Food allergy in children in 2023

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Keywords

Food hypersensitivity ; allergens ; anaphylaxis ; allergic dysmotility disorder ; proctocolitis ; enterocolitis ; atopic dermatitis ; child.

Abstract

The aim of this article is to describe the most common clinical presentations of non-IgE-mediated, IgE-mediated and mixed forms of food allergy.

Four clinical groups of non-IgE-mediated food allergy can be distinguished: food protein-induced dysmotility, food protein-induced allergic proctocolitis (FPIAP), food protein-induced enterocolitis syndrome (FPIES) and food protein-induced enteropathy (FPE). In non-IgE mediated food allergy, cow's milk and soy are the 2 most common offenders, but other food allergens may be involved. Diagnosis is based on clinical criteria, elimination of the suspected food and, if necessary, oral food challenge.

IgE-mediated food allergy has a wide spectrum of clinical manifestations which can involve several organ systems. The most severe manifestation is anaphylaxis. Eight food allergens are responsible for 90% of allergic reactions in children: cow's milk, hen's egg, hazelnut, peanut, soy, wheat, fish and shellfish. Diagnosis is based on a thorough medical history, skin prick testing and serum IgE testing.

Food allergy can also occur as a mixed IgE and non-IgE mechanism, with atopic dermatitis and eosinophilic oesophagitis being the most common clinical manifestations.

Strict avoidance of the offending foods is the main goal in the management of food allergy. This is best achieved in multidisciplinary collaboration with dieticians experienced in food allergy.

Introduction

When talking about food allergy terms as “allergy”, “intolerance” and “sensitisation” are often inadequately and inappropriately used, causing confusion about which underlying mechanism or diagnosis is exactly meant. In 2001 a taskforce of the European Association of Allergy and Clinical Immunology (EAACI) introduced a revised nomenclature for allergy (1). They proposed the term “hypersensitivity” to be used as an umbrella term for all unexpected reactions (Figure 1). Since then, the term “allergy” is used to describe a hypersensitivity reaction initiated by immunologic mechanisms, which can be antibody- or cell-mediated. In the non-allergic hypersensitivity reactions, an immunologic mechanism cannot be proven. The antibodies typically involved in allergic reaction belong to the IgE-isotype, so we refer to this mechanism as an IgE-mediated allergy. The non-IgE-mediated allergic reactions are often T-cell mediated reactions.

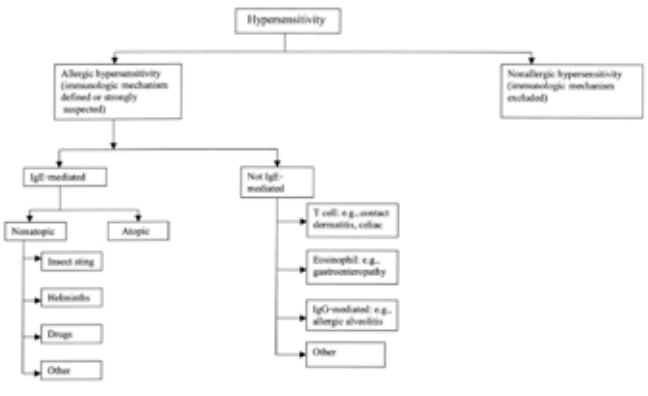


Figure 1: A revised nomenclature for allergy: An EAACI position statement from the EAACI nomenclature task force (Johansson SGO et al. Allergy. 2008;56(9):813-24).

This article describes the most common clinical presentations of food allergy in children; non-allergic non-immunologic food hypersensitivity reactions, such as lactose intolerance, are not included in this review.

In IgE-mediated food allergy symptoms arise shortly after ingestion of the culprit food, within minutes to two hours. A thorough anamnesis is the first key to a correct diagnosis of IgE-mediated allergy, i.e. reconstructing the food and contact history in detail, taking into account the time frame, detailed list of the ingredients, previous exposures and reactions, family history, history of eczema, asthma etc. An anamnestically suspected allergy can be confirmed by skin prick tests (with commercial extracts or fresh food allergens) or by measuring specific IgE-levels in a blood sample (CAP-tests). Spontaneous tolerance is rarely seen before two years of age. In 90% of the cases of IgE-mediated food allergy in children, the trigger can be found in the “big 8” group, i.e. cow’s milk, egg, nuts, peanuts, soy, wheat, fish and crustacea.

In non-IgE-mediated allergies, symptoms can develop over a period of one hour to several days, making it more difficult to establish a link between ingestion of the allergen and the onset of symptoms. The diagnosis is suspected after a thorough anamnesis and needs to be confirmed with an elimination diet and possible provocation; other diagnostic tests are not available for this type of food allergy. Cow’s milk and soy are the two most common culprits. In most cases non-IgE-mediated food allergy is infantile pathology; 90-95% of the children are tolerant by the age of one year (2).

Mixed forms of these two types of allergy may also occur, for example in eosinophilic oesophagitis and eczema. And in some patients, we see a switch from the non-IgE to the IgE-mediated form.

Non-IgE mediated food allergy

Non-IgE-mediated food allergies can be divided into 4 clinical groups: Food protein-induced allergic dysmotility disorders, food protein-induced allergic proctocolitis (FPIAP), food protein-induced enterocolitis syndrome (FPIES) and food protein enteropathy (FPE).

A child suffering from multiple digestive problems, such as gastro-oesophageal reflux disease (GERD), irritability, food refusal/aversion, abdominal discomfort, abnormal bowel frequency and consistency, sometimes in combination with persistent atopic dermatitis, is a frequent reason for parents to seek help from a paediatrician. These symptoms heavily impact the families' quality of life. Non-IgE-mediated allergy is often the cause, with cow's milk protein being the most common trigger. The diagnosis of non-IgE-mediated food allergy is challenging, because of the variable onset of symptoms after ingestion, intervals ranging from 2 hours to several days. The spectrum of symptoms of non-IgE-mediated allergy is also broad, ranging in severity from GERD or mild rectal bleeding to severe vomiting and collapse or failure to thrive (3).

A. Food protein-induced allergic dysmotility disorders

All infants with multiple digestive/abdominal symptoms in the first months of life such as gastro-oesophageal reflux, vomiting, diarrhoea and severe constipation, should be suspected of having cow's milk allergy. Food proteins are detectable in breast milk for many hours or days after the mother's meal, so breastfed infants are also prone to food allergy. These children often cry for several hours a day, leaving their parents desperate for help. They are categorised as "food protein-induced allergic dysmotility disorders" (4).

The 2009 joint ESPGHAN-North American Society for Paediatric Gastroenterology Hepatology and Nutrition guidelines on GERD already recognised the possible role of non-IgE mediated cow's milk allergy (CMA), and the 2018 updated guidelines this have further increased its importance in the treatment pathway by considering a cow's milk elimination diet prior to the use of medications in infants <1 year of age (5,6). In 2009, Cavataio et al. suggested a role for cow's milk allergy in up to 40% of infants with GERD, but dysmotility disorders can also occur with other food allergens such as soy, egg and wheat (4,7).

A strict cow's milk elimination diet for at least 2 weeks is the first-choice treatment, ideally implemented with the support of an allergy dietitian. If symptoms persist, other allergens such as egg, soy and wheat have to be eliminated from the diet of the infant and, if breastfeeding, the mother. Allergens have to be eliminated sequentially, and non-responsible allergens have to be reintroduced (8).

Most children with food protein-induced allergic dysmotility disorders develop tolerance around the age of one year. Reintroduction of the allergen is best done gradually. The milk scale is an easy and effective recent tool for safe home reintroduction in children with non-IgE-mediated cow's milk allergy. The Flemish milk ladder provides several recognisable products, making it easy for the parents to reintroduce cow's milk into their child's diet step by step, giving larger amounts and less heated milk the higher up the ladder (Figure 2a) (9). The French scale works on the same principle and was inspired by the Flemish scale (Figure 2b).

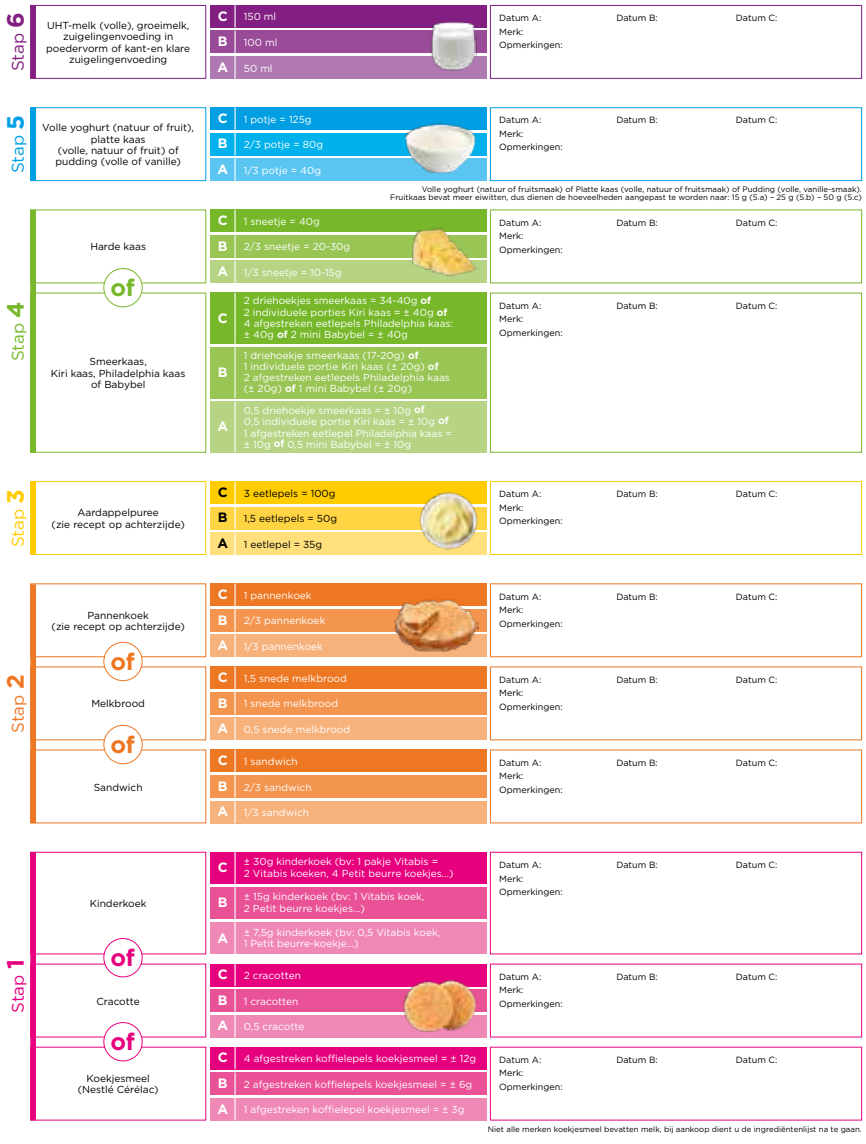
B. Food protein-induced allergic proctocolitis (FPIAP)

Food protein-induced allergic proctocolitis (FPIAP) is an eosinophilic colitis that causes blood-streaked and mucous stools in otherwise well-appearing and well-growing infants. Symptoms typically begin in the first weeks of life. Onset is rarely after six months of age, with a later onset in breastfed infants compared with formula-fed children. Up to 60% of cases of FPIAP develop during exclusive breastfeeding. Cow's milk is the most frequently involved allergen, but soy, egg and wheat can also trigger FPIAP. FPIAP is estimated to account for up to 60% of healthy infants with rectal bleeding. Sometimes increased gas and bowel movements, colic and intermittent emesis can be present (2). A strict cow's milk elimination diet often results in the disappearance of visible blood in the stool within a few days, and a minimum trial period of 2 weeks is recommended. Better results are seen if the mother receives dietary advice from a dietician. As in children with food protein-induced allergic dysmotility disorder, tolerance can be expected around 12 months of age, and the milk ladder can be used for gradual introduction for most of the children. Tolerance in FPIAP is often seen in some children even sooner, between 6 and 8 months.

C. Food protein-induced enterocolitis syndrome (FPIES)

Food protein-induced enterocolitis syndrome (FPIES) is a non-IgE-mediated food allergy typically diagnosed in infancy and childhood. It was first described in the 1970s. Diagnosis is based on clinical

Figure 2a: 2a: The Flemish milk ladder ; **2b**: The French échelle du lait.



criteria and there are no diagnostic laboratory tests for this type of allergy. Many cases of FPIES go unrecognized and therefore FPIES is still under-reported. However, in the last several years more and more epidemiologic studies were published, estimating incidence rates of 0.015% to 0.7% worldwide (10,11). The incidence of milk FPIES is close to that of IgE-mediated cow's milk allergy (12). FPIES typically presents within the first year of life, although the age of onset varies depending on the triggering food and the timing of solid food introduction. Often cow's milk or soy is the first culprit, causing FPIES within 1 to 4 weeks after birth, in most cases before the age of six months. Cow's milk is the most common trigger of FPIES in infants, followed by soy in countries where infant soy formula is also used. Approximately 60% of the infants with cow's milk or soy FPIES will also develop solid food FPIES, this type of FPIES develops later because solid foods are usually not introduced before six months of age. Multiple solid food allergens can cause FPIES and the trigger foods vary geographically. In our regions the most frequent culprits are cow's milk, followed by egg and fish.

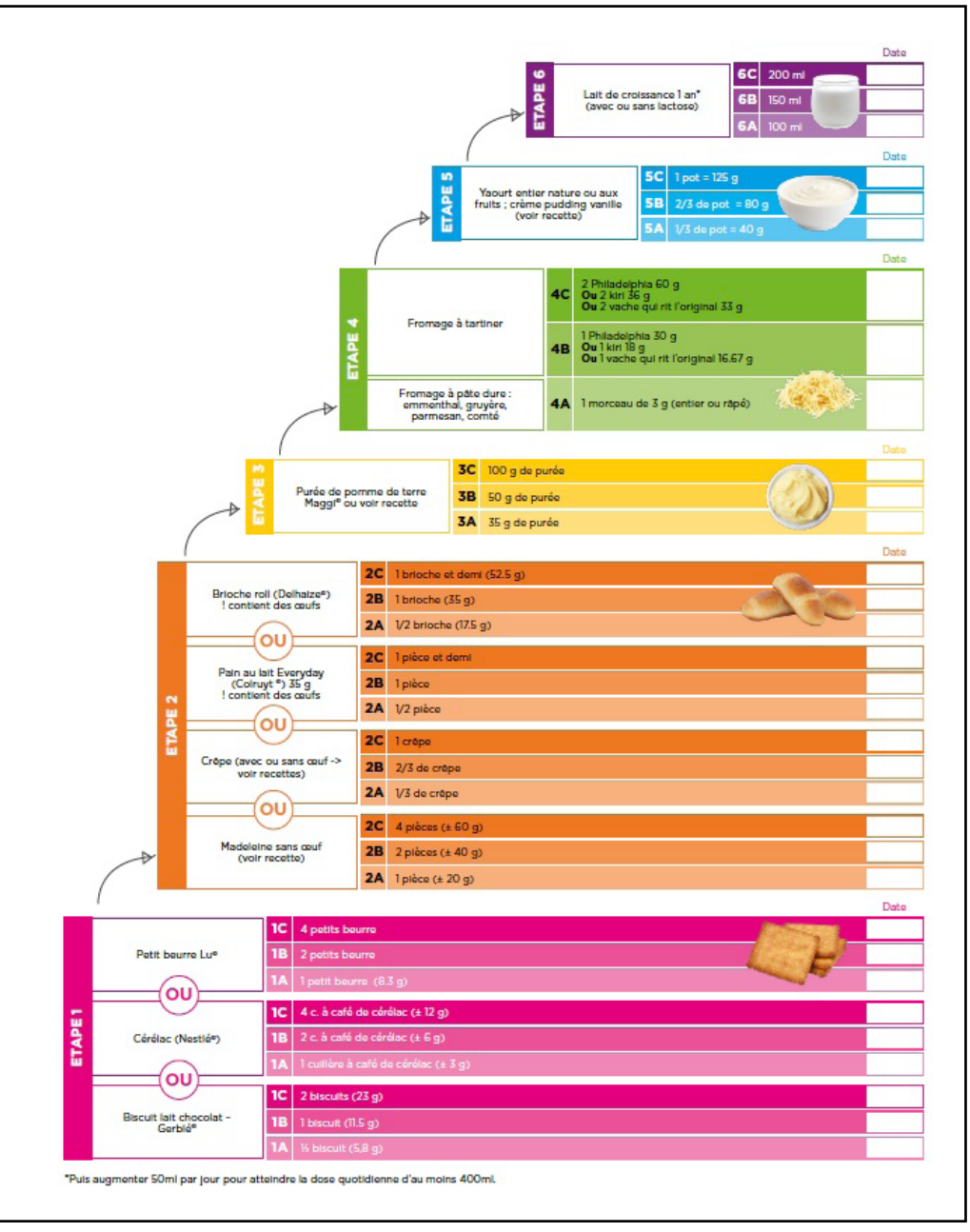
Worldwide the most commonly reported solid triggers are oats and rice, but also egg, seafood, wheat, tree nuts, peanuts, vegetables (sweet potato, carrot) and fruits (avocado, banana, apple) and several others have been described as triggers (10). One third of the patients have problems with different food allergens. A recent large French multicentre study examined 179 cases of FPIES and showed that cow's milk (60,3%), hen's egg (16,2%) and fish (11,7%) were the most frequent triggers (11). Patients with solid food FPIES tend to have more severe reactions and a longer time to tolerance (10).

FPIES is a clinical diagnosis, develop in two forms: acute and chronic FPIES, the acute form being the most common. Chronic FPIES is more difficult to diagnose and is often associated with cow's milk and soy. Transition from one form to the other is possible. The international consensus guidelines for the diagnosis of FPIES, published in 2017 by Nowak-Wegrzyn et al., were updated in 2022. FPIES is diagnosed when one major criterion (vomiting 1 to 4 hours after ingestion of the suspected food trigger and absence of skin or respiratory symptoms) and at least 3 minor criteria are present as shown in Table 1.

Acute reactions can be classified as mild-to-moderate and severe, depending on the severity of dehydration and lethargy and the therapeutic interventions needed. In a mild to moderate reaction sometimes leucocytosis with a neutrophilic predominance, thrombocytosis and faecal leukocytes or eosinophils can be found. Children with severe acute episodes can develop metabolic acidosis and methaemoglobinaemia. The most important diagnostic criterion for chronic FPIES is resolution of the symptoms within days of eliminating the trigger food and acute relapse on reintroduction. Laboratory findings may include anaemia and hypoalbuminemia (10).

If the clinical history is not clear enough sometimes a supervised oral food challenge (OFC) is needed to diagnose FPIES, this is the gold standard for diagnosis (13). The OFC is considered diagnostic when the major criterion and 2 or more minor criteria are present (Table 2). OFC in FPIES patients is also used to determine whether the child has developed tolerance to a specific food and is best performed 12 to 18 months after the last documented reaction (10). Lemoine et a.l found that performing an OFC earlier increased the risk of failing the test (11). The age of resolution is strongly influenced by food, country, and study design, but overall most patients develop tolerance by school age.

Serum sIgE and/or skin prick testing should be performed prior to OFC as a small number of FPIES patients may develop IgE-mediated allergic reactions (10).



D. Food protein enteropathy (FPE)

Food protein enteropathy is a less frequent but severe form of non-IgE mediated food allergy. Patients generally present before the age of 9 months, with chronic symptoms of diarrhoea, anorexia, vomiting, abdominal distension and malabsorption. 50% progress to failure to thrive, sometimes with hypoalbuminemia. Cow's milk is the most frequent causative agent, but soy, cereals and hen's egg can also trigger this type of allergy. An atopic predisposition is found in 50 % of patients. Endoscopy shows villous atrophy with lymphocyte infiltration, mimicking celiac disease (14).

Mixed IgE-Non IgE mediated food allergy

Food allergy can also present as a mixed IgE and non-IgE mechanism with atopic dermatitis (AD) and eosinophilic oesophagitis being the major clinical presentations. Eosinophilic oesophagitis will not be discussed in this review.

Table 1: criteria for the diagnosis of FPIES (adapted from (22).

Diagnosis requires meeting the major criterion and more than 3 minor criteria	
Major criterion	Vomiting 1 to 4 hours after ingestion of the suspected food trigger and absence of skin or respiratory symptoms
Minor criteria	More than 2 repetitive episodes of vomiting after ingestion of a suspected food trigger
	Repetitive vomiting 1 tot 4 hours after eating a different food
	Diarrhoea within 24 hours (typically within 5-10 hours)
	Hypotension
	Hypothermia
	Extreme lethargy with any kind of suspected reaction
	Any suspected reaction requiring emergency care
	Any suspected reaction requiring intravenous fluid support

Table 2: criteria for diagnosis of FPIES by oral food challenge (adapted from (22).

Diagnosis requires meeting the major criterion and more than 2minor criteria	
Major criterion	Vomiting 1 to 4 hours after ingestion of the suspected food trigger and absence of skin or respiratory symptoms
Minor criteria	Lethargy
	Pallor
	Diarrhoea within 5 to 10 hours
	Hypotension
	Hypothermia
	Increased neutrophil count

In the allergic march of IgE-mediated allergy, AD is the first presenting atopic disease. Food sensitisation is much higher in the first 3 months of life in these children with AD compared to controls. Even in non-IgE-mediated allergy, AD is present early, often within the first three months of life, and often in combination with gastrointestinal symptoms (15). In children with moderate to severe AD, food allergy is a frequent cause of eczema flares. However, prior to allergy testing, eczema exacerbations need to be treated with topical steroids and daily moisturising creams to make the skin less vulnerable (16). In infants from atopic families with moderate-to-severe eczema that frequently relapses and requires corticotherapy, despite correct daily hydration and avoidance of classic triggers (perfumes etc.), food allergy has to be excluded. The most frequent food triggers in infancy are cow's milk, soy, egg and peanut (17).

IgE-mediated allergy

IgE-mediated food allergy has a wide spectrum of clinical manifestations, presenting as cutaneous, gastrointestinal, respiratory, cardiovascular or neurological symptoms, in an isolated or concomitant manner, in acute, recurrent and/or chronic episodes, ranging from mild local to fatal or near-fatal reactions. Classic symptoms include AD, erythema, urticaria, angio-oedema, failure to thrive, food refusal, oral allergy syndrome, rhinoconjunctivitis, asthma and anaphylaxis, with anaphylaxis being the most severe manifestation. The severity of the reactions depends on the type and amount of allergen ingested, the preparation of the food and whether or not cofactors are involved (e.g. exercise, stress, infection, non-steroidal anti-inflammatory drugs and alcohol), which can aggravate the reaction.

In 2021, the European Academy of Allergy and Clinical Immunology Anaphylaxis Multidisciplinary Task Force updated the 2014 guideline. It suggested the use of clinical criteria to identify anaphylaxis (Figure 3), supplemented by serum tryptase measurement 30 minutes to 2 hours after the onset of symptom if blood sampling does not delay the treatment (18).

Diagnosis of IgE-mediated food allergy begins with a thorough anamnesis, mapping all acute reactions, chronic symptoms such as AD, duration of breastfeeding, age of introduction of formula and solid foods, family history etc. Skin prick testing (SPT) with commercial extracts or fresh foods and measurement of specific IgE in the blood (Cap-testing) can confirm the diagnosis. The advantages of SPTs over in vitro measurement of specific IgE antibodies are the short duration of the test (15-20 minutes), the minimally invasive nature and the low cost. The measurement of specific IgE's in serum is an important complementary tool, especially in children who cannot undergo SPTs because of severe eczema, dermographism, urticaria or the use of antihistamines (19). Often a combination of the two tests is necessary for a complete diagnostic work-up.

Component resolved diagnostics (CRD) uses purified native or recombinant allergens to detect the sIgE antibody response to the individual allergenic molecules. CRD can discriminate between genuine sensitisation and sensitisation due to cross-reactivity. It can be useful in estimating the clinical risk associated with a sensitisation pattern and in predicting the outcome of an oral food challenge (OFC) (20). The OFC remains the gold standard for diagnosis but is a time-consuming test and must be performed under controlled conditions. In 2012 the PRACTALL guidelines for provocation were written, a collaboration between the European Academy of Allergy and Clinical Immunology (EAACI) and the American Academy of Asthma, Allergy & Immunology (AAAAI) (21). It is a useful tool to organize and compare provocation test in different centres.

In Europe, 8 food allergens are responsible for 90% of the food allergic reactions in children: cow's milk, hen's egg, hazelnut, peanut, soy, wheat, fish and shellfish. But also, less common allergens such as cashew nuts, pine nuts, lentils and sesame seed are increasingly being identified as triggers of severe IgE-mediated food allergic reactions in children.

In the management of FA, strict avoidance of the trigger foods is the main goal. Referral to an allergy dietician is recommended to learn how to read food allergen labelling, prevent deficiencies and provide a varied and palatable diet for the child and his parents. As accidental ingestion

Figure 3: Clinical criteria for diagnosing anaphylaxis.

Anaphylaxis is highly likely when any one of the following three criteria is fulfilled:
1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue or both (e.g., generalized hives, pruritus or flushing, swollen lips–tongue–uvula)
AND AT LEAST ONE OF THE FOLLOWING
a. Respiratory compromise (e.g., dyspnoea, wheeze–bronchospasm, stridor, reduced PEF and hypoxemia)
b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to
several hours):
a. Involvement of the skin–mucosal tissue (e.g., generalized hives, itch-flush, swollen lips–tongue–uvula
b. Respiratory compromise (e.g., dyspnoea, wheeze–bronchospasm, stridor, reduced PEF, hypoxemia)
c. Reduced BP or associated symptoms (e.g., hypotonia, [collapse], syncope, incontinence)
d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
a. Infants and children: low systolic BP (age specific) or >30% decrease in systolic BP*
b. Adults: systolic BP of <90 mmHg or >30% decrease from that person's baseline PEF, peak expiratory flow; BP, blood pressure.
*Low systolic blood pressure for children is defined as <70 mmHg from 1 month to 1 year, less than (70 mmHg + [2 × age]) from 1 to 10 years and <90 mmHg from 11 to 17 years.

can always occur, every food allergic patient needs a detailed action plan must attend a training session to learn how to recognise anaphylaxis symptoms and how to use the epinephrine autoinjector (18).

Conclusion

IgE and non-IgE mediated food allergies are a growing medical problem. A detailed anamnesis and clinical examination, supplemented with skin prick tests and measurement of sIgE's, can lead to the diagnosis of IgE-mediated allergies, but provocation tests remain the gold standard when in doubt. Elimination and reintroduction diets are the only way to confirm clinically suspected non-IgE mediated allergy. The milk ladder can be used to reintroduce milk in mild to moderate non-IgE-mediated cow's milk allergy. Oral immunotherapy, gradually increasing the daily amount of protein ingested, is a promising treatment for IgE-mediated food allergy.

Conflicts of interest

The author has no conflicts of interest to declare with regard to the topic discussed in this manuscript.

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