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Advice on diagnosis and assessment of food allergic disorders

Introduction

Food allergy describes an adverse immune-mediated response (usually IgE mediated), which occurs when a person is exposed to specific food allergen(s), usually by ingestion and more rarely by inhalation or skin contact. IgE -mediated food allergy produces immediate (within 1-2 hours) and reproducible symptoms which affects multiple organs including the mouth, throat, skin, gastrointestinal tract, respiratory, cardiovascular, and neurological systems. Mixed IgE and non-IgE food allergy syndromes include cow milk protein allergy, and eosinophilic gastro-intestinal tract diseases.

Food sensitization describes the production of serum-specific IgE to food allergens, without the clinical symptoms of an allergic reaction on food exposure. It is far more common than food allergy and is one reason as to why screening or indiscriminate use of allergy testing is not recommended.
Food intolerances are non-immune adverse reactions to foods and/or food additives which are distinct from food allergy. Conditions often present with non-specific gastrointestinal and musculoskeletal symptoms, headache and fatigue. Symptoms may be like those reported in irritable bowel syndrome or fibromyalgia. There is usually a delay in symptom onset and prolonged symptomatic phase. The exact cause is unknown, in some cases enzyme deficiencies or pharmacological reactions to chemicals such as caffeine or tyramine are contributory factors.

The reported prevalence of food allergy varies depending on the definitions of food allergy used, the study population and design, and time period assessed. Self-reported symptoms of allergy are far more common than confirmed food allergy. The prevalence of food allergy has increased over the last 30 years. The point prevalence of physician confirmed food allergy in Europe is 3.8% in children and 6.9% in adults. Prevalence of positive IgE blood tests to any food allergen is 18.4% in children and 11.2% adults (up 21.4% for skin prick tests). Prevalence of symptoms and positive blood IgE blood test to any food allergen is 2.9% (3.5% for children and 2.4% for adults).

Allergy may develop to almost any food; common food allergens include cow's milk, hen's egg, peanuts, soyabean, tree nuts (walnut, almond, hazelnut, pecan, cashew, pistachio, and Brazil nuts), crustacean shellfish (such as shrimp, crab, and lobster), fish and wheat. Other prominent allergens in Europe include celery, mustard, sesame, lupine, and molluscan shellfish. There is significant cross reactivity within certain food families (tree nuts, shellfish, and fish) causing allergic symptoms to multiple family members. Allergic reaction can also occur between different food families; peanuts, tree nuts, ~~and~~ sesame and raw food allergens for the pollen food allergy syndrome.

Complication of food allergy include anaphylaxis: risk depends on type of food, allergy to allergy to peanuts, tree nuts, fish, and shellfish are associated with a higher risk of anaphylaxis. A systematic review and meta-analysis of 13 European studies found the incidence rate of fatal food anaphylaxis in people with food allergy was 1.81 per million person-years (which is lower than the rate of accidental death in the general population).

Other complications include anxiety, stress, reduced quality of life restricted diet and malnutrition.

Allergy focused history

Clinical history is the key to diagnosis of IgE mediated food allergy

The history should focus on the following:

- identity of suspected food allergens
- timing of onset of symptoms after exposure to suspected allergen
- type of food (raw, semi-cooked, cooked, or baked)
- quantity of food ingested which provoke symptoms
- the reproducibility of symptoms on repeated food exposure

Details of any previous treatment:

- including medication to previous episodes of suspected allergen inspection
- has there been any response to the elimination and reintroduction of foods
- are there any co-factors which may increase the likelihood of a clinical reaction: age (teenager and young adults), exercise, infection, nonsteroidal anti-inflammatory drugs (NSAIDs), or alcohol
- setting of reactions (such as school or home)
- check for personal or family history of other allergic conditions such as asthma, eczema, or allergic rhinitis
- in young children details of feeding history (age of complementary feeding [weaning], breast- or formula-fed), weight gain, nutritional status and mother's diet if child is currently being breastfed should be ascertained

IgE mediated food allergy exhibits the following characteristic features:

- symptoms develop almost immediately or within minutes to 2 hours usually with oropharyngeal pruritus and angioedema of the lips, oral mucosa and soft palate after ingestion of food and resolve within 12 hours.
- skin: pruritus, erythema, angioedema (swelling of lips, tongues, eyelids), urticaria (wheals or 'hives' which can be generalized or localised), flushing
- respiratory tract: cough, SOB, wheeze, sneezing, nasal congestion, discharge, itch and sneezing
- gastrointestinal tract: nausea, vomiting and diarrhoea
- systemic symptoms: (faint, dizzy, collapse, blackout; signs of hypotension, tachycardia or bradycardia,) respiratory distress, wheeze, drowsiness, confusion, which indicate life threatening anaphylaxis.
- self-limiting oropharyngeal symptoms (mild, transient localized oropharyngeal pruritus and angioedema of the lips, oral mucosa and soft palate after ingestion of raw fruit or vegetables) are features of pollen food allergy syndrome (see later)

Physical Examination:

- signs of faltering growth (in children) and malnutrition — nutritional status, including weight, length/height, and calculation of body mass index (BMI)

- any signs of comorbid conditions (such as asthma, atopic eczema, and allergic rhinitis)

Differential diagnosis of IgE-mediated food allergy syndrome

Acute spontaneous urticaria and angioedema: no allergen trigger, can be seen post viral infection in children, persistent symptoms for days/weeks despite allergen avoidance or lack of symptoms following ingestion of suspected allergen. Symptoms of urticaria and angioedema lasting more than 6 week are termed chronic urticaria and angioedema: aetiology unknown, in some cases autoimmune disease. Patients are often highly anxious that these symptoms are due to food allergy but if the timing is random in relation to food, especially if many hours later or overnight they can be reassured this is not due to food allergy.

Food intolerance syndrome: non-immune non-specific food reaction, may be related to enzyme deficiencies such as lactase deficiency (causing diarrhoea, abdominal pain, and increased flatus after ingestion of dairy products); pharmacological causes (such as caffeine or tyramine in cheeses); or have no clear mechanisms (including reactions to food additive flavours and preservatives, such as glutamates and sulphites). It should be suspected if there is a delay in symptom onset and prolonged symptoms. People with irritable bowel syndrome may report increased symptoms following foods rich in carbohydrates, fatty food, coffee, alcohol, and spices.

Food refusal or aversion —in young children, food allergy may present as food refusal due to symptoms the child cannot articulate, such as oral tingling and burning, difficulty swallowing, abdominal pain, or nausea.

Food poisoning and toxic reactions including scombroid poisoning caused by bacterial production of excess amines, particularly histamine. Presents with paraesthesia, burning sensations, headaches, and itch after spoilt food ingestion. Associated with ingestion of brown fish meat such as tuna, mackerel, sardines, anchovy, and mahi-mahi fish.

Other conditions which have overlapping symptoms with food allergy include acute asthma, atopic dermatitis, coeliac disease, gastroenteritis, gastro-oesophageal reflux disease, inflammatory bowel disease and irritable bowel syndrome. A careful history will usually distinguish these as above but where there is doubt, consider referral.

Allergy testing

Allergy testing may involve initial skin prick testing or measuring serum-specific immunoglobulin (Ig)E levels to different food allergens, and **should be undertaken by healthcare professionals with the appropriate facilities, expertise, and training to select and perform tests, and interpret results. Allergy testing** is needed to confirm the diagnosis, or to assess whether tolerance has developed to a specific food allergen, depending on local referral pathways and availability.

Skin prick testing involves the epicutaneous introduction of allergen extracts with a lancet, typically to the volar aspect of the forearm. Local wheal and flare responses if present are measured after 15 minutes and compared with positive (histamine) and negative (diluent controls). Serum-specific IgE testing involves detection of detection of IgE to whole allergen extract or to individual protein (component) within an allergen extract using automated fluoro-immunoassays.

Indications for food allergy testing:

1. The diagnosis is uncertain.
2. There is clinical suspicion of multiple food allergies.
3. Atopic eczema with immediate hypersensitivity symptoms: screening for food allergy is not recommended due to increased risks of false positive reactions.
4. Children of any age with immediate hypersensitivity reactions.
5. Persistent food allergy beyond the age of tolerance for egg, milk and wheat allergy (allergy to baked egg at 6-7 years) or adult onset allergy.
6. Although some guidelines indicate that persistent parental or carer suspicion of food allergy (particularly if there are difficult or perplexing symptoms) despite a lack of supporting history, or persistent anxiety about the diagnosis of food allergy, we caution about the risks of false positive responses and **DO NOT RECOMMEND THIS APPROACH.**

Indications for serum specific IgE blood food allergy tests in primary care.

Blood test should be requested according to local allergy clinics guidelines:

1. Confirm diagnosis of allergy following allergy focussed history where access to skin prick testing is limited
2. Patient unable to stop anti-histamines, tricyclic anti-depressants medication
3. Patients with a history of dermatographism, extensive eczema
4. Patient with a recent history of anaphylaxis

Other indication for serum IgE test in secondary care include diagnosis of primary nut or lipid transfer protein (LTP) allergy syndromes, assessing risk of moderate severe allergic reaction in patient with complex food allergy profiles, equivocal skin prick test results and to assess prognosis (resolution of egg, milk, wheat allergy). In addition, the IgE blood test can also be used to select the most appropriate immunotherapy allergen (grass pollen immunotherapy) and monitoring response to anti-IgE therapy (asthma, allergic rhinitis)

Food allergen blood tests are sensitive but not specific for allergic disorders. **Allergy tests cannot distinguish between sensitisation (positive IgE test) and allergic symptoms**. Sensitisation to food allergens is far commoner than allergic symptoms and test results must be interpreted in the context of the clinical history. **Indiscriminate use of large panels of food allergens or allergen screening is not recommended due to high false positive rate for diagnosis of allergic disease and potential to cause patient harm**. Some of the harmful consequences of false positive allergy test results include nutritional deficiencies and growth disorders as a result of unnecessary elimination of food, anxiety disorder and reduced quality of life. In addition, use of elimination diets in management of atopic dermatitis based on allergen screening is linked to induction of allergic disorders including anaphylaxis to previously tolerated control. Although elimination diets for non-IgE cow's milk allergy does not carry a risk of anaphylaxis on re-introduction of food.
Clinical history is used to select what allergens should be ordered for skin prick or blood tests.In the context of an appropriate history, larger skin wheals and higher specific blood IgE values are more likely to be associated with an allergic disorder. Results of skin prick test or serum specific IgE do not predict the severity of reaction.

Specialist referral (NICE guidelines)

Referral to an allergy specialist for further assessment and management is indicated for patients with a history of anaphylaxis, atypical clinical features (one or more severe delayed reactions), individuals at increased risks of anaphylaxis (food allergy and difficult to control asthma, or a severe reaction to a trace amount of food allergen). Children with a food allergy and asthma should be also be referred to an allergy specialist.

Arrange referral to a dietitian if a child or young person has faltering growth in combination with one or more of the following gastrointestinal symptoms: nausea, colicky abdominal pain, vomiting, diarrhoea. Dietitian input is also needed if there are concerns about nutritional status, or inappropriate dietary restriction or advice on specific food allergen avoidance or re-introduction of food is needed. Patient who are already on a restricted diet due to multiple food allergies, lifestyle, or religious reasons should be reviewed by a dietitian.

Sources of information and support for patients:

The Allergy UK factsheets on food allergy covers multiple different specific food allergies.

British Dietetic Association patient leaflets on food allergy and food intolerance.

The patient information leaflets food allergy and intolerance, Nut allergy and Oral Allergy syndrome available on the www.patient.info website.

References

National Institute for Health and Care Excellence (NICE) guideline *How should I assess a person with suspected food allergy* [NICE May 2023]

National Institute for Health and Care Excellence (NICE) guideline *Food allergy in under 19s: assessment and diagnosis* [NICE, 2018a]

The British Society for Allergy and Clinical Immunology (BSACI) guidelines *Guideline for the diagnosis and management of peanut and tree nut allergy* [Stiefel, 2017]

The British Society for Allergy and Clinical Immunology (BSACI) *guideline for the diagnosis and management of pollen food syndrome in the UK* [Skypala, 2022]

Skypala IJ et al. Diagnosis and management of allergic reactions in patients sensitised to non-specific lipid transfer proteins Allergy 2021 76 2433-2446

Cox AL et al. Clinical Relevance of cross reactivity in food. J Allergy Clin Immunol Pract 2021; 9:82-99