered by most paediatric allergy clinics in children below 2 years of age. Other food allergens including fish, shellfish, wheat and peanut are tested based on history. Panels of tests should not be offered in the absence of supporting history in view of the low positive predictive value and possibility of false positive tests. For instance, 11.7% of local healthy oriental adults have been shown to demonstrate positive SPT to at least one food allergen without clinical evidence of FA.12 Intradermal testing (IDT) is not used in the diagnosis of FA because of the higher risk of anaphylaxis and absence of clinical reactivity in the presence of a negative SPT.

Radioallergosorbent tests (RAST) and similar in vitro assays may be used to identify food-specific IgE antibodies. Currently, the use of a quantitative measurement of food-specific IgE antibodies (Pharmacia® CAP System fluorescent enzyme immunoassay, FEIA) has been shown to be highly predictive of symptomatic IgE-mediated FA when these levels exceed 95% positive predictive values (Table 2).[13] Specific IgE levels less than 0.35 kU_A/mL have an excellent negative predictive value (NPV) exceeding 95%. In clinical practice, these tests are usually reserved for cases where SPT may not be possible e.g. dermographism, severe AEDS with widespread skin involvement or patients who have difficulty stopping anti-histamines prior to skin testing. They also have low specificity and thus should not be used as "screening" tests for FA.

Food challenges can be avoided in those with a consistent history of IgE-mediated FA and positive SPT with glycerinated food extracts, prick-to-prick tests to fresh food (especially fruit), or positive food-specific IgE, especially if these are above the 95% positive predictive value (PPV) for the respective tests. Although the double blind placebo controlled food challenge (DBPCFC) is the gold standard for the diagnosis of FA, especially in research, open challenges are more commonly done in the clinic setting.[14] This is because FA can be reasonably well diagnosed from the clinical history, SPT and specific IgE measurements alone. Open challenges are often offered where the clinical history is not suggestive of FA in the presence of negative SPT and low specific IgE levels, especially in patients with a history suggestive of non-allergic food hypersensitivity/ intolerance. In children, open challenges are also used to verify clinical resolution of FA in the presence of diminishing SPT wheal size and low specific IgE levels.[15] Neither SPT wheal size nor specific IgE levels are predictive of the severity of subsequent clinical reactions.

Table 2. Levels of specific IgE antibodies yielding positive predictive values of 95% and negative predictive values of 90% for positive DBPCFC

Food	Specific IgE (kU_A/L) > 95% PPV	Specific IgE (kU_A/L) > 90% NPV
Egg	6	0.6
Cow's milk	32	1.0
Peanut	15	0.35 (> 85% NPV)
Fish	20	5
Soy	65 (50% PPV)	5
Wheat	100 (75% PPV)	79

DBPCFC: double blind placebo control food challenge
NPV: negative predictive value
PPV: positive predictive value

Adapted from [13]

The use of patch testing for the diagnosis of delayed (type IV) hypersensitivity in the form of food sensitive eczema in infants and children is currently investigational. It has no role in the diagnosis of IgE-mediated FA.

Non evidenced-based tests

There are a number of commercially available tests offered by laboratories, healthcare and/or non-healthcare professionals claiming to be able to diagnose FA. These include:

- measurement of IgG RAST or food-specific IgG assays
- provocation-neutralization testing and therapy
- electrodermal testing
- applied kinesiology followed by acupressure or acupuncture
- changes in cell size upon in-vitro exposure of leukocytes to food extract (using automated assays) followed by elimination diets or rotary diets.

The first two tests deserve some elaboration as they are often misunderstood by the medical community. The production of serum IgG and IgA to food that we eat is normal. Thus the presence of these antibodies to food does not indicate FA. Provocation–neutralization testing involves either sublingual or (more commonly) intradermal 'provocation' by a test antigen, followed by an observation period of 10 minutes after each injection, at which time the wheal response is measured and any subjective symptoms reported. Symptoms such as drowsiness, dry mouth, an inability to concentrate or headache are considered a positive challenge, meaning that the individual is 'allergic' to the food. The patient is then given a different dose of the antigen as either a sublingual drop or another injection until the 'reaction' is 'neutralized'. This 'neutralization' dose would then be taken in a desensitization series or to neutralize a reaction. This has been disproved by two blinded controlled studies.[16,17] As for the other techniques, there have been no scientific studies supporting their use. A beneficial placebo effect may be responsible for the perceived clinical effectiveness in many cases of non-allergic food hypersensitivity/intolerance.[18]

The importance of a correct diagnosis of FA

Undiagnosed IgE-mediated FA may result in fatal anaphylaxis, especially in children and adolescents with asthma.[19] Conversely, inappropriate testing and misinterpretation of test results may lead to a misdiagnosis of FA, resulting in unnecessary anxiety, dietary restriction and effects on growth, development and quality of life especially of children and their families. In adults, dietary restriction may not have as far-reaching consequences as in children, although psychosocial effects on quality of life may be similar. As such, individuals, in particular children and adolescents with suspected FA should be systematically evaluated in a clinical immunology/allergy clinic with its multidisciplinary team involving an allergist/immunologist, dietician and allergy nurse specialist. Individuals with confirmed FA will need to be educated on avoidance measures, reading food labels, cross-reacting food groups, and the emergency use of anti-histamines and the epinephrine autoinjector (Epipen®). A dietician may need to be involved in the nutritional assessment and monitoring of children with failure to thrive as a result of FA. The allergy nurse specialist helps the family and child to come to terms with the diagnosis, reinforcement of the treatment and emergency plan, and facilitating liaison between the family and day care/nurseries so that the latter play an active role in preventing accidental ingestions and in managing emergencies. In individuals with non-allergic food hypersensitivity/intolerance, reassurance and a change of mindset may be an uphill task, at times requiring specific testing and open challenges to demonstrate tolerance. This may particularly be so in children and adolescents on severely restricted diets due to misdiagnosed FA.

CONCLUSION

Skin prick tests, measurement of food-specific IgE levels and food challenges are well-established, evidence-based diagnostic tests for FA. There is no basis for food-specific IgG assays and provocation-neutralisation tests in the diagnosis of FA. Accurate diagnosis of FA is important as it may have both short and long-term medical and psychosocial implications for the patient and family.

USEFUL INTERNET RESOURCES

1. The Allergy Report: A manual for primary care health professionals (www.theallergyreport.org/reportindex.html).
2. Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology. Practice parameters for allergy diagnostic testing (www.jcaai.org/Param/Aller.HTM).

REFERENCES

1. Johansson SGO, Hourihane JO, Bousquet J, et al. A revised nomenclature for allergy. An EAACI position statement from the EAACI nomenclature task force. Allergy 2001; 56:813-24.
2. Sampson HA. Food allergy. J Allergy Clin Immunol 2003; 111:S540-7.
3. Hourihane JO, Roberts SA, Warner JO. Resolution of peanut allergy: case control study. BMJ 1998; 316:1271-5.
4. Crespo JF, Rodriguez J. Food allergy in adulthood. Allergy 2003; 58:98–113.
5. Goh DLM, Lau YN, Chew FT, Shek LPC, Lee BW. Pattern of food-induced anaphylaxis in children of an Asian community. Allergy 1999; 54:84-6.
6. Thong BY, Cheng YK, Leong KP, Tang CY, Chng HH. 73 cases of anaphylaxis referred to a Clinical Immunology/Allergy service in Singapore. Ann Acad Med Singapore 2003;32(5):S151 (abstract).
7. Sampson HA. Food allergy. Part 2: diagnosis and management. J Allergy Clin Immunol 1999; 103:981-9.
8. Eigenmann PA, Sicherer SH, Borkowski TA, Cohen BD, Sampson HA. Prevalence of IgE-mediated food allergy among children with atopic dermatitis. Pediatrics 1998; 101:e8.
9. Novembre E, de Martino M, Vierucci A. Foods and respiratory allergy. J Allergy Clin Immunol 1988; 81:1059-65.
10. Roberts G, Lack G. Relevance of inhalational exposure to food allergens. Curr Opin Allergy Clin Immunol 2003; 3:211-5.

11. Ortolani C, Bruijnzeel-Koomen C, Bengtsson U, et al. Controversial aspects of adverse reactions to food. European Academy of Allergology and Clinical Immunology (EAACI) Reactions to Food Subcommittee. Allergy 1999; 54:27-45.
12. Chng HH, Tang CY, Leong KP. Healthy adults demonstrate less skin reactivity to commercial extracts of commonly ingested food than to D. farinae. Asian Pac J Allergy Immunol 1999; 17:175-8.
13. Sampson HA, Ho DG. Relationship between food-specific IgE concentrations and the risk of positive food challenges in children and adolescents. J Allergy Clin Immunol 1997; 100(4):444-51.
14. Bindslev-Jensen C, Balmer-Weber B, Bengtsson U, et al. Standardization of food challenges in patients with immediate reactions to foods. Position paper from the European Academy of Allergy, Asthma and Immunology. Allergy 2004 (in press).
15. Thong BY, Hourihane JO. Monitoring of IgE-mediated food allergy in childhood. Acta Paediatrica 2004 (in press).
16. Jewett DL, Fein G, Greenberg MH. A double-blind study of symptom provocation to determine food sensitivity. N Engl J Med 1990; 323:429–33.
17. Fox RA, Sabo BMT, Williams TPW, Joffres MR. Intradermal testing for food and chemical sensitivities: a double-blind controlled study. J Allergy Clin Immunol 1999; 103:907–11.
18. Teuber SS, Porch-Curren C. Unproved diagnostic and therapeutic approaches to food allergy and intolerance. Curr Opin Allergy Clin Immunol. 2003; 3:217-21.
19. Bock SA, Munoz-Furlong A, Sampson HA. Fatalities due to anaphylactic reactions to foods. J Allergy Clin Immunol 2001;107(1):191-3.