Food allergy varies with time and usually declines for most allergens, triggering less severe reactions: regular clinical testing of the reactivity to food is necessary

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Food Allergy: Recent Advances in Pathophysiology and Diagnosis by Christophe Dupont

Key insights

The availability and improvement of replacement dietary foods as well as research on desensitization techniques have affected food allergy (FA) outcomes. New aspects and many questions still remain as to the origins of the disease. Nevertheless, better education and descriptions of the clinical pattern of food allergy should help improve diagnosis and treatments.

Current knowledge

The vast majority of FA in infants and children arise from milk, wheat, egg and peanuts. Immune reactions are triggered by epitopes in these foods – small amino-acid sequences that are able to bind to antibodies or to cells. Thus, an allergy is considered to be due to an imbalance of the immune response to allergens. An allergic reaction that occurs without detectable IgE is considered a non-IgE-mediated allergy. Increased hygiene, the enhanced allergenicity of some foods as well as genetic predisposition leads to the abrogation of oral tolerance, which in turn leads to allergy (or intolerance). Clinical symptoms vary widely – affecting the skin, gastrointestinal and/or respiratory tracts – and differ in their nature, severity and outcome, depending on whether the production of a food-specific IgE (i.e. sensitization) occurs.

Practical implications

FA outcomes differ according to the allergens. Diagnosis requires a precise medical history, laboratory tests, and, importantly, an oral food challenge test to detect food-specific IgE.

Allergy pathophysiology relies on immune reactions triggered by epitopes in foods. Some food allergens have characteristics that allow them to resist digestion, enhancing allergenicity.

Recommended reading

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Food Allergy: Recent Advances in Pathophysiology and Diagnosis

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Key Messages

- Food allergy predominates in infants and children, and usually tends to disappear later on.
- Only a small number of foods are responsible for the vast majority of food allergies, particularly milk, wheat, egg and peanut.
- A classification of the symptoms according to their clinical pattern and the presence/absence of IgE sensitization allows a better evaluation of the risk and of the prognosis of the disease.

Key Words

Food allergy · Endoscopic diagnosis · IgE-mediated allergy · Non-IgE-mediated allergy · Pathophysiology

Abstract

Approximately 5% of young children and 3–4% of adults exhibit adverse immune responses to foods in westernized countries, with a tendency to increase. The pathophysiology of food allergy (FA) relies on immune reactions triggered by epitopes, i.e. small amino-acid sequences able to bind to antibodies or cells. Some food allergens share specific physico-chemical characteristics that allow them to resist digestion, thus enhancing allergenicity. These allergens encounter specialized dendritic cell populations in the gut, which leads to T-cell priming. In case of IgE-mediated allergy, this process triggers the production of allergen-specific IgE by B cells.

Tissue-resident reactive cells, including mast cells, then bind IgE, and allergic reactions are elicited when these cells, with adjacent IgE molecules bound to their surface, are re-exposed to allergen. Allergic reactions occurring in the absence of detectable IgE are labeled non-IgE mediated. The abrogation of oral tolerance which leads to FA is likely favored by genetic disposition and environmental factors (e.g. increased hygiene or enhanced allergenicity of some foods). For an accurate diagnosis, complete medical history, laboratory tests and, in most cases, an oral food challenge are needed. Noticeably, the detection of food-specific IgE (sensitization) does not necessarily indicate clinical allergy. Novel diagnostic methods currently under study focus on the immune responses to specific food proteins or epitopes of specific proteins. Food-induced allergic reactions represent a large array of symptoms involving the skin and gastrointestinal and respiratory systems. They can be attributed to IgE-mediated and non-IgE-mediated (cellular) mechanisms and thus differ in their nature, severity and outcome. Outcome also differs according to allergens.

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Introduction

Food allergy (FA) is an important public health problem that affects adults and children, and may be increasing in prevalence (table 1). Despite the risk of severe allergic reactions and even death, there is no current treatment: the disease can only be managed by allergen avoidance or the treatment of symptoms. Moreover, a di-

agnosis of FA may be problematic given that non-allergic food reactions, such as food intolerance, are frequently confused with FA. Additional concerns relate to the differences in the diagnosis and management of FA in different clinical settings. Basic as well as clinical research in this field is very active, aiming to both improve the diagnosis and provide a more detailed clinical pattern of this disease. This article is a synthesis of the current concepts of the pathophysiology and diagnosis of FA.

Pathophysiology

Reviews from different countries summarizing the current concepts of FA have been published recently [1–3]. The emerging concept is the mechanism of oral tolerance, which would not function appropriately in FA.

The Epithelial and Immune Machinery of the Gut

Columnar intestinal epithelial cells constitute the major part of the surface area in the human body, separate the sterile ‘milieu intérieur’ from the external environment and are devoted to the absorption of nutrients [4]. This mucosal barrier has the difficult task of developing an ‘oral tolerance’ to the enormous quantities of antigens regularly ingested and to the commensal organisms that develop an active immune suppression of digestive pathogens. The tight junctions between columnar cells reinforce the physical line of defense, and a thick mucus layer contains factors that trap particles, bacteria and viruses. This mucosal barrier also has strong immunity components, which are either *innate* (e.g. polymorphonuclear neutrophils, macrophages, natural killer cells, epithelial cells and toll-like receptors) or *adaptive* (e.g. intraepithelial and lamina propria lymphocytes, Peyer’s patches, secretory IgA and cytokines). These components participate in the ‘tolerance’ of foreign antigens that are not harmful to the body and cooperate with a number of immune cells (e.g. antigen-presenting cells, including intestinal epithelial cells, dendritic cells and regulatory T cells), which

This mucosal barrier has the difficult task of developing an ‘oral tolerance’ to the enormous quantities of antigens regularly ingested and to the commensal organisms that develop an active immune suppression of digestive pathogens.

Table 1. Estimated food allergy rates in North America [2]

Prevalence	Infant/child	Adult
Milk	2.5%	0.3%
Egg	1.5%	0.2%
Peanut	1%	0.6%
Tree nuts	0.5%	0.6%
Fish	0.1%	0.4%
Shellfish	0.1%	2%
Wheat, soy	0.4%	0.3%
Sesame	0.1%	0.1%
Overall	5%	3–4%

play a central role in the development of oral tolerance [4–6]. Regulatory T cells represent a vast complex, with TH3 cells (CD4+ cells that secrete TGF-β), TR1 cells (CD4+ cells that secrete IL-10), CD4+ and CD25+ regulatory T cells, CD8+ suppressor T cells, and γδ T cells [4].

Although poorly understood, oral tolerance might rely on these intestinal epithelial cells, which present luminal antigen to T cells on an MHC class II complex, but lack a ‘second signal’, thus leading to anergy. This suggests that the role of intestinal epithelial cells in tolerance induction to food antigens is like a ‘non-professional’ antigen-presenting cell. Nevertheless, around 2% of ingested food antigens still cross this efficient gastrointestinal (GI) barrier and are transported throughout the body in ‘immunologically’ intact forms, even through the normal mature gut [7].

This mucosal barrier might be less efficient or ‘immature’ in infants and young children. This would explain the increased prevalence of both GI tract infections and FA in the first years of life: the activity of the secretory IgA system is not fully mature until 4 years of age [4].

The development of oral tolerance might also be influenced by several non-host factors, such as the physical properties of the antigen, and the amount and frequency of exposure. In murine models, high-dose tolerance involves deletion of effector T cells, and low-dose tolerance is the result of activation of regulatory T cells with suppressor functions [4].

Lastly, the commensal gut flora is likely to play a role in oral tolerance, as suggested by studies in mice raised in a germ-free environment and treated with antibiotics or lacking toll-like receptor 4, which recognizes bacterial lipopolysaccharides [8, 9], and by studies relating the presence of atopic dermatitis to bacterial cultures from human stool samples [10].

IgE-Mediated Hypersensitivity

Allergy is considered to be due to an imbalance of the immune response to allergens. Levels of IgE, originally a defense mechanism against worms, are increased in the blood of allergic patients during the so-called IgE-mediated hypersensitivity, where the IgE response is attributed to the generation of TH2 cells that produce IL-4, IL-5 and IL-13 [11].

Non-IgE-Mediated Hypersensitivity

However, many patients with 'allergic' reactions lack the hallmark of FA, i.e. increased blood IgE levels against the offending food. The immunopathophysiology of these non-IgE-mediated allergic disorders in the GI tract is still unknown for more or less obvious reasons, e.g. their particular frequency in young infants, in whom pathophysiological investigations remain difficult and ethically questionable, and the lack of animal models in particular. In infants with food protein-induced enterocolitis syndrome (FPIES), TNF- α secreted from peripheral blood mononuclear cells cultured with food proteins has been shown to be responsible for the reaction [12]. Duodenal biopsy specimens of affected infants have increased staining for TNF- α and decreased staining for the regulatory cytokine receptor TGF- β [13].

Eosinophilic Esophagitis and Other Disorders

As recently summarized by a consensus statement [14], eosinophilic esophagitis (EoE) is a chronic, immune-/antigen-mediated disease, which is characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation. It appears to be an antigen-driven immunologic process that involves multiple pathogenic pathways, leading to a new conceptual definition.

The diagnostic guidelines continue to define EoE as an isolated chronic disorder of the esophagus, which is diagnosed based on both clinical and pathologic features. In EoE patients, concurrent allergic diatheses, particularly food sensitization, are more frequent than in the general population.

Genetic studies have indicated a unique transcriptional response in vivo that defines EoE and that appears to be partially attributable to the TH2 cytokine IL-13 [15]. EoE susceptibility is caused at least in part by some polymorphisms, such as in the thymic stromal lymphopoietin

protein gene and its receptor [16]. Also, there could be a place for a potential new disease phenotype, i.e. proton pump inhibitor-responsive esophageal eosinophilia. Further advances and controversies regarding diagnostic methods, predictive surrogate markers of allergy as well as treatment approaches are under investigation.

Other eosinophilic disorders involving the stomach and the intestines are rarely associated with EoE, apparently (for the most part) less frequent, and, at present, less investigated.

Different Routes of Sensitization in the Development of Allergy

Susceptible individuals might not develop oral tolerance after antigen ingestion, or tolerance might be bypassed by the presentation of proteins via the respiratory tract or skin, representing alternative routes leading to sensitization. In patients with the oral allergy syndrome (OAS)/pollen-food-related syndrome, sensitization occurs via the respiratory route [17]. Following this sensitiza-

tion, the oral pruritus of allergic patients eating raw apples originates from the cross-reactivity of the apple protein Mal d 1 to a homologous birch pollen protein Bet v 1.

Skin might also be a route of sensitization, as exemplified in several mouse models [18]. Epidemiologic studies from Israel and the United Kingdom suggest that environmental exposure to peanut might promote sensitization and allergy [19, 20]. Thus, the role of the skin barrier has attracted increasing attention. Constitutive alterations in the skin, for example, such as a defect in the filaggrin gene, might lead to sensitization [21].

Differences and Similarities in Food Proteins

Any food can trigger an allergic response, but few protein families account for the vast majority of allergic reactions: egg, milk, peanut, tree nuts, fish, shellfish, wheat and soy [2].

Cross-reactivity may exist between foods (table 2). Major food allergens share a number of common features, water solubility of glycoproteins, size (10–70 kDa), and relative stability to heat, acids and proteases. Animal food allergens share sequence identities with their human homologues based on protein families, sequence analysis and evolutionary relationships. These similarities, when >62%, exclude the protein from being allergenic in human subjects [2, 22].

However, many patients with 'allergic' reactions lack the hallmark of FA, i.e. increased blood IgE levels against the offending food.

Table 2. Rates of clinical cross-reactivity among foods [2]

Allergy to	Related food	Approximate clinical reaction rate
Peanut	most beans	5%
A tree nut	other tree nuts	35% (higher for: walnut-pecan, almond-hazel, cashew-pistachio)
A fish	other fish	50%
Shellfish	other fish	50%
Grain	other grain	20%
Cow's milk	goat/sheep milk	>90%
	mare's milk	5%
	beef	10%

Differences according to Food Preparation

Food preparation can affect allergenicity. In westernized countries, peanut allergy has a higher rate and peanuts are consumed roasted, whereas in China, where peanut is primarily boiled or fried, peanut allergy prevalence is low [23]. At high temperature, roasting peanuts >180°C leads to a Maillard reaction that appears to increase stability and allergenicity [24, 25]. Two studies suggest that the carbohydrate moiety of certain glycoproteins might play a significant role in the allergenicity of food proteins, with the recent demonstration of IgE antibodies directed at a carbohydrate epitope leading to clinical symptoms. The glycosylated Ara h 1 (a major peanut allergen), as opposed to the deglycosylated form, functions as a TH2 adjuvant and activates dendritic cells towards the maturation of TH2 cells [26].

Emulsification (peanut butter) might increase allergenicity through an adjuvant effect [23].

Recent studies suggest that 70–80% of young children allergic to eggs can tolerate baked (heat-denatured) forms of the protein while reacting to the raw form [27, 28]. At least partially, this might be true for milk. These differences in tolerance might be due to the role of conformational epitopes, which are much more denatured by heat than linear epitopes.

Diagnosing a Potential FA: Medical History Taking

As always in medicine, taking a thorough medical history and a detailed physical examination allows, most of the time, a good evaluation of the medical issue, ascertaining the possible FA triggers and approaching the like-

ly general pathophysiological basis, i.e. whether the food-induced allergic disorder is IgE mediated or not.

FA may be responsible for different clinical symptoms that can affect the skin, and the digestive and respiratory tracts. Skin symptoms are mainly atopic dermatitis and urticaria. Digestive symptoms are very protean and include permanent distress (colic), protracted regurgitations or gastroesophageal reflux, vomiting, diarrhea, constipation, failure to thrive or blood in the stool. Respiratory symptoms may manifest as asthma or even some ear-nose-throat conditions [29].

The clinical setting may vary considerably. In young infants, especially in those fed formula, milk is the more likely food allergen. In older children, especially in the case of eczema, the potential role of eggs is at its highest. In the growing child, the first consumption of peanut-containing food may trigger an acute reaction owing to an allergy that had not been noticed before. Symptoms commonly overlap: for example, children with cow's milk-sensitive eczema commonly have GI-related symptoms, and, indeed, these can be an important clue as to the role of cow's milk allergy in the underlying eczema [3].

Diagnosing Food Allergens: The Different Tests

Different tests may help in the diagnosis of FA, e.g. using blood samples, skin reactivity, GI procedures for developing eosinophilic disorders, as well as an oral food challenge (OFC) to detect the food ingredient responsible.

Food-Specific IgE Antibodies and 'Component-Resolved' Diagnosis

RAST® (RadioAllergoSorbent Test; Phadia, Stockholm, Sweden) is applied to determine food-specific IgE (sIgE) levels in blood samples. Detectable levels of blood

sIgE may indicate allergy when associated to clinical reactivity, or only sensitization if the patient tolerates the food. For example, in a given patient, a peanut sIgE level of 2.5 kU/l may be associated with a risk of severe anaphylactic shock or it may only indicate sensitization. However, the likelihood of a clinical reaction increases with increasing sIgE concentration [30], and sIgE cutoff values predictive of clinical reactivity are now available for different food ingredients (table 3). Using these threshold values, diet, age, disease and

Animal food allergens share sequence identities with their human homologues based on protein families, sequence analysis and evolutionary relationships.

Table 3. Diagnostic cutoff values for sIgE levels and SPTs for the diagnosis of CMPA with a positive predictive value $\geq 95\%$ (from Du Toit et al. [3])

Predictive value	
Cow's milk-specific serum IgE	
All children	≥ 15 kU/l
Infants ≤ 2 years	≥ 5 kU/l
Wheal size in SPTs	
Children >2 years	≥ 8 mm
Infants ≤ 2 years	≥ 6 mm

IgE levels were determined using Phadia ImmunoCAP. SPTs were performed with commercial extracts.

challenge protocols should also be taken into account. Values associated with a high likelihood of clinical allergy (e.g. $>95\%$) are often referred to as diagnostic values. Values do not generally correlate very well with reaction severity [2 and references therein].

Decreasing blood sIgE may be associated with an increasing chance of allergy resolution [31]. This also allows the determination whether the allergy is transient (type 1) or permanent (type 2).

Furthermore, changes in sIgE to the particular proteins for each food, such as casein and/or whey proteins in milk, could help to better define severity and prognosis [32]. Hence, research now focuses on sensitization toward the specific allergens that constitute the 'components' of the food extract, which may bear different prognostic values. For example, casein is relatively heat stable and resistant to pepsin digestion; these characteristics probably account for the variability in clinical reactivity and tolerance to milk and dairy products between patients and in the same patient over time [3]. Specific epitope profiles may play a role: sIgE may bind to conformational epitopes, i.e. areas of an allergen that depend on protein folding, are more labile and likely responsible for mild/transient allergy, whereas in other cases, sIgE may bind to linear epitopes that are more stable, which might suggest a severe persistent allergy [33].

OAS is related to a cross-sensitization between food allergens and aeroallergens, e.g. between the birch pollen allergen Bet v 1 and the apple protein Mal d 1. In this case, there is no specific sensitization to the particular food, even though the patient reacting orally to this food may have a positive skin prick test (SPT) and an apparently increased sIgE level. Thus, diagnosing OAS needs con-

comitant testing of the potential cross-reacting food allergens and aeroallergens.

The recent availability of an sIgE microarray (Phadia Isac[®]), allowing the detection of sIgE for a whole batch of food and aeroallergens, might considerably improve this 'component-resolved' diagnosis, although further investigation is still largely needed [34].

An indirect approach to sensitization may be given by a basophil activation test using flow cytometry, which assesses the percentage of basophils bearing sIgE activation and expresses the CD63 marker after in vitro stimulation with allergens. The technique could result in future diagnostic modalities [35, 36].

Recent studies suggest the contribution of an immunoglobulin free light chain in addition to IgE in the allergic reaction to cow's milk proteins (CMP) [37].

Skin Prick Tests

SPTs, when positive, provide a rapid means to detect sensitization for IgE-mediated disorders. A positive SPT, with specificity $<100\%$, does not necessarily prove that the food is causal. In contrast, a negative SPT, with a negative predictive accuracy $>90\%$, suggests the absence of IgE-mediated allergic reactivity. This, however, may not be true for milk allergy in young infants, whose skin reactivity frequently lags behind the rise of sIgE in the blood. Increasing SPT wheal size correlates with an in-

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creasing likelihood of clinical allergy (table 3), and some studies define 'minimum' wheal sizes, above which an allergy may be diagnosed based on the test result alone [38–40]. For fruits and vegetables, commercially prepared extracts may be often inadequate because of the lability of the allergen(s); fresh foods may be better for testing.

Atopy Patch Test

Clinical reactions may occur despite undetectable serum food sIgE; 10–25% of cases presented with clinical reactions according to one study [41], and percentages may probably be markedly higher in infants, underlining the need for further clinical diagnostic tools. Several studies evaluated the utility of the atopy patch test for dis-

Fig. 1. EoE: endoscopic aspects. **a** White granular material. **b** Furrows. **c** Circular esophageal rings: trachealization of the esophagus.

orders in which symptoms are delayed after food ingestion, such as atopic dermatitis, EoE and FPIES [42–44].

The atopy patch test is performed by placing foods under Finn chambers for 48 h, then removing the chamber and reading the skin modifications 24 h later. The atopy patch test seems promising, particularly since in the absence of IgE-mediated reactions, it is the sole diagnostic test allowing the detection of reactivity to one food or another. However, there are currently no standardized reagents, methods of application or interpretations. In France, a ready-to-use atopy patch has been commercialized, paving the way to a standardization of the technique [45].

GI Procedures

Various tests and procedures might be required to evaluate a possible GI allergy, in particular, endoscopy (fig. 1), with biopsies that are mandatory for the diagnosis of EoE [46]. Pathologically, 1 or more biopsy specimens must show eosinophil-predominant inflammation. With some exceptions, 15 eosinophils/high-power field (peak value) is considered a minimum threshold for a diagnosis of EoE. The disease is confined to the esophagus, and other causes of esophageal eosinophilia should be excluded, specifically proton pump inhibitor-responsive esophageal eosinophilia [14].

Oral Food Challenge

FA varies with time and usually declines for most allergens, triggering less severe reactions: regular clinical testing of the reactivity to food is necessary. During the OFC, the offending food is introduced under strict med-

ical supervision in order to determine tolerance or clinical reactivity. There is a risk of severe reaction; thus, the medical staff must be properly trained with medications and equipment to treat anaphylaxis on hand, according to validated and well-known procedures. Caution is especially advised after prolonged dietary elimination [47]. The challenge is stopped only in the presence of objective or persistent subjective symptoms [48].

Screening usually relies on an open or single-blind OFC proven to be safe, provided it is carried out in an allergist's office [49], whereas the double-blind, placebo-controlled OFC is usually restricted to clinical studies or to conditions where the result of the open challenge remains dubious. Numerous reviews have outlined the procedures involved in OFC [50, 51]. A recent Work Group report describes OFC testing in a comprehensive and clinically oriented guide [48]. When the blinded challenge is negative, it must be confirmed by means of an open, supervised feeding of a typical serving of the food in its natural form to rule out a false-negative challenge result (approximately 1–3%).

In case of chronic disorders, the offending food is currently part of the diet. The test thus first includes a period of elimination of the possible trigger food(s) to determine whether symptoms resolve, before going to an OFC for diagnosis.

Diagnosing the Clinical Pattern

Based on the different tests and clinical situation (table 4), it is now possible, and probably better, to classify patients not only in reference to the responsible allergen

but also to a typical clinical pattern [2]. This allows a better understanding of the clinical conditions, and better information of the patient or his parents on the severity of the potential acute episodes and the prognosis of the condition.

IgE-Mediated Disorders

The Oral Allergy Syndrome. The oral allergy or (pollen-food-related) syndrome is characterized by pruritus, mild edema confined to the oral cavity, rarely progressing beyond mouth (7%) or anaphylaxis (<2%). It may increase after the pollen season, probably due to the stimulation of IgE production, and corresponds to sensitization to pollen proteins by the respiratory route, resulting in IgE that binds certain homologous, typically labile, food proteins in certain fruits/vegetables (e.g. apple Mal d 1 and birch Bet v 1). OAS occurs only in patients with established pollen allergy, and hence, it is more frequent in adults than in young children, with raw fruit/vegetables being opposed to cooked forms, which are tolerated. Some examples of relationships are birch (apple, peach, pear and carrot) and ragweed (melons); it may last even with seasonal variations.

Urticaria/Angioedema. Urticaria/angioedema is usually triggered by ingestion of the offending food or by direct skin contact (contact urticaria), resulting in acute urticaria. Food is much less involved in chronic urticaria (2%).

Anaphylaxis. It is usually rapidly progressive, and the multiple-organ-system reaction can include cardiovascular collapse, accompanying other symptoms of the al-

OAS occurs only in patients with established pollen allergy, and hence, it is more frequent in adults than in young children, with raw fruit/vegetables being opposed to cooked forms, which are tolerated.

lergic reaction, such as rhinitis, asthma and antiracial, with severe pruritus. It is related to the massive release of mediators, such as histamine, but not always with high mast cell tryptase levels. Any food may trigger this reaction, but more commonly, the responsible foods are peanut, tree nuts, shellfish, fish, milk and egg.

Rhinitis and Asthma. They may accompany FA according to different situations. Symptoms may accompany a

food-induced allergic reaction, such as during the anaphylactic shock (see above). Symptoms may be triggered by inhalation of aerosolized food protein, such as fish or seafood, in infants/children more so than in adults, except for some occupational diseases, such as baker's asthma.

In infants, early chronic rhinitis and repeated bouts of otitis media or bronchiolitis/asthma may be related to the consumption of some major food allergen, such as milk or wheat.

Mixed IgE- and Non-IgE-Mediated Disorders

Eosinophilic Esophagitis. A distinct entity that occurs mainly in children 5–15 years old, EoE, appears to be related to FA and, to a lesser extent, aeroallergens, in the majority of cases. There seems to be an increasing prevalence of new cases of EoE in children, and the annual incidence could be approximately 1/10,000 population [1]. The symptoms are dominated by the conventional symptoms of reflux, but also include abdominal pain and dysphagia, highly specific to EoE. Significantly increased thickness of the esophageal wall has also been demonstrated in patients with EoE. Treatment includes allergen avoidance and, if ineffective, local steroid treatment.

Other Eosinophilic Disorders. Eosinophilic gastroenteropathies other than EoE are less clearly defined, may vary in terms of site(s) and degree of eosinophilic inflammation, and may mimic irritable bowel syndrome. They are likely persistent. They usually respond to an elimination diet, and even more to an amino acid-based formula, but the persistence of the disease has been demonstrated 2.5–5.5 years after initiation [52]. Eosinophilic proctocolitis is characterized by rectal bleeding, with approximately 20% of cases caused by CMP allergy (CMPA), diarrhea and colic, and occurs in infants 0–24 months old, even when they are exclusively breastfed [53, 54].

Eczema. Atopic dermatitis is associated with food in 35% of children with moderate-to-severe skin disease. This high prevalence might relate to the homing of food-responsive T cells to the skin, which could be higher in infants than in children and adults. The major allergens involved are egg and milk, particularly the latter. The disease may typically resolve with FA disappearance but reappear in predisposed children developing allergy to house dust mites or other aeroallergens.

Non-IgE-Mediated Disorders

Dietary FPIES. It primarily affects infants and usually resolves after the age of 2 years. During chronic exposure to food, the child suffers from emesis, diarrhea, poor growth and lethargy. Following elimination and re-

Table 4. Clinical patterns of common food allergies

Symptoms		Remarks
<i>IgE-mediated disorders</i>		
OAS	pruritus, mild edema confined to the oral cavity, uncommonly progressing beyond mouth (7%) or anaphylaxis (<2%)	more frequent in adults than in young children
Urticaria/angioedema	triggered by ingestion or by direct skin contact	typically acute in nature; food is less involved in chronic cases
Anaphylaxis	rapidly progressive, allergic reaction: rhinitis, asthma, severe pruritis	related to the massive release of mediators, e.g. histamine
Rhinitis and asthma	multiple-organ-system reaction can include cardiovascular collapse	
	triggered by inhalation of aerosolized food protein, e.g. fish or seafood	may be related to the consumption of a major food allergen, e.g. milk or wheat
<i>Mixed IgE- and non-IgE-mediated disorders</i>		
EoE	GI reflux, abdominal pain and dysphagia	distinct entity; mainly in children 5–15 years old
Other eosinophilic disorders	less clearly defined, may vary in terms of site(s) and degree of eosinophilic inflammation, may mimic irritable bowel syndrome; likely persistent	proctocolitis caused by CMPA (20%); diarrhea and colic in infants, even when they are exclusively breastfed
Eczema/atopic dermatitis	moderate-to-severe skin disease	associated with food in 35% of children, particularly milk and egg
FPIES	emesis, diarrhea, poor growth and lethargy; following elimination and re-exposure, symptoms may be severe, with emesis, diarrhea and hypotension (15%) occurring 1–5 h after ingestion	affects infants and usually resolves after the age of 2 years; responsible foods are cow's milk, soy, rice and oat
Food protein-induced enteropathy syndrome	protracted diarrhea, sometimes associated with vomiting, which may result in malabsorption and faltering growth	affects infants and usually resolves after the age of 2 years; may be difficult to distinguish from untreated celiac disease
GI dysmotility	uncertain mechanism; patient presents with impaired GI motility abnormalities	allergic GI motility disorders are common in infancy and early childhood and are shared by many IgE and non-IgE CMP-induced disorders

exposure, symptoms may be severe, with emesis, diarrhea and hypotension (15%) occurring 1–5 h after ingestion. Responsible foods are cow's milk, soy, rice and oat. Four cases of FPIES in breastfed infants have recently been reported [55]. Mechanisms might involve an increased TNF- α response and a decreased response to TGF- β . To circumvent adverse reactions, e.g. dehydration leading to shock, following food challenge, this syndrome has to be excluded, since severe reactions even occur in the absence of any detectable sIgE to the corresponding food.

Food Protein-Induced Enteropathy Syndrome. Symptoms encompass protracted diarrhea, sometimes associated with vomiting, which may result in malabsorption and faltering growth. The natural history is similar to

other forms of non-IgE-mediated FA presenting in infancy and resolving by 1–2 years. Histological findings include mucosal inflammation and distortion of the villous architecture with a 'patchy' distribution, features which may be difficult to distinguish from untreated celiac disease [3].

Uncertain Mechanism: GI Dysmotility

CMPA may present with a range of GI motility abnormalities, including vomiting, gastroesophageal reflux and diarrhea [3]. Allergic GI motility disorders are common in infancy and early childhood, and are shared by many IgE and non-IgE CMP-induced disorders, without easy labeling according to the above-mentioned syndrome.

Fig. 2. Decision tree, summarizing the recommendations from the Nutrition Committee of the French Society of Pediatrics for dietary treatment of CMPA in childhood. AAF = Amino acid-based formula; EHF = extensively hydrolyzed formula (from Dupont et al., reproduced with permission [58]).

Diagnosis in a Decision Tree: The Example of CMPA

CMPA has a particular feature: in formula-fed infants, milk is the main, if not the only, source of protein and, thus, the therapeutic scheme for a suspected CMPA pattern in the child needs to be adapted by both pediatricians and general practitioners who may frequently encounter this disease. Several authors or working parties [3, 29, 56, 57] have suggested decision diagrams allowing the diagnosis of this condition based on symptoms and on the use of the replacement formulas that can be either CMP hydrolysates or an amino acid-based formula for children who do not tolerate these hydrolysates. The diagram presented in figure 2 shows the proposition recently published by the Nutrition Committee of the French Society of Pediatrics [58].

Explaining the Disease to Parents: Some Clues

FA remains difficult for parents to understand as well as for practitioners, particularly since education on this matter in medical schools is largely lacking. Here are some concepts that can be addressed by physicians directly to explain to parents when they are confronted with this kind of disorder.

What Kind of Allergy Is It?

Explain that a certain class of immunoglobulins (i.e. IgE) is responsible for an allergy, but that some allergies are IgE mediated and some are not. To detect an IgE-me-

diated allergy, a blood sample test (which measures the sIgE serum level) is mandatory. However, a 'negative' test cannot rule out an allergy, if the latter is non-IgE mediated. IgE-mediated CMPA reactions usually occur within 20 min of exposure and always within 2 h thereof. Non-IgE-mediated immune reactions are typically more delayed in onset.

What Allergen Is Responsible for the Symptoms?

In young children, allergies to cow's milk tend to dominate, whereas this is not true later on: allergies to wheat, egg and peanut tend to largely outgrow milk allergy after age 1 year.

Can Breast Milk Be Responsible for the Allergy? (Very Frequent Question)

The question is not appropriate. Breast milk in itself is not responsible for the allergy. However, breast milk is able to transmit small amounts of allergens, such as cow's milk, to the infant's digestive tract, and infants sensitive to these allergens will react. The treatment is not to stop breastfeeding but to start the elimination diet in the mother.

When Did the Child Get Sensitized to the Allergen?

The answer is still tricky: sensitization may have occurred in utero (probably through swallowing of the amniotic fluid), following birth, through the digestive tract (so-called 'dangerous bottle' given in the maternity ward during the first days of life, or allergens transmitted via

the breast milk or given at the beginning of complementary feeding), through inhalation of particles or even through skin contact.

What Is the Reason Why Some Children React to Heat-Treated Milk or Eggs and Others Not?

Heating transforms the allergen and modifies its structure in some locations. If those locations are the ones involved in the child's reactivity to the allergens, then the child will tolerate the heated food even though he/she does not tolerate the raw food.

What Is the Relationship with Allergic Disease?

This depends on the FA reaction the child suffers from. When children have IgE-mediated CMPA, they are likely to have eczema, at least 25% of children with CMPA will go on to develop additional FAs and infants with FAs are at risk for the development of asthma. In addition, asthma in itself is a risk factor for more severe food-induced allergic reactions. If CMPA is not IgE mediated, then, most of the time, it is a self-limited, isolated disease.

Conclusion

FA has been transformed by the availability and constant improvement of replacement dietary foods and, more recently, through the investigation of desensitization techniques, which seem to affect the outcome of protracted FAs. In the meantime, new aspects of the disease, such as EoE, seem to expand, underlining the fact that many questions still remain, especially as to the origin of the disease. The development of future treatments requires a perfect description of the clinical pattern of the disease and research focusing on the physiopathological mechanisms in the ongoing promising studies.

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