Food allergy

Penny Fitzharris and Rohan Ameratunga

Correspondence to: pennyf@adhb.govt.nz

***Penny Fitzharris** is a specialist physician in Clinical Immunology and Allergy at Auckland Hospital.*

***Rohan Ameratunga** is a specialist physician in Clinical Immunology and Allergy and immunopathologist at Auckland Hospital and in private practice.*

Introduction/definitions

Adverse food reactions are 'any untoward reactions following the ingestion of a food', and are reported by one third of children and adults. They may result from food allergy, but also from a range of other causes.

Food intolerance

This term is used to describe adverse food reactions that are non-immunologic in origin, potentially arising from anatomic, toxic, metabolic and/or infectious disorders. Lactose intolerance, a deficiency of the enzyme lactase, and histamine fish poisoning (scombroid poisoning), associated with eating toxic quantities of histamine, are examples. It is not uncommon for foods to play a role in irritable bowel syndrome or in triggering migraine. Poorly defined symptoms may also be attributed to foods.

Food allergy

Food allergy (or hypersensitivity) is a specific immune-mediated reaction to a protein food component. The term includes both IgE-mediated and non-IgE mediated reactions. The term 'sensitisation' indicates that specific IgE antibodies can be detected to that particular allergen, but does not indicate that there is necessarily clinical reactivity to the food.

Symptoms of IgE mediated food allergy

Symptoms of IgE mediated food allergy are usually rapid in onset, often occurring within minutes of eating the food, but sometimes as long as two hours. Multiple organ systems are often involved. Clinical manifestations result from the release of chemical mediators, including histamine, from mast cells and basophils and include itching, vasodilatation and vascular leakage, mucus production and smooth muscle contraction.

Manifestations include:

- acute urticaria, angioedema
- throat or chest tightness, stridor, wheeze, cough, voice change, rhinitis, conjunctivitis
- nausea, vomiting, abdominal pain, diarrhoea
- alteration of consciousness, hypotension
- anaphylaxis.

Some cases of anaphylaxis occur only when the patient exercises after eating a particular food – 'food-dependant exercise-induced anaphylaxis'. This syndrome accounts for a significant proportion of anaphylaxis that occurs during exercise.[1]

Symptoms of non-IgE mediated food allergy

Symptoms of non-IgE mediated food allergy, usually more sub-acute or chronic, may be isolated to the gastro-intestinal tract and include:

- coeliac disease and dermatitis herpetiformis
- food protein-induced enterocolitis
- food protein-induced proctitis
- food-induced pulmonary haemosiderosis.

Coeliac disease is an auto-immune lymphocyte mediated disease of the small bowel, with strong HLA associations. The immune response is to gliaden, a gluten protein of wheat and other cereals. Biopsies show characteristic histology with flat mucosa, loss of villi and a chronic inflammatory cell infiltrate.

Some conditions, such as eosinophilic oesophagitis, which may involve both IgE and non-IgE mechanisms, are being increasingly recognised and affect both children and adults. Eosinophilic oesophagitis may present as a feeding disorder, or as difficulty swallowing, vomiting, or abdominal pain. Food impaction is common. There is failure to respond to anti-reflux and antacid therapy. IgE mediated food allergy is common and elimination diets may be helpful. It is usually diagnosed by endoscopic biopsy.[2]

Prevalence of adverse food reactions

In European studies one third of parents report adverse food reactions in their children, with a similar proportion of adults self-reporting in both European and US studies. Detailed studies in both the US and Europe, using double blind placebo controlled food challenge, show that approximately 2.5–4% of adults and 6–8% of children have demonstrable food allergy.[3,4] Data for New Zealand is limited, but figures are likely to be similar to those in the US and Europe. IgE based disease is more common than disease caused by other immune mechanisms.

The prevalence of food allergy appears to be increasing. Studies from the Isle of Wight suggest a tripling of the prevalence of peanut allergy in less than 10 years. In the UK over the 1990s there was a sevenfold increase in hospital admissions for anaphylaxis, with food allergy being the most common cause of community-based anaphylaxis.[5] There is a strong genetic influence, involving multiple genes, in IgE-mediated food allergy, family history being the strongest predictor for the development of food allergy. Increasing prevalence of allergic disease, including food allergy, is particularly evident in nations with higher socioeconomic status. At least in part this is thought due to increased hygiene, especially in early childhood, resulting in altered regulation of immune responses, perhaps especially affecting the gut. Urbanisation may also contribute other factors.

Coeliac disease has been considered to have a population prevalence of approximately 1:1000, but recent studies suggest that this may be an underestimate.

The natural history of food allergy

Typical onset is in the first or second years of life, with peak prevalence at one year. In New Zealand, cow's milk, affecting around 2.5% of children under two years of age, and egg, affecting 1–2% of young children, are the main food allergies of infancy and early childhood. Both cow's milk and egg allergies frequently remit by mid-childhood, but a proportion of children will maintain their allergy into adult life. The non-IgE mediated allergies, e.g. milk protein enteropathy, generally resolve during early childhood.[6]

Children identified with an IgE mediated food sensitivity are at substantially increased risk of developing further food sensitivities, as well as inhalant sensitivities, asthma and rhinitis.[7]

Peanut allergy usually develops before the age of five years, and is present in 0.4–1.3% of children and 0.5–1% of adults, with evidence of increasing prevalence of sensitisation over recent years. Recent data suggests 20–25% of children, particularly those with low to moderate levels of peanut-specific IgE will remit, but the majority remain peanut allergic for life.[8] Consumption has increased considerably over recent decades, and evidence shows that roasted peanuts are more allergenic than raw or boiled peanuts.

Children identified with an IgE mediated food sensitivity are at substantially increased risk of developing further food sensitivities, as well as inhalant sensitivities, asthma and rhinitis

Allergy to fresh fruits often develops in teenagers or young adults and is commonly associated with sensitivity to tree nuts, particularly hazel and almond. Shellfish allergy may appear in adults who have eaten shellfish without problems in the past and allergy to other foods may also develop in adults.

Food allergens are proteins, with foods eaten early in life generally being important. Rice allergy is common in Japan, sesame allergy increasingly recognised in the Middle East and Australia, fish allergy very common in Scandinavia. Lupin has been recently recognised as an allergen in Europe. It seems that essentially all protein containing foods may induce an allergic reaction, although these may be rare. With continuing immigration, patterns of food allergy may change in New Zealand.

Cross reactivity of allergens

IgE antibodies may cross-react with allergens present in closely related foods. For example, up to 50% of patients with tree nut allergy react to other tree nuts. There is often cross-reactivity among crustacea, including prawns, crabs, crayfish, or among scaly fish, but cross reactivity between crustacea and bivalves, e.g. mussels, or with scaly fish, is less common.

'Oral allergy syndrome' is seen in up to 50% of patients with certain pollen allergies. In New Zealand it is usually associated with birch tree pollen allergy, where symptoms of itching and mild swelling of the mouth, tongue, palate and throat develop immediately when eating a range of fresh fruit and vegetables, including apple, cherry, kiwi, carrot, celery. The usual shared allergens are heat-labile proteins, so the reaction usually occurs with raw food.[9]

Sensitisation to some fruit and vegetables, commonly avocado and banana occurs in 30–50% of latex allergic patients because of allergen cross-reactivity, rather than close botanical relationships.[10]

Diagnosis of food allergy

Both over-diagnosis and under-diagnosis may have major health implications, with over diagnosis potentially leading to inappropriate dietary restrictions, malnutrition, eating disorders, other psychological problems and family disruption. Under-diagnosis may result in growth failure, inadequate treatment, including of life-threatening reactions and unnecessary anxiety and stress.

The clinical history is extremely important in food allergy diagnosis. Important questions in any adverse reaction to food include details of:

- specific symptoms
- any of the signs and symptoms typical of IgE-mediated reactions
- which food was suspected to have provoked the reaction and is this a reproducible reaction
- quantity of the food eaten
- other foods eaten at that time
- possible hidden ingredients
- whether any of the major food allergens were eaten
- time elapsed between eating the food and onset of symptoms

- any exercise involved
- any medications taken, including OTC drugs especially NSAIDs
- other possible variables e.g. menstrual period, season, temperature
- details of treatment and response to treatment.

These questions will help to suggest whether an IgE-mediated reaction could be present. If so, the patient should be advised to avoid that food until further investigation or consultation takes place.

Physical examination in the acute situation should focus on assessing the severity of the acute allergic disease, including angioedema/urticaria, respiratory and/or cardiovascular symptoms. In young children, severe vomiting, associated with hypotension may suggest dietary protein enterocolitis. In more routine assessment any complications from food allergy, e.g. growth retardation, should be looked for. About 40% of young infants with atopic dermatitis will have contributing food allergy.

Testing for food allergy, both skin testing and blood tests must be interpreted in the context of the patient's history.

Skin prick tests are reproducible, cause little discomfort, provide results within 20 minutes and are cheaper than in vitro tests. However they must be performed by appropriately trained individuals, in settings with necessary medications, equipment and staff to treat anaphylaxis, although this complication is very rare.

About 40% of young infants with atopic dermatitis will have contributing food allergy

As well as negative (saline) and positive (histamine) controls, drops of relevant commercial allergen extracts are placed on the skin and the skin then gently pricked with a specialised lancet. If specific IgE antibodies are present on mast cells in the skin, histamine and other chemical mediator release will result in a wheal and a flare response, peaking at 15 minutes. A wheal greater than the negative control by 3mm or more is generally considered positive, although wheals may be smaller in infants. Many commercial extracts are of good quality but for certain foods, particularly fresh fruit and vegetables, 'prick-prick' testing is used with the lancet pricking the fruit and then the arm directly, as the allergenicity of these foods is often lost in extract preparation.

As routinely used, the skin prick test has high sensitivity (>90%), but only moderate specificity (approx 50%). With good quality extracts the negative predictive value of a skin test is thus high at 90–95%.

When the traditional 3mm wheal size is used to define a positive response, a substantial proportion of subjects will not show an objective clinical response to these foods when challenged with them and these results are considered to be 'false positives'. However, this does not indicate that the patients do not have specific IgE to the food, simply that this IgE has not been linked to a clinical response. A large Australian study has identified a wheal size for peanut, egg and milk skin testing, which was 100% diagnostic of a subsequent positive food challenge.[11] Further studies from other clinics and in adults is needed to validate these results for more general use.

Intradermal skin tests are not used for foods but the atopy patch test has shown some promise in detecting non-IgE mediated food allergy, potentially relevant in eosinophilic gut disorders and possibly in atopic eczema.

In vitro measurement of food-specific IgE antibodies by RAST is a little less sensitive than skin prick tests and considerably more expensive. It is useful if antihistamines, which suppress SPT, cannot be avoided, if the patient has skin disease such as severe atopic dermatitis, is dermographic or if there is considered an unacceptable degree of risk from skin testing.

Skilled interpretation of results is essential. While higher concentrations of food-specific IgE do correlate with an increased risk of reaction after eating the food, they do not indicate the likely severity of the reaction, which will be influenced by many factors including the amount eaten, speed of absorption, exercise, concurrent disease, especially asthma. Patients with negative RASTs may react to the food, while this is much less likely with a negative skin test.

Several large studies on children in the US have identified 95% predictive levels for reaction to:

- milk 15 kUA/L (5 kUA/L for infants <2 years)
- egg 7 kUA/L (2 kUA/L for infants <2 years)
- peanut 14 kUA/L
- tree nut approx. 15 kUA/L
- fish 20 kUA/L

These levels indicate that a child with a suggestive history of peanut allergy has a >95% likelihood of experiencing an allergic reaction to peanut on challenge. Therefore oral challenge is not necessary to confirm the presence of allergy at the time of these results.[7]

These have been measured with the Pharmacia CAP-RAST method, which is used in New Zealand laboratories, but these levels have not been validated in adults.

RAST levels can be used to monitor children over time. If levels fall and there have been no clinical reactions for some time, careful challenge in an appropriate clinical setting, usually hospital based, may be appropriate. Once a child has been shown to tolerate a food, regular intake of that food is recommended to maintain tolerance.

Other forms of evaluation of food allergy include the use of short-term elimination diets, with the specific food(s) being eliminated from the diet for two to three weeks. Substitution with a hypoallergenic formula (e.g.

Pepti Junior) may be necessary in a younger child where cow's milk allergy is suspected.

Another type of elimination diet is an 'oligo-antigenic' diet, nutritionally complete but containing only foods uncommonly implicated in allergic reactions, potentially useful in chronic conditions in which the role of food allergy is questioned, but without identification of particular foods.

Elemental diets involve the use of extensively hydrolysed or amino-acid based formulae and may be useful in investigation or treatment. The help of an experienced dietician is invaluable when using elimination diets.

Food challenges, using structured protocols, should only be undertaken by specialists familiar with food-allergic reactions and in settings where there are facilities to treat any severe reaction.[11]

Currently the main treatment strategy is avoidance of the relevant foods. While simple in theory, this actually requires very considerable patient/caregiver education

Unvalidated tests for food allergy include food-specific IgG and IgG4 tests, often showing multiple positive results which are likely to be the result of normal immune responses to foods, hair analysis, Vega testing and cytotoxic tests. None have been scientifically validated.

Treatment of food allergy

Currently the main treatment strategy is avoidance of the relevant foods. While simple in theory, this actually requires very considerable patient/caregiver education. Patients need guidance in how to read package labels, cautions with unpackaged foods, meal preparation at home, strategies for eating out safely, allergen content of non-food items including medications, and potential risk from exposure to allergen containing saliva. Day care, schools and camps need appropriate management plans.

Many food allergic individuals will, despite their efforts to avoid relevant allergens, have episodes of accidental exposure and therefore must be prepared to treat an unexpected reaction at any time in any place.[12]

Strict avoidance is recommended in patients who have experienced severe reactions but in practice individuals vary greatly in the amount of allergen that will induce symptoms, from less than one milligram to 20–40 grams. Some individuals will tolerate cooked, but not raw allergens. Some types of mild reactions such as oral allergy syndrome with fresh fruit are not usually associated with severe reactions, so strict avoidance is less important.

Skin exposure to foods will generally cause little or only local reactions while inhalation of aerosolised food, from cooking vapours, grinding or chopping of the food is able to trigger allergic reactions.

Food substitution with a hypo-allergenic formula is particularly important in infants with a proven allergy to cow's milk, while in older children (>12 months) soy formula can be used as a milk substitute. Soy should not be used in younger children as there is a significant risk of soy sensitisation. Goat's milk formula is not a satisfactory alternative for children with cow's milk allergy given that the allergens are almost identical.

Recently there have been a number of reports of the use of various protocols for attempted oral tolerance induction. This may well be a treatment that becomes more widely available in the future.

Anaphylaxis treatment

Any patient who has previously had anaphylaxis to food, or is considered to be at risk, should have access to specialist assessment, an appropriate management plan, medications and identification (Medic Alert bracelet

Allergy prevention

Strategies to avoid the development of food allergy in children with a family history of atopic disease include:[16]

- Avoidance of smoking during pregnancy, in the presence of the child or in enclosed spaces where the child will sleep or play
- Breastfeeding where possible for six months. Maternal dietary restrictions during breastfeeding are generally not recommended unless the child has definite food allergy, as food allergens are present in breast milk. Young children can be tested for food allergy at any age. Tests may need to be repeated at an older age.
- If it is not possible to breastfeed, a partially or extensively hydrolysed formula is preferred to conventional cow's milk formula for the first six months of life. In NZ extensively hydrolysed formula is only subsidised for children who have already developed food allergy and for most parents the cost of preventive use is prohibitive. Soy formulas and goat's milk are not recommended for reducing food allergy risk.
- Studies suggest that delaying the introduction of solid foods may reduce the incidence, or delay the onset, of infantile allergic diseases in the first year of life, but that these effects are modest. It is common clinical practice to recommend avoidance of solids until six months of age, with subsequent introduction, one at a time, of vegetables (e.g. carrot, kumara, pumpkin, potato), rice, meat and fruit. Potentially allergenic foods such as wheat, soy and cow's milk are delayed until 12 months of age, eggs at two, fish at three with peanuts, nuts and shellfish at three to four years. Benefit is not proven by randomised controlled studies.

or similar) as a person who has food allergy and carries adrenaline. School aged children can use a Medic Alert emblem with a Velcro strap. Their school should be informed and teachers educated about using adrenaline and calling for help. A DVD about anaphylaxis can be obtained from Allergy New Zealand and is a valuable training resource.

Unfortunately Clinical Immunology & Allergy services in New Zealand are largely restricted to the main centres, despite the high prevalence of allergic disease. At present Pharmac funds only ampoule adrenaline, to be drawn up by needle and syringe and injected intramuscularly. The great majority of specialists, patients and caregivers do not find this a realistic option for treatment so most patients are prescribed an autoinjector device, the wholesale cost of which is $135, retail up to $200. It is essential that patients are trained in the appropriate use of adrenaline and the need to carry it. Fatal outcome from food allergy has been associated with delayed use of adrenaline in numerous studies, with the presence of asthma also a significant risk factor.[13,14]

Further detailed treatment of anaphylaxis was covered extensively in the April 2006 issue of *NZFP*.[15] There is widespread agreement internationally that first medical responders should use adrenaline 0.3–0.5mg IM (adults) as the primary treatment.

A suitable written management plan can be downloaded from the Australasian Society for Clinical Immunology and Allergy (ASCIA) www.allergy.org.au

Support for patients and families dealing with food allergy is available from Allergy New Zealand, www.allergy.org.nz, who provide both written materials, email alerts regarding food recalls and additional training materials.

Information on the allergen content of manufactured foods is available from the therapeutic database www.mfd.co.nz

The New Zealand Food Safety Authority NZFSA) www.nzfsa.govt.nz is responsible for the implementation of the Australia and New Zealand Food Standards Code. Food sold in New Zealand must be labelled in accordance with this code, including mandatory labelling of common food allergens including cereals, crustacea, egg, fish, milk, nuts and sesame seeds, peanuts and soybeans and added sulphites in concentrations of 10mg/kg and more. In New Zealand, 22 of 47 food recalls during 2005 and 2006 were a result of unlabelled allergen content. All allergic reactions resulting from unexpected exposure to allergen in food should be reported to regional Public Health services.

Fatal outcome from food allergy has been associated with delayed use of adrenaline in numerous studies, with the presence of asthma also a significant risk factor

The difficulties that allergic patients and families experience with food labelling are discussed by Food Standards Australia New Zealand (FSANZ) www.foodstandards.gov.au with particular problems associated with the use of 'may contain traces' labels.

Competing interests

Assoc Prof Rohan Ameratunga is actively involved in food allergy research. He has received partial funding for a post-doctoral research Fellow from Nutricia to undertake a national food allergy project.

References

1. Shadick NA, Liang MH, Partridge AJ, et al. The natural history of exercise-induced anaphylaxis: survey results from a 10-year follow-up study. J Allergy Clin Immunol 1999; 104(1):123-7.
2. Noel RJ, Putnam PE, Rothenberg ME. Eosinophilic oesophagitis. N Engl J Med 2004, 351:940-1.
3. Zuberbier T, Edenharter G, Worm M, Ehlers I, Reimann S,Hantke T, Roehr CC, Bergmann KE & Niggemann B. Prevalence of adverse reactions to food in Germany – a population study. Allergy 2004; 59:338-345.
4. Sicherer SH, Munoz-Furlong A, Sampson HA. Prevalence of peanut and tree nut allergy in the United States determined by means of a random digit dial telephone survey: a 5 year follow-up study, J Allergy Clin Immunol 2003; 112:1203-7
5. Gupta R, Sheikh A, Strachan DP, Anderson HR. Time trends in allergic disorders in the UK Thorax. 2007; 62:91-96
6. Sicherer SH. Food protein-induced enterocolitis syndrome: case presentations and management lessons. J Allergy Clin Immunol 2005; 115:149-56.
7. Sampson HA. Update on food allergy. J Allergy Clin Immunol 2004; 113:805-19.
8. Van der Leek TK, Liu AH, Stefanski K, Blacker B, Bock SA. The natural history of peanut allergy in young children and its association with serum peanut-specific IgE. J Pediatr 2000; 137:749-55.
9. Mari A, Ballmer-Weber BK, Vieths S. The oral allergy syndrome: improved diagnostic and treatment methods. Curr Opin Allergy Clin Immunol 2005; 5:267-73.
10. Brehler R, Theissen U, Mohr C, Luger T. 'Latex-fruit syndrome': frequency of cross-reacting IgE antibodies. Allergy 1997; 52:404-10.
11. Bock SA. Pediatric Food Allergy Diagnostic Evaluation. Pediatrics 2003; 111:1636-1644.
12. Hill DJ, Heine RG, Hosking CS. The diagnostic value of skin prick testing in children with food allergy. Paediatr Allergy Immunol 2004; 15:435-41.
13. Bock SA, Muñoz-Furlong A, Sampson HA. Fatalities due to anaphylactic reactions to foods. J Allergy Clin Immunol 2001; 107:101-3.
14. Pumphrey RS. Lessons for management of anaphylaxis from a study of fatal reactions. Clin Exp Allergy 2000; 30:1144-50.
15. Crump V. Management of anaphylaxis. N Z Fam Physician 2006; 33:115-124.
16. Prescott SL and Tang MLK. The Australasian Society of Clinical Immunology and Allergy position statement: summary of allergy prevention in children. Med J Australia 2005; 182 (9): 464-467.