



SPECIAL ARTICLE

Food allergies in paediatrics: Current concepts[☆]



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oesophagitis

Abstract The concept of allergic reaction currently includes all those where an immunological reaction depends on a reaction mediated by IgE, as well as those that involve other immune mechanisms, such as T-cell regulators. There are many different clinical situations, like the classic immediate reactions (IgE mediated) such as urticaria, angioedema, immediate vomiting, abdominal pain, both upper respiratory (aphonia or rhinitis) and lower (wheezing or dyspnoea) symptom, and cardiovascular symptoms. The reactions that involve more than one organ, such as anaphylaxis, which could be an anaphylactic shock if there is cardiovascular involvement. The clinical signs and symptoms produced by non-IgE mediated reactions are usually more insidious in how they start, such as vomiting hours after the ingestion of food in enterocolitis, diarrhoea after days or weeks from starting food, dermatitis sometime after starting food. In these cases it is more difficult to associate these clinical symptoms directly with food.

In this article, we attempt to clarify some concepts such as sensitisation/allergy, allergen/allergenic source, or the relationship of different clinical situations with food allergy, in order to help the paediatrician on the one hand, to prescribe strict diets in case of a suspicion based on the cause/effect relationship with the food, and on the other hand not to introduce unnecessary diets that very often have to last an excessively long time, and could lead to nutritional deficiencies in the children.

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PALABRAS CLAVE

Alergia a alimento;
Sensibilización a
alimento;
Fuente alérgica;
Alérgeno alimentario;

Alergia alimentaria en la edad pediátrica, conceptos actuales

Resumen En la actualidad se engloba en el concepto de reacción alérgica tanto aquellas cuyo mecanismo inmunológico depende de una reacción mediada por IgE, como las que implican a otros mecanismos inmunitarios como las células T reguladoras. Existen situaciones clínicas muy diferenciadas, como son las clásicas de las reacciones inmediatas (IgE mediadas), como

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Reactividad cruzada;
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alérgica;
Dermatitis atópica;
Esofagitis eosinofílica

urticaria, angioedema, vómitos inmediatos, dolor abdominal, síntomas respiratorios tanto de vías altas (afonía o rinitis), como de vías bajas (sibilancias o disnea), síntomas cardiovasculares y la reacción que implica a más de un órgano, como la anafilaxia que puede ser choque anafiláctico si hay afectación cardiovascular; la clínica producida por las reacciones no mediadas por IgE suele ser más insidiosa en su comienzo, así vómitos pasadas 2 h de la ingesta del alimento en las enterocolitis, diarreas al cabo de días o semanas de iniciar el alimento, dermatitis al cabo de un tiempo de iniciar el alimento; en estos casos es más difícil relacionar dicha clínica directamente con el alimento.

En este artículo pretendemos clarificar algunos conceptos como sensibilización/alergia, alérgeno/fuente alérgica o la relación de diversas situaciones clínicas con la alergia a alimento para ayudar así al pediatra, por una parte, a efectuar dietas estrictas en caso de sospecha fundada de relación causa efecto con el alimento y, por otra, a no inducir dietas innecesarias que, muchas veces, se prolongan durante un tiempo excesivo y pueden provocar importantes deficiencias nutricionales en los niños.

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Definitions

Sensitisation: presence of elevated levels of IgE antibodies to one or more foods demonstrated by in vivo methods (usually a skin prick test) or in vitro methods (determination of circulating specific IgE).

Allergy: adverse effect detrimental to health compatible with an allergic reaction to a food resulting from a specific immune response that resolves when the food is removed from the diet and can be reproduced when the food is reintroduced.

Allergen source: food that causes the reaction.

Food allergen: specific component of the food (usually proteins, but can also be haptens) that is recognised by the immune system and that causes the characteristic clinical manifestations through an immunological mechanism.

Cross-reactivity: phenomenon that occurs when an antibody (Ab) recognises not only the original allergen, but also similar allergens. Cross-reactivity is common for foods in the same family, for example different nuts or types of shellfish.

At present, a large proportion of children have clinical manifestations of food allergy, which is more marked in developed countries. Its prevalence peaks at 6–8% at age 1 year, declining progressively until the end of childhood, when the prevalence plateaus at around 3–4%, the same percentage described in the adult population.^{1,2} The prevalence of primary food allergy seems to be stable, but the prevalence of cross-reactivity reactions is on the rise.³

Up to one third of children with food allergy have severe reactions to more than one food allergen.⁴ During infancy, asymptomatic sensitisation to some foods, especially milk and egg, is common, so the rate of sensitisation to foods in the first two years of life (6%)⁵ drops to 2.2% for cow's milk allergy confirmed by characteristic clinical manifestations, a positive aetiological investigation (skin prick test and measurement of specific IgE) and positive challenge test.⁶ Egg is the food most frequently involved in allergic reactions to food, but in early childhood there are children sensitised to eggs that have never consumed them, many of whom tolerate egg at first ingestion.⁷

Food allergy is a significant problem.⁸ Food allergy in early childhood, especially egg allergy, is frequently associated with future development of respiratory allergy, asthma and/or allergic rhinitis in the first or second decade of life.

We must clearly understand two specific concepts: allergy to one or more foods, and food sensitisation. Sensitisation refers to the presence of IgE antibodies to a food detected by in vitro (specific IgE measurement) and in vivo (usually skin prick test) methods in the absence of clinical manifestations, whereas allergy refers to clinical conditions compatible with an allergic process in which immune system involvement can be evinced or a challenge test clearly demonstrates the association between the involved food or foods and the presenting clinical manifestations (see *Definitions* box).

The ratio of sensitisation to allergy varies with age, and it is much higher in infants aged less than one year, as IgE levels consistent with sensitisation are found in up to 20%, but only 3% have symptoms of allergic reactions that are later confirmed by food challenge tests.⁹

The foods involved in allergic reactions also vary with age. Thus, in the first two years of life, cow's milk is food that produces allergic reactions most frequently, followed by egg; in early childhood, other foods become prevalent, such as wheat, soy, peanuts and other nuts, fish and shellfish; and by the end of the first decade and in the second decade of life, vegetables gain prominence as allergens. The foods involved in allergic reactions also vary depending on regional dietary patterns.

In Spain, where the Mediterranean diet is widespread, legumes are a food group that is frequently involved in food allergy, compared to other countries with different dietary patterns. We must keep in mind that the peanut is a legume that is usually consumed dried and belongs to the family of the Fabaceae; in other regions, such as America, peanut allergy is a serious public health problem, but due to the dietary habits in Spain the frequency of allergic reactions to peanuts is not as significant. Our group was first in identifying the importance of sensitisation to legumes in disease processes with an allergic component, such as eosinophilic oesophagitis.¹⁰

When we classify allergic diseases, we must distinguish between two clearly differentiated situations: IgE-mediated allergy, which is the cause of most immediate reactions, and non-IgE-mediated allergy, which involves other immunological mechanisms.

Allergic reactions can cause a broad range of symptoms involving different organs:

- Skin: erythema, pruritus, urticaria, morbilliform rash, angioedema.
- Eyes: pruritus, conjunctival erythema, tearing, periorbital oedema.
- Upper respiratory tract: nasal congestion, pruritus, rhinorrhoea, sneezing, laryngeal oedema, unproductive cough.
- Lower respiratory tract: cough, tightness in the chest, dyspnoea, wheezing, intercostal retractions, use of accessory muscles.
- Gastrointestinal tract: labial, lingual or palatine angioedema, oral pruritus, nausea, colicky abdominal pain, reflux, vomiting, diarrhoea.
- Cardiovascular system: tachycardia (occasionally bradycardia in episodes of anaphylaxis), hypotension, loss of consciousness.
- Other: uterine contractions.

Characteristics of a food allergy reaction: *anaphylaxis* (involvement of more than one organ or one or more of the symptoms listed above, with a rapid onset and fast progression, and potentially lethal) usually develops within minutes or a few hours following ingestion of the food, especially if the symptoms have developed more than once in the past following its consumption.

Infants presenting with moderate to severe atopic dermatitis should undergo testing for the potential involvement of a food, even if they are exclusively breastfed. Food allergy testing is also warranted in children presenting with eosinophilic oesophagitis, enterocolitis or allergic proctocolitis.

Allergic reactions to food are classified into immediate and delayed. Immediate reactions occur minutes to a few hours (usually no more than two) following ingestion and are characteristic of IgE-mediated allergy. Delayed reactions occur a few hours to a few days after ingestion, and typically involve cell-mediated immune responses.

In all these presentations, a clinical history taking is very helpful in identifying the food allergen, especially in IgE-mediated reactions, although at times it is insufficient and a food challenge test is required to confirm the diagnosis. In IgE-mediated processes, the presence of IgE antibodies to the food suspected on the basis of the history can be assessed by means of different methods: skin prick test, determination of total and specific serum IgE, patch test, or a combination thereof.

Delayed reactions frequently involve the gastrointestinal tract, have a more insidious onset and do not resolve immediately when the food is eliminated from the diet. They are classified as mixed-IgE and non-IgE reactions, and one example is *eosinophilic oesophagitis*.

Another type of delayed reaction is what is known as *food protein induced enterocolitis*; these reactions usually do not result from an IgE-mediated mechanism and the clinical

manifestations depend on the part of the bowel that is involved. Thus, if the duodenum is involved, the reaction starts between two and four hours after ingestion of the food and is characterised by uncontrollable vomiting that does not subside until all the noxious protein has been eliminated from that intestinal region, followed by a state of weakness and lethargy, often in the absence of hypotension, possibly followed by diarrhoea with onset a few hours later which, if untreated, can lead to significant dehydration. The process resolves favourably and the symptoms only recur if the culprit protein is ingested again. Usually, these children eventually develop tolerance to these proteins after a relatively long period (years) of elimination from the diet.

The reactions that involve the end of the large intestine and the distal colon and rectum have a better prognosis. They are known as *allergic proctocolitis* and affect young infants in good general health that present with rectal bleeding that is usually mild (bright red blood and mucus in stools), frequently produced by cow's milk protein, and that resolves in a few days by the elimination of cow's milk from the diet. The disease usually resolves before age 1 year, and further diagnostic tests are not needed if the child has the expected outcome. Cow's milk is reintroduced gradually before age 1 year, and if the symptoms do not recur 15–20 days after its reintroduction, the child can start consuming the usual diet for his or her age. Allergic proctocolitis may be caused by any dietary protein, although it is most frequently caused by cow's milk proteins, even in exclusively breastfed infants.

Enteropathies induced by food proteins pose a greater diagnostic challenge. They have a more insidious onset, cause a chronic diarrhoea of varying intensity, and in most cases various restrictive diets are tried out without success. These reactions may be caused by any type of food protein and usually affect older infants and toddlers aged 6 months to 2 years. They can cause weight loss and faltering, and symptoms may be similar to those of coeliac disease, although manifesting in younger children. They are managed with dietary measures through the strict elimination of the culprit protein from the diet for a period of varying duration, followed by gradual reintroduction after several years on the diet (usually two or three). The diagnosis occasionally requires more invasive tests, such as intestinal biopsy, which evinces eosinophilic infiltration.

Atopic dermatitis in infants

When infants present with moderate to severe atopic dermatitis, food allergy should be considered as one of the possible aetiologies, and the infant should undergo allergy testing. The most frequent allergic causes of atopic dermatitis in this age group are egg allergy or cow's milk protein allergy, so these are the foods that should be investigated first.

Confirming the diagnosis of food allergy

If an IgE-mediated reaction is suspected, a detailed history must be taken to determine whether there has been more than one exposure to the suspected food followed by the same clinical manifestations. From most to least

cost-efficient, a skin prick test for the suspect foods should be performed first, followed by measurement of specific IgE antibodies to the food or components of the food, and in most cases a food challenge test under observation, which, at present, is the gold standard for diagnosis. Forgoing the food challenge test is acceptable when the clinical manifestations are highly suggestive, the skin prick test is positive to one food and no others, and the levels of specific IgE are significantly high for that food, but not for any others. Thus, for instance, there is evidence that in infants with a history suggestive of cow's milk protein allergy, a positive skin prick test to milk or any of its components and levels of specific IgE to milk or one of its components greater than 2.5 kIU/L have a positive predictive value of 90% for a positive challenge test¹¹ and can be considered diagnostic without performing the challenge test. In cases of mixed-IgE- and non-IgE-mediated reactions, making the diagnosis usually requires performing the food challenge test following elimination of the food from the diet for a period of variable length.

Management of children sensitised to several foods

If possible, a single food should be eliminated from the diet for a few days. Usually one week to 15 days suffice to assess improvement in cases with clinical manifestations suggestive of an IgE-mediated reaction. If the improvement is clear, the child will continue on a diet excluding the involved food, but if the improvement is not clear or there are any doubts, a food challenge test should be performed under close observation to confirm the diagnosis. If the symptoms do not recur with the challenge test, the food should be reintroduced in the diet, and a new cycle should be started with the elimination of another of the foods that the child is sensitised to. It is important to avoid putting children on unnecessary diets that, if maintained for a long time, may have an impact on growth and development and cause nutrient deficiencies (See *Key points* box).

Is it appropriate to perform skin prick tests for foods prior to their introduction in infants with food allergy?

Based on the available evidence, performing skin prick tests prior to the introduction of new foods in the diet of allergic children offers no benefits, given the high prevalence of sensitisation to foods in allergic individuals; such a practise could lead to placing children on restrictive diets that are absolutely unnecessary. As noted above, performance of skin prick tests for cow's milk and egg is only indicated in infants with moderate to severe atopic dermatitis that do not respond favourably to appropriate topical treatment, and if these are positive, a complete allergy evaluation is performed to assess the potential role of this sensitisation in the dermatitis process. However, we do recommend that new foods be introduced one at a time in atopic children, so that the food involved in a reaction, should one occur, can be correctly identified.

When should foods be introduced in infants with food allergy?

There is currently no evidence that delaying the introduction of potentially allergenic foods reduces the incidence of allergy to those foods in atopic infants. Solid foods, such as fruits, cereals and vegetables, should be introduced between 4 and 6 months of age, and preferably in combination with breastfeeding; other foods, such as eggs or fish, should be introduced according to the usual schedule.

Management of children with positive IgE results for previously tolerated foods

The determination of specific IgE antibodies to one or more foods is frequently ordered in children along with other laboratory tests, and sometimes the specific IgE test is positive for a food the child had been eating to that date. When this happens, we should be cautious before eliminating the food from the diet, taking a detailed history of the clinical manifestations of the child and assessing whether there is a causal relationship with that specific food. When in doubt, the food can be eliminated for a few days and the clinical manifestations reassessed, and if there is not evidence of a cause-effect relationship, the food should be reintroduced in the child's diet to avoid unnecessary dietary restrictions. We must keep in mind that IgE is the mechanism involved in immediate reactions, and improvement should be observed after a short period of elimination if the food is the cause of the disease.

If a child is allergic to a food, is the child allergic to all foods in the same group?

This depends on the type of food. Thus, children that are allergic to cow's milk are usually also allergic to the milk of other mammals, such as goat or sheep, because these milks have many proteins in common, but may tolerate other milks, such as camel's or donkey's milk; it is also unnecessary to restrict beef from these children's diet, as most of them can tolerate beef well as usually cooked. Children allergic to chicken eggs are usually allergic to the eggs of other avian species, although the literature includes reports of children that could tolerate eggs of other birds. Fish and shellfish belong to completely different families and thus there is no reason why children allergic to one should be allergic to the other; those allergic to fish frequently react to many different species because parvalbumin is the protein most commonly involved in fish allergy and most fish contain it, although rare cases of allergy to a single fish have also been reported. The shellfish group includes highly differentiated families: molluscs, cephalopods and crustaceans do not share many of their proteins, and therefore allergies to these shellfish must be tested separately. When it comes to vegetables and nuts, cross-reactivity between different families is found quite frequently. A high proportion of the cross-reactivity found in foods from the plant kingdom is due to highly conserved proteins, such as profilin or lipid transfer protein (LTP), two of the best-known at present, and while profilin tends to cause mild reactions

(oral pruritus after eating various fruits, for instance), LTP is a thermostable protein resistant to digestion that causes more severe reactions. Reactions to LTP are frequent in Mediterranean countries (see *Definitions* box).

Conflict of interest

The authors have no conflict of interests to declare.

Key points

- Sensitisation to a food is not the same as food allergy.
- In children, a food should not be removed from the diet based solely on the detection of elevated levels of IgE antibodies to that food, but only if these levels are associated with clinical manifestations consistent with allergy.
- Dietary restrictions for one or more foods should be implemented only after the diagnosis of food allergy has been confirmed.

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