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PEDIATRIC ALLERGY AND IMMUNOLOGY

Educational Clinical Case Series

Mechanisms of food allergy

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Allergy type sensitization occurring in the gut results from a break in oral tolerance, mostly occurring in early childhood. In these patients, a minute amount of the large load of potential food allergens not only will result in immunoglobulin E (IgE) type sensitization mostly, but also in food allergies resulting from other mechanisms including eosinophil-driven disease or resulting from T-cell-mediated inflammation. Symptoms elicited by subsequent exposure to foods in these patients will be mostly in relation to the mechanism of the disease. In this educational review series, we described three cases of food allergy, first, a child with typical IgE-mediated food allergy, second, a child with eosinophilic proctocolitis and in the third patient, we will address tolerance acquisition mechanisms. These cases are discussed with regards to their specific immune events.

Philippe A. Eigenmann
Department of Pediatrics, Geneva University Hospitals and University of Geneva, Geneva, Switzerland

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Philippe A. Eigenmann, Geneva University Children's Hospital, 6 rue Willy-Donze, 1211 Geneva 14, Switzerland
Tel.: +41 22 382 4531
Fax: +41 22 322 4779
E-mail: philippe.eigenmann@hcuge.ch

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Food allergy is distinguished from other adverse reactions to food by a mechanism involving the immune system. According to the type of immune reaction, children with food allergy will present with a specific clinical picture, e.g. with immunoglobulin E (IgE)-mediated symptoms or with non-IgE-mediated gastrointestinal symptoms. In this educational review, we will illustrate various mechanisms occurring in food allergic patients by three clinical cases.

All immune phenomena related to a food require an initial encounter with the antigen. It is commonly accepted that the initial sensitization to a food allergen occurs either via the gut mucosa or through cutaneous exposure (1), and primary sensitization possibly through aerosolized foods has also been described. In the case of pollen-related cross-reactivity to food, the first exposure happens through the respiratory mucosa. We will focus here on the first type of manifestations of food allergy, which is largely dominant in younger children.

During lifetime, large quantities of nutrients including potentially allergenic food proteins are processed through the gut. Among mechanisms regulating incursion of food antigens into the sub-mucosa, the first barrier is of a physical nature. The mucus at the inner surface of gut epithelial cells plays a major role as a barrier to potential foreign antigens. However, this protection is also reduced in the first weeks of life, as mucin is only present in low amounts in the newborn (2). Secretory immunoglobulin A (IgA) not only prevents micro-organisms from adhering to the mucosal surface, but also activates the clearance of antigens. This antibody isotype is synthesized in large amounts by local plasma cells. In addition, food proteins reaching the gut mucosa are already partially digested by proteases as well as by gastric acidity. Reduced gastric acidity in young infants as well as the use of proton pump inhibitors has been suspected to play a role in the pathogenesis of food allergy (3, 4). Finally, the mucosa is partially permeable in all individuals, but with an increased permeability shortly after birth (5). This may leave the young infant particularly prone to sensitization with food antigens. In addition, despite an efficient first line of protective barriers, a significant load of potential food antigens will reach antigen presenting cells. Under physiologic conditions, antigen presenting cells, mostly dendritic cells, will process the food antigen and will present it on a major histocompatibility complex

(MHC) class II receptor to the T cells, resulting physiologically in oral tolerance (Fig. 1), or in genetically predisposed individuals towards allergic sensitization (Fig. 2). In addition to MHC class II processing, it is suspected that other regulatory mechanisms such microbiota-induced signaling by the innate immune system will influence the fate of the immune reaction towards allergy or tolerance (6).

Case 1

An 18-month-old boy is observed at the allergy clinic with a history of diffuse urticaria as well as an acute episode of wheezing, after ingestion of a cereal-bar containing peanut-butter. This was the first known ingestion of a food containing peanut protein as his mother had been avoiding feeding him peanuts previously. Peanut-avoidance was motivated by a history of a similar reaction without respiratory symptoms after ingestion of pasta containing egg at 12 months of age, as well as after an urticarial rash at the same age, due to a cow's milk protein-based formula. In addition, the child had a history of atopic dermatitis with moderate to severe symptoms until 15 months of age, followed by gradual improvement. Skin prick testing disclosed positive tests to peanuts with a weal of 12-mm mean diameter, to egg with 7 mm, and to skimmed milk with 9 mm. Serum-specific IgE measurement by UniCAP (Phadia, Uppsala, Sweden) was positive for peanut (46.5 kU/l), for egg white (15.2 kU/l) and cow's milk (12.7 kU/l). In addition to the previous diagnosis of cow's milk and egg allergy, the child was diagnosed with peanut allergy and the parents were instructed to avoid these foods.

Discussion of the case

The symptoms reported by the mother of this child, rapid onset of urticaria followed by an acute respiratory distress including wheezing, within minutes after ingestion of peanuts, followed by rapid recovery, are suggestive of an IgE-mediated food allergy. Airway reactions (bronchial and nasal) are a common feature assessing for the severity of an IgE-mediated reaction and is reported in up to 60% of patients experiencing a positive food challenge (7). In addition, this patient presented with urticaria, a symptom observed most commonly in IgE-type reactions to foods. Other symptoms might also include the gastrointestinal tract. Furthermore, several organs might be involved leading possibly to an anaphylactic reaction. Positive skin prick tests and specific IgE to peanuts, hen's egg white and cow's milk, in conjunction with the suggestive history confirm an immediate-type, IgE-mediated food allergy.

The cardinal feature of immediate type symptoms such as in this child is the production of food-specific IgE. An initial exposure to the food antigen by antigen presenting cells and priming of naïve T cells such as described above will lead to a TH2 type response with secretion of interleukin (IL)-4 and IL-13 (Fig. 2). These two cytokines initiate class-switching towards an 'allergy phenotype' and will facilitate food-specific IgE production by plasmocytes. Circulating IgE will then bind to the FCϵRI receptor on mast cells present in potential target organs. It is not clear yet why a given patient might react more specifically with a given target organ. However, upregulation of homing receptor has been linked to specific clinical pictures of food allergy. The

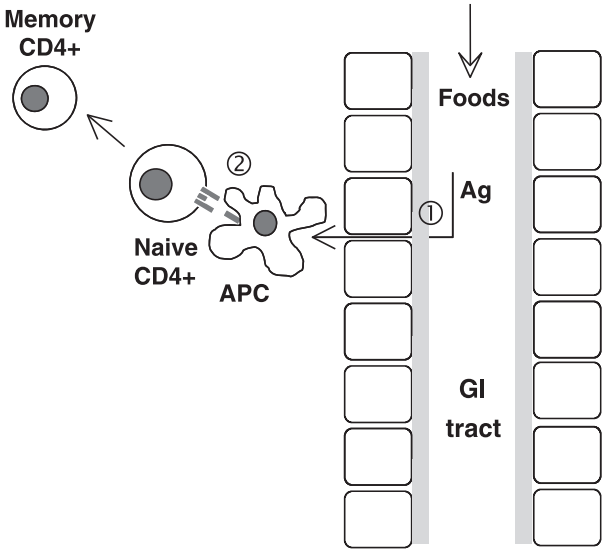

Fig. 1. Schematic representation of sensitization to foods in the gut mucosa. (1) Evading physical barriers including epithelium-lining mucin, secretory IgA antibodies, and the cell epithelium, small amounts of food proteins can (2) be endocytosed by antigen presenting cells (APC) and activate naïve $CD4^+$ lymphocytes.

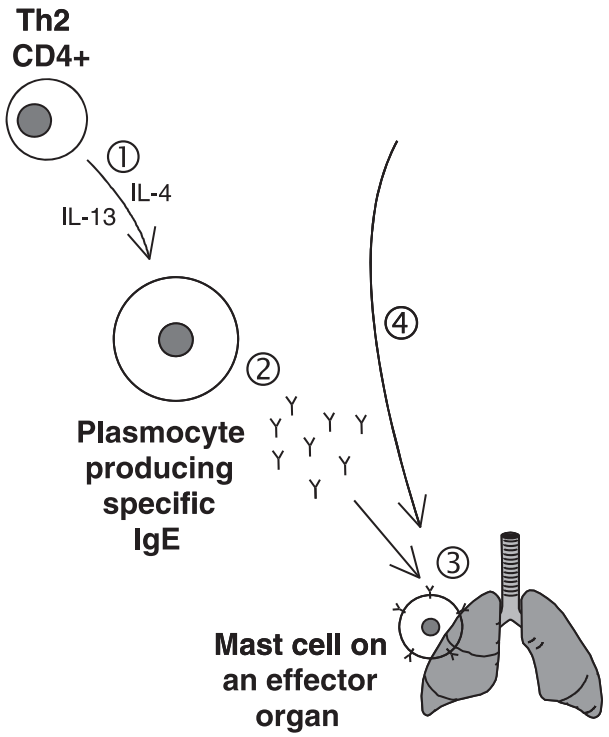

Fig. 2. Schematic representation of an IgE-mediated reaction. (1) Antigen-specific, Th2-type lymphocytes will secrete IL-4 and IL-13 promoting specific IgE secretion by plasmocytes. (2) IgE will circulate in the serum and (3) bind to organ-resident mastocytes. (4) Subsequent ingestion of the food antigen will directly provoke mast cells degranulation after binding of the antigen to mast cell bound IgE antibodies.

cutaneous lymphocyte antigen has been found upregulated on food-activated lymphocytes from patients with atopic dermatitis (8), and the mucosal receptor $\alpha 4\beta 7$ in patients with IgE-mediated symptoms, including but not exclusively gut symptoms (9).

Upon reexposure to the food, antigens will activate FCϵRI-bound specific IgE and initiate degranulation of the mast cell. A massive release of vasoactive and inflammatory mediators will occur and result in various symptoms such as the urticaria and broncho-constriction observed in the patient described here. Clinically, this mechanism of food allergy is made apparent by positive IgE tests, as well as by the measurement of mediators released by mast cells and basophils after an anaphylactic reaction. This feature of the allergic reaction could be demonstrated by increased plasma histamine levels after double-blind placebo-controlled food challenges in patients with atopic dermatitis (10), or by *in vitro* food antigen-activated histamine release (11). Recently, a classic but slightly forgotten mediator of anaphylaxis, the platelet activating factor (PAF), has been the subject of some interest. It has been shown in a series of patients that the severity of food-induced reactions was associated with an enzyme regulating the activity of PAF, PAF acetylhydrolase which was found to be significantly decreased in patients with severe or fatal anaphylaxis (12). These findings suggest that intrinsic mechanisms of mast cell or basophil activity might influence the severity of an allergic reaction to foods.

Mice models of intestinal anaphylaxis have also shown that there might be two specific pathways of reactions. FcϵRI, mast cells, histamine and PAF; and an alternative pathway mediated by immunoglobulin G (IgG), FcγRIII, macrophages and PAF (13). However, it is so far unknown how this alternative pathway might be involved in human food-induced anaphylaxis. Recently, it has been suggested in a mouse model that IL-9-mediated mast cell responses have an important role in food allergy (14).

Case 2

A fully breastfed 6-wk-old boy is observed by his pediatrician for blood stains in his feces. The history discloses an unremarkable pregnancy and delivery. Post-natal growth and development were normal. The child is fully breastfed and is not receiving any other food. Bowel movements are otherwise normal and occur usually twice daily. No other gastrointestinal symptoms were noted. The physical examination was normal, in particular the anal margin was without lesions. The pediatrician suspected a cow's milk allergy induced by the minute amounts of cow's milk protein contained in the mother's milk and advised the mother to stop breastfeeding for 4 days. During this time, the infant was receiving an extensively hydrolyzed formula. Breastfeeding

was then resumed with a maternal avoidance diet of cow's milk, resulting in no recurrence of the symptoms. No further investigations were made at this time.

Discussion of the case

In this young infant, the clinical diagnosis made by the pediatrician was cow's milk-induced proctocolitis. This form of milk allergy is provoked by the minute amounts of cow's milk protein present in the mother's milk. In these patients, a rectal biopsy shows chronic inflammation with eosinophilic infiltration. A cow's milk avoidance diet by the lactating mother leads to a rapid resolution of the symptoms. This type of food allergy belongs to the non-IgE-mediated type food allergies, and is called food-induced proctocolitis, or 'breast-milk colitis' (15). Besides food-induced proctocolitis, other eosinophilic diseases of the gut have been increasingly recognized in the last decade (16). These diseases are characterized by infiltration of eosinophils in the mucosa disclosed on endoscopic biopsy specimens (Fig. 3) (17). Infiltration affects not only the esophagus but also, as observed in this case, other parts of the gut. Studies on the pathogenesis of eosinophilic disease suggest a TH2-type response characterized by elevated levels of IL-4, IL-5 and IL-13. IL-5 is the cytokine leading to a recruitment and activation of eosinophils. In experimental models of eosinophilic esophagitis, sensitization leads to over expression of IL-5 and IL-13 (18, 19). The complex cellular mechanisms of eosinophilic diseases are demonstrated by the presence of CD8 lymphocytes within the epithelium in biopsy specimens, suggesting that mechanisms leading to the pathogenesis of these disorders involve only partially TH2-type lymphocytes and eosinophils (20). As a result, the diagnosis of food-related eosinophilic diseases is difficult and cannot rely exclusively on positive IgE or delayed skin tests (21).

Other non-IgE-mediated food allergies comprise the food protein-induced enterocolitis syndrome. These patients, mostly infants, typically present with profuse vomiting after a symptom-free period of 2–6 h after ingestion of the food. Food involved in the original description of this syndrome were cow's milk and soy (22), however, more recently enterocolitis syndromes induced by various solid foods such as grains, fish or poultry have been reported (23, 24). Colonic biopsies in these patients reveal diffuse cell inflammation with plasma cells and crypt abscesses. In some cases, eosinophilia and focal erosive gastritis and esophagitis were also found (25). In addition, the presence of circulating memory cells disclosed by positive lymphocyte transformation tests suggests involvement of T cells in the pathogenesis of this disease (26), as well as the secretion of tumor necrosis factor α by activated lymphocytes (27). Finally, patients may present with a clinical diagnosis of food-induced enteropathy. Non-specific inflammation of the gut mucosa such as lymphonodular hyperplasia of the duodenal bulb and lymphoid follicles with an increased number of γ/δ T lymphocytes has been shown in these patients, but without identification of a clear pathogenic mechanism (28).

Case 3

The 18-month-old boy, described in case number 1, is observed again at age 3 for a follow-up food challenge to milk. His history discloses that he had a negative challenge to cooked egg but that he has had a recent accidental ingestion of raw egg contained in a dessert. No accidental ingestion of peanut has occurred so far, and as specific IgE titers to peanut remained at similar level to those at diagnosis, no peanut challenge was performed. However, his specific IgE to milk decreased to 2.3 kU/l and a follow-up challenge to milk was done. The child was able to drink a total of 240 ml of milk without any symptoms, attesting that he had outgrown his milk allergy.

Discussion of the case

It is well known to clinicians that the natural history of food allergy is dependent on the food the patient was diagnosed allergic to. Prospective and retrospective studies have shown that patients with cow's milk allergy tend to loose their allergy mostly within childhood (29, 30). Similarly to milk, egg allergy is often outgrown during childhood (31). However, the natural history of other foods such as peanuts is different, as only 15–20% of patients diagnosed with peanut allergy will naturally outgrow there clinical reactivity to the food (32, 33). It has also become recently evident that the natural history depends on prognostic factors such as the initial titer of specific IgE. In addition, clinical studies show that the decrease of specific IgE titers accompanies tolerance acquisition in food allergic children.

Although the mechanism of tolerance to food is not completely understood, it is suspected that T-regulatory cells are involved in tolerance acquisition (Fig. 4). Animal models have shown increased levels of IL-10 and transforming growth factor (TGF)-β secreted by T cells

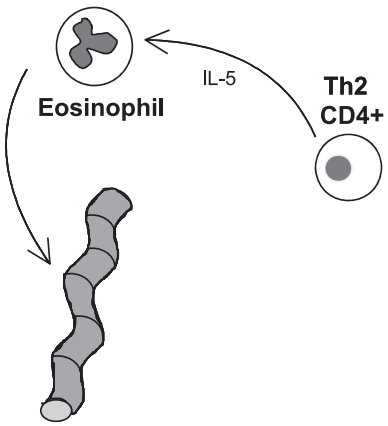

Fig. 3. Schematic representation of an eosinophilic food allergy. After the initial sensitization by the antigen, antigen-specific Th2-type lymphocytes will secrete IL-4, recruiting and activating eosinophils.

isolated from food tolerant mice when compared to cells from allergic mice (34). Human studies reinforce the hypothesis for a key tolerogenic role of regulatory T cells, as children having outgrown food allergy with mostly gastroenterologic symptoms, have increased number of $CD4^+CD25^+$ T-regulatory cells in their gut mucosa (35). Clearly, promoting the IL-10 rich environments in the gut seems to be an option to prevent or even treat food allergy. Various studies have been performed in animal models of food allergy. Recently, we demonstrated that food allergy could be prevented by administering either an IL-10 secreting *Lactococcus lactis* (36) or an avirulant *Salmonella typhimurium* strain promoting IL-10 secretion in the gut (37). These studies suggest a key role for regulatory T cells. Similarly, helminths generating IL-10 in the gut could prevent sensitization to foods in mice (38).

Sensitization to specific epitopes will also play an important role in tolerance acquisition mechanisms as patients with milk allergy most often are sensitized to casein and patients with egg allergy have an epitope-specific pattern of IgE antibodies (39, 40). However, it is so far unclear why specific epitopes may predispose to a more prolonged natural course of the disease.

In summary, it is now well recognized that most symptoms of food allergy observed in childhood results from initial antigen recognition in the gut mucosa. However, phenomena leading to tolerance acquisition or to allergy are not well understood yet. In addition, allergic sensitization might result in various types of immune response, i.e. predominantly IgE type symptoms, or eosinophil-driven symptoms or gastrointestinal symptoms probably related to T-cell-driven inflammation. The natural history of food allergy often leads to spontaneous recovery from allergy. T-cell-related regulatory mechanisms are strongly suspected, however, the exact mechanisms leading to a tolerance acquisition are so far unknown.

MCQ

Question 1. Which of the following is **not** true regarding sensitization to foods in infants?

(A) Infancy is a peculiar time window in the immune system for sensitization to foods
(B) Physical barriers such as mucin on the gut mucosa are mature already in early infancy, and contribute efficiently to avoid early sensitization to foods
(C) The innate immune system is suspected to play a major role in modulating the immune response to foods early in life
(D) Secretory IgA promotes clearance of potential food or microbial allergens in the gut

Question 2. Which factor contributing to an IgE-type allergic reaction to foods is true?

(A) Continuous presentation of a food antigen, including by cross-reactivity, is needed in order to have a persistent IgE-mediated food allergy such as peanut allergy
(B) IgE production by gut mast cells is clearly promoted by IL-4 and IL-13
(C) A specific activity of histamine activating factors acetylhydrolase is responsible for the severity of an anaphylactic reaction to foods
(D) In an animal model of intestinal anaphylaxis, FcγRIII was found to be implicated in the pathogenesis of the reaction

Question 3. Mechanisms involved in non-IgE-mediated food allergy, do **not** include:

(A) Eosinophils in gut-related symptoms
(B) Increased cell proliferation in antigen-specific lymphocyte activation tests
(C) Occasional non-specific findings of inflammation in biopsies with increased numbers of γ/δ lymphocytes
(D) MHC class I antigen presentation leading to IgG antibody switching

Question 4. Which one of the interventions could promote tolerance acquisition in a food allergic patient?

(A) Monthly anti-CD25 antibody injections in conjunction with anti-IgE antibodies
(B) Oral administration of slow-releasing micro beads containing IL-10 and TGF-β, that would specifically target gut-resident dendritic cells
(C) Twice yearly titrated food challenges with immunodominant epitopes in egg allergic

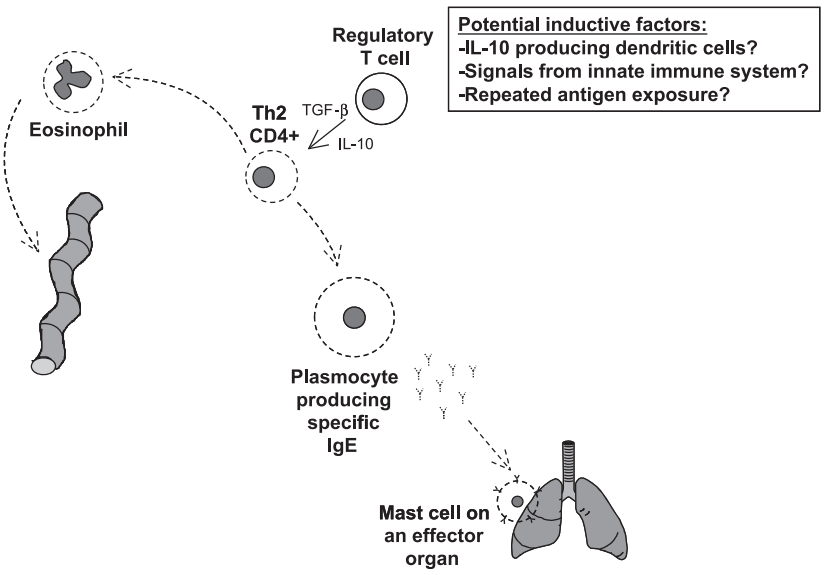

Fig. 4. Potential mechanisms involved in tolerance acquisition to foods. Regulatory T lymphocytes will secrete IL-10 and TGF-β which may down-regulate the immune initially promoting IL-5 secretion and IgE-driven reactions.

individual with a profile by epitope screening for allergy persistence

(D) Gene therapy with a non-pathogenic virus carrying the gene coding for PAFs acetylhydrolase

Answers to MCQ: Question 1, correct response B; question 2, correct response D; question 3, correct response D; question 4, correct response B.

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