

The diagnosis of food allergy in children

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Purpose of review

To give an update about the optimal diagnostic work-up for children with suspected food allergy.

Recent findings

Food allergy has become a very severe health problem not only for many children and parents, but also for the entire medical and paramedical community. The financial and social costs related to these conditions are increasing, but, contemporarily, basic and clinical research are deeply involved in the search of possible solutions to facilitate the management of these patients.

Summary

Food allergy is defined as an abnormal immunological reaction to food proteins, which causes an adverse clinical reaction. Over 90% of food allergies in childhood are caused by eight foods: cow's milk, hen's egg, soy, peanuts, tree nuts, wheat, fish and shellfish. The evaluation of a child with suspected food allergy includes detailed medical history, physical examination, screening tests and response to elimination diet and to oral food challenge. None of the screening tests, alone or in combination, can definitely diagnose or exclude it. The main principle of food allergy management is avoidance of the offending antigen. An incorrect diagnosis is likely to result in unnecessary dietary restrictions, which, if prolonged, may adversely affect the child's nutritional status and growth.

Keywords

atopy patch testing, food-specific serum immunoglobulin E levels, gastrointestinal symptoms, oral food challenge, skin prick testing

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Introduction

Food allergy, defined as an adverse immune response to food allergens, is among the most frequent allergic disorders and has been recognized as a major paediatric health problem in western countries due to the severity of the reactions and the dramatic increase over the past decades. At present, food anaphylaxis is the leading single cause of anaphylactic reactions treated in the European emergency departments [1•,2,3•,4,5]. Food allergy is more common in paediatric age and it has also a better prognosis in these patients [1•,6]. Major food allergens, in general, are water-soluble glycoproteins ranging from 10 to 70 kDa that are abundant in the food and possess multiple immunoglobulin E (IgE)-binding epitopes [1•,2]. Interestingly, only a limited number of the numerous proteins in a given allergenic food act as allergens and it remains to be elucidated why, even in atopic individuals predisposed to mounting allergic responses, only a small proportion of food proteins are associated with allergic disease. Although any food can provoke a reaction, relatively few foods are responsible

for the vast majority of significant food-induced allergic reactions in children: cow's milk, hen's egg, soy, wheat, fish, peanuts and shellfish [2,6]. A recent meta-analysis estimates self-reported prevalence ranging from 3 to 35% for any foods, with great heterogeneity among different studies [1•,3•]. Considering the foods involved, the prevalence of food allergy varies from 1.2 to 17% for milk, 0.7 to 7% for hen's egg, 0 to 2% for peanuts and fish, and 0 to 10% for shellfish [3•]. There is an increase in prevalence of new food allergens such as sesame and kiwi [7]. It has been reported that an increase of food allergy in children who were recipients of liver transplantation was mainly related to immunocompetence of the transplanted organ, rather than the pharmacological therapy used [8].

Clinical presentation

Food allergy may cause a wide variety of clinical manifestations depending on the mechanism involved in the reaction (acute or delayed, IgE-mediated or non-IgE-mediated or mixed) [2]. In children, the gastrointestinal

Table 1 Food-induced allergic disorders in children

	IgE-mediated/acute onset	Non-IgE-mediated/delayed onset	IgE or non-IgE-mediated/delayed onset
Gastrointestinal tract	Oral allergy syndrome, gastrointestinal anaphylaxis	Proctitis, proctocolitis, enterocolitis, enteropathy, constipation, gastroesophageal reflux disease	Eosinophilic gastroenteropathies
Respiratory tract	Rhinitis, conjunctivitis, asthma	Chronic pulmonary disease (Heiner syndrome)	Asthma
Skin	Urticaria, angioedema	–	Atopic dermatitis
Systemic	Anaphylaxis	Food-dependent, exercise-induced anaphylaxis	–

Modified from [1[•]].

tract seems to be the most common target organ, followed by the skin, and the respiratory tract and multiple systems can be involved with rapid progression to systemic anaphylaxis. Food-induced eosinophilic oesophagitis and gastroenteritis are becoming more recognized by paediatricians even at early ages (Table 1). Generally, IgE-mediated reactions have an acute onset, whereas non-IgE/T-cell-mediated reactions have a late onset or chronic evolution [1[•]].

Diagnostic work-up

The evaluation of a child with suspected food allergy includes detailed medical history, physical examination, screening tests and the response to elimination diet and to oral food challenge (see Fig. 1) [2]. In children with multiple food allergies, the response to elimination of single antigens is incomplete and lengthy assessment

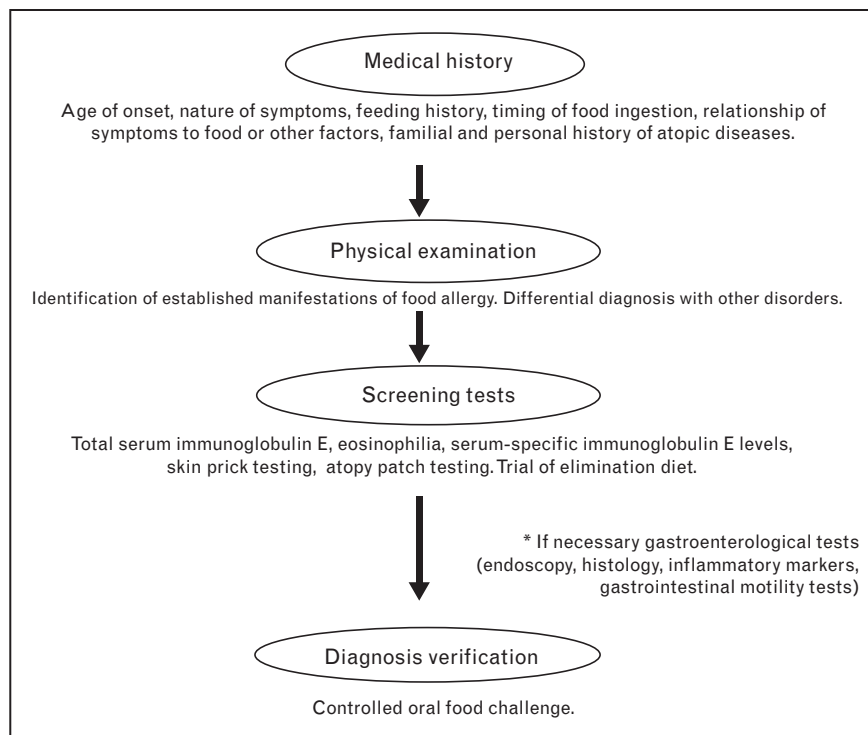
with a very restricted diet is often required. Unfortunately, medical history and physical examination are often inconclusive and allergy-screening tests, together with other diagnostic procedures, are frequently used [6]. However, none of the screening tests, alone or in combination, can definitely diagnose or exclude food allergy.

Screening tests

The most used screening tests for children with suspected food allergy are described below.

Skin prick testing

Skin prick testing (SPT) provides a readily available and inexpensive means of assessing IgE-mediated food allergy [9]. There is no minimum age for SPT, which can be performed in babies and infants with useful results. Together with specific food serum-IgE levels,

Figure 1 Evaluation of a child with suspected food allergy

Modified from [6].

SPT can detect the presence of antibodies against specific allergens, which indicates a sensitization to a food, but not necessarily allergy [1•]. Skin prick testing has a very high sensitivity and in the presence of a negative reaction (<3 mm wheal diameter) it is possible to exclude an IgE-mediated food allergy in over 95% of cases, whereas a positive test is less meaningful because of a low specificity [2,7]. There is a debate about the usefulness of commercial extracts or fresh foods (prick-by-prick) and the optimal cut-off values to predict a positive oral food challenge. There is a great variety of commercial extracts available worldwide, with some differences in their concentration. Therefore, it is difficult to compare results of different studies [9,10].

Concerning the diagnosis of cow's milk allergy (CMA), both fresh milk and cow's milk extracts of the three main proteins (casein, β -lactoglobulin and α -lactalbumin) could be useful. Casein has the better specificity and positive predictive value (PPV) 85%, whereas fresh milk has the best negative predictive value (NPV) 98%, better than each of the three milk proteins (94.7%). Calvani *et al.* [9] found that fresh milk has better sensitivity and NPV than the three milk proteins. They reported best cut-off values to predict a positive oral challenge of 12 mm for α -lactalbumin, 9 mm for casein, 10 mm for β -lactoglobulin and 15 mm for fresh cow's milk.

Regarding peanut allergy, Nolan *et al.* [10] reported that oral food challenge could be avoided in patients with a wheal diameter of SPT using commercial peanuts' extract of at least 7 mm (sensitivity 83% and specificity 97%). In this case, an oral challenge is likely to be positive with a PPV of 93%. Wainstein *et al.* [11] found that a wheal diameter larger than 15 mm and specific-IgE level at least 10.0 kU/l have a specificity of 100%, and the combination of SPT of at least 8 mm and positive peanut-specific-IgE levels at least 0.37 kU/l has a better specificity than the single test used alone. Ramesh [2] reported that a wheal diameter of at least 8 mm shows a good correlation with a positive challenge in children with peanut and tree nut allergies.

Specific serum immunoglobulin E

Studies [7] have investigated food specific-IgE levels as a method to predict the result of food challenge. Predictive decision points can be calculated for each allergen separately, which may help to avoid oral food challenges in some cases [7,12•] (Table 2). Above these levels, food challenge is not recommended because of the high probability (95%) of clinical reactions [13]. In daily clinical practice, it could be useful to define optimal cut-off values in each centre. The correlation between the levels of specific IgE and the outcome of a food challenge seems to be significantly influenced by the age of the patient.

Table 2 Predictive values of food allergen-specific immunoglobulin E levels

Allergen	95% PL (kU/l)	PPV (%)
Hen's egg	7	98
Hen's egg ^a	2	95
Cow's milk	15	95
Cow's milk ^a	5	95
Peanuts	14	100
Fish	20	100
Soybean	30	73
Wheat	26	74

PL, predictive level; PPV, positive predictive value.

^a infants <2 years.

Younger children with high levels of specific IgE have a major risk of adverse reactions to food challenge [14–16].

Results of testing surveys available in the literature already suggest that not all in-vitro tests for serum-specific IgE measurements yield similar results. At present, the Pharmacia CAP (Pharmacia Diagnostics, Uppsala, Sweden) is the most widely accepted reference method for serum-specific IgE measurements. Recently, the results of the ADVIA Centaur system (Bayer Diagnostics, Puteaux, France), a newly developed immunochemiluminometric in-vitro assay for determination of serum-specific IgE antibody, were compared with the results obtained with the Pharmacia UniCAP100 system (Pharmacia Diagnostics) with good correlation. Although the two in-vitro tests seem to perform equally on hen's egg, fish and peanut, the ADVIA Centaur (Bayer Diagnostics) may provide a more reliable test for serum-specific IgE against cow's milk, wheat and soy [15].

The latest technology trend is toward microarrays in which crude or purified native and recombinant allergens can be spotted in microdot arrays on silica chips to permit extensive panels of specific-IgE measurements to be performed with small quantities of serum. Reports on mutational analysis of food allergens such as the peanut allergens Ara h1, Ara h2 and Ara h3, Jug r 1, an English walnut major allergen, and ω -5 gliadin showed that single amino acid substitutions within each IgE-binding epitope led to elimination or marked reduction in IgE-binding by antibodies within pooled sera from allergic patients. The most important allergens in cow's milk are α s1-casein, α s2-casein, β -casein and κ -casein, as well as the whey proteins α -lactalbumin and β -lactoglobulin, and, in particular, there are identified six IgE-binding sites on cow's milk proteins that differentiated between patients with persistent CMA and those with transient CMA. The presence of IgE antibodies against at least one of three of these epitopes (amino acid 123–132 on α s1-casein, amino acid 171–180 on α s2-casein, and amino acid 155–164 on κ -casein) might be useful as a marker of persistent CMA [16,17]. Similarly, patients with persistent hen's egg allergy develop IgE antibodies against more sequential and conformational

epitopes of ovomucoid and ovalbumin. The presence of serum IgE antibodies to specific sequential epitopes of ovomucoid may be used as a screening instrument for persistent hen's egg allergy [17].

Atopy patch testing

The introduction of atopy patch testing (APT) in the diagnostic work-up of food allergy is relatively recent. The APT is based on cutaneous, cell-mediated responses after epicutaneous application of food allergens. Studies [18–25] on the use of APT have been performed in patients affected by atopic dermatitis, eosinophilic oesophagitis and children with suspected food allergy-related gastrointestinal symptoms, confirming their clinical diagnostic utility (Table 3). Although a positive SPT seems to reflect early reactions to food challenges, the APT has a higher diagnostic efficacy for late phase clinical reactions. Combining the APT with the SPT or sIgE measurement could increase predictive values [18,21–25]. There are several aspects of APT that deserve further investigation to achieve better standardization. These include optimum allergen concentrations, vehicles for different allergens, optimum sizes of Finn chambers for different allergens and other materials for occlusion than Finn chambers. To date, the APT with foods is not well standardized and different methods in preparing the test materials are likely to cause controversial results. Most studies with foods have been performed with cow's milk, hen's egg and wheat only. Until validation data are available, fresh foods should be preferred for testing over commercial extracts [20].

Gastroenterological tests

Several gastroenterological procedures are currently used in the diagnostic approach and in the follow-up of children affected by food allergy. These include endoscopic procedure, histologic evaluation and oesophageal pH monitoring, together with several noninvasive diagnostic tools such as intestinal permeability and inflammatory markers'

measurement (histamine, eosinophilic cationic protein, tryptase and faecal calprotectin) [26]. Although the measurement of these inflammatory markers would be convenient to accurately detect an intestinal mucosal reaction to foods, no conclusive studies are available on the diagnostic accuracy of these tests, alone or in combination, in the approach of a child with suspected food allergy.

Patients with allergic eosinophilic oesophagitis or gastroenteritis have peripheral eosinophilia and children with severe allergic eosinophilic gastroenteritis might have anaemia, blood in the stool and decreased serum albumin and IgG levels. Endoscopy with biopsies is the most definitive approach and might help in the differential diagnoses. Density greater than 15–20 eosinophils/high-power field (HPF) in the oesophagus is diagnostic for allergic eosinophilic oesophagitis, especially if the oesophageal pH monitoring is normal and there is lack of response to high-dose proton pump inhibitor medication [27,28]. If gastrointestinal food-induced enteropathies or colitis are suspected, intestinal biopsies revealing primarily eosinophilic infiltration of the mucosa may be helpful, if positive. The mucosal lesions in food allergy enteropathies are characteristically focal. Thus, sampling error results in negative biopsies in a discrete number of cases. Colonic biopsies are more often helpful in patients with allergic colitis, usually seen in infants with food allergy-induced haematochezia. Recent experiences with wireless capsule endoscopy support the use of this tool to examine the entire small bowel for areas of focal mucosal damage in cases of food allergy [29].

In children with food allergy, electrogastrographic evidence of severe gastric dysrhythmia and delayed gastric emptying during food challenge has been demonstrated. Recent improvements in the assessment of gastrointestinal motility, including multichannel intraluminal electrical impedance testing, micromanometric techniques, gastroelectrophysiological studies and measurement of

Table 3 Diagnostic accuracy of atopy patch testing in children with food allergy

Authors	<i>n</i>	Symptoms		Sensitivity	Specificity	Predictive value	
		<i>n</i>				Positive	Negative
Majamaa <i>et al.</i> [21]	143	68 21 54	cutaneous gastrointestinal cutaneous and gastrointestinal	44	71	63	52
De Boissieu and Dupont [22]	35	35	gastrointestinal	79	91	95	66
Kalach <i>et al.</i> [23]	49	5 20 24	cutaneous gastrointestinal cutaneous and gastrointestinal	44	94	92	52
Keskin <i>et al.</i> [24]	37		gastrointestinal, cutaneous, respiratory	73	86	89	67
Fogg <i>et al.</i> [25]	19	19	gastrointestinal	100	71	75	100
Berni Canani <i>et al.</i> [18]	60	60	gastrointestinal	65	96	95	67

Reproduced from [18,21–25].

gastric emptying by ^{13}C -octanoic acid breath test, are likely to facilitate further investigations on food allergy-related motility disorders [29].

Other diagnostic tests

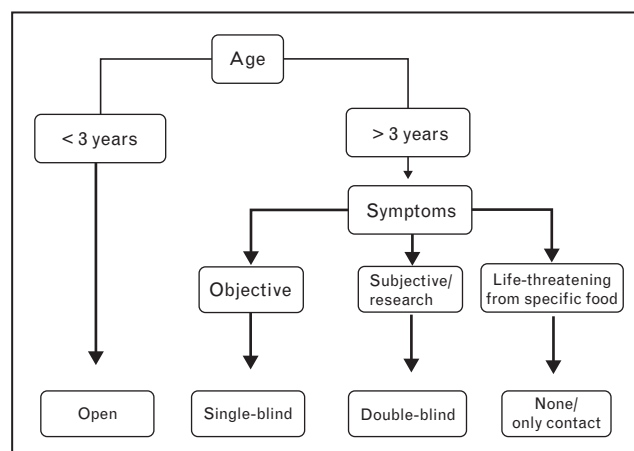
Some cellular tests determining the reactivity of blood cells *in vitro* to allergens are available. The low diagnostic accuracy of these tests [i.e. determination of histamine release, basophil degranulation, cellular allergen stimulation test (CAST)-determination of sulfidoleukotrienes produced by interleukin-3-primed basophils stimulated by allergens *in vitro* and flow cytometric basophil activation test] and lack of standardization are not acceptable in clinical practice. Complementary/alternative tests [e.g. antigen leukocyte cellular antibody test (ALCAT test), bioresonance, kinesiology, leukocytotoxic test, electrodermal tests, iridology and hair analysis] are popular and largely used in clinical practice, but there is no evidence of their diagnostic value. These alternative tests were unable to identify correctly the responsible foods in patients with suspected food allergy, or provided an unacceptable number of false positives. As a general consideration, the high rate of false positive results leads to time-consuming and useless consultations, with a not negligible waste of resources. All these techniques may lead to misleading advice or treatments and their use is not advised [30].

Infrared thermography has been shown to detect small increases in temperature associated with positive SPT, areas of atopic dermatitis and histamine or allergen-induced rhinitis. In a first report of the application of thermography in oral food challenges, the temperature changes observed in the facial area during positive and negative challenges suggested the utility of this method to aid in interpretation of food challenge outcome [31].

Food challenge testing

The oral food challenge is done by feeding gradually increasing amounts of the suspected food under observation by a physician over hours or days. It still represents the gold standard for the diagnosis of food allergy in order to avoid both unjustified diets, which may be harmful to the child, and severe clinical consequences, if an underlying food allergy is not correctly identified as a cause of the patient's symptoms. In most cases, they are best performed in a double-blind-placebo-controlled (DBPCFC) manner and in hospital because of the risk of anaphylaxis. Several articles have been published recently on this topic aiming to standardize the procedure. Main problems are related to the wide variety of symptoms possibly related to food allergy that lead to difficulties in the interpretation of test results and to the optimal timing and dosage of this procedure [32,33]. The

Figure 2 Selection of type of food challenge according to age and symptoms



Modified from [34*].

choice of the optimal timing should be oriented by the type of symptoms from 2 weeks for gastroesophageal reflux disease (GERD) up to more than 8 weeks in the case of food allergy-related eosinophilic oesophagitis [27**]. The DBPCFC could be unnecessary in patients with a recent history of anaphylaxis. Another issue is when to use open food challenges (OFC) as opposed to DBPCFC. Many studies have used either OFC or DBPCFC or a combination of both. It has been suggested that OFC is acceptable in children under the age of 3 years and that DBPCFC should be used in older children, and that OFC may be suitable for diagnosing immediate (mostly objective) symptoms, whereas a DBPCFC may be needed for the diagnosis of delayed (mostly subjective) symptoms or in a research setting (see Fig. 2) [32,33,34*]. The false negative rate of DBPCFC is about 3%, so negative challenges should always be followed by a supervised open feeding of a normal portion of the tested food in its commonly prepared state [35].

Conclusion

The correct diagnosis of food allergy is important to ensure appropriate patient care and to accurately establish the prevalence and incidence of this condition in different populations. The essential criterion for diagnosis is a clear response to an elimination diet and other diagnostic tests are secondary to this. Oral food challenge plays a crucial role in the diagnosis of food allergy, but it is largely underutilized even by allergy specialists. Responsible factors are multiple and include lack of training on the procedure, increased reliability of screening methods (medical history, skin testing, and *in-vitro* tests), extensive time needed, fear of risk and suboptimal fee reimbursement. Research has renewed our hopes for better diagnostic tests.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 623–624).

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