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Review article

The interplay between risk and preventive factors explains why some children develop allergies to certain foods and others show tolerance

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Headings: Development of food allergies or tolerance

Abstract

Aim

A number of studies have clarified the tolerance mechanisms and risk factors for food allergies. Our aim was to explore food allergy symptoms by target organs, together with the risk factors and how to prevent food allergies and induce tolerance.

Methods

We carried out a thorough review of studies on paediatric food allergies published in the last decade.

Results

Food allergy symptoms may affect the skin, nasal and oral mucosa, conjunctivae, gastrointestinal tract, or, in severe cases, the respiratory tract and cardiovascular organs. Immunoglobulin E (IgE) mediated symptoms appear rapidly after exposure to the offending allergen, whereas non-IgE mediated symptoms are typically delayed. The immunological processes involved in non-IgE mediated allergic reactions are poorly understood, but T cell activation is probably involved. There are several factors that influence the food sensitisation process: genetic predisposition, disruption of oral tolerance development, impaired skin barriers in atopic eczema and the influence of microbiomes.

Conclusion

The symptoms and intensity of reactions vary considerably with regard to food allergies and these depend on the individual's concomitant immunological and regulatory mechanisms. There is strong evidence that dietary diversity is important for children, even when they come from families with high allergy risks.

Key notes

- This review explored food allergy symptoms by target organs, together with the risk factors and how to prevent food allergies and induce tolerance.
- Studies published in the last decade showed that symptoms and reactions varied considerably and these depended on the individual's concomitant immunological and regulatory mechanisms.
- The literature provides strong evidence that dietary diversity is important for children, even when they come from families with high allergy risks.

Key words: Food allergies, immunological processes, regulatory mechanisms, symptoms, target organs

INTRODUCTION

Food allergies are one of the most common chronic diseases in children and an important public health problem in many western countries. It has been estimated that they affect approximately 1% to 10% of children in developed countries (1) and that they are highest in children under the age of two, then decrease due to spontaneous recovery (2). The 2014 European guidelines define food allergies as adverse reactions to food mediated by an immunologic mechanism, involving specific immunoglobulin E (IgE) mediated mechanisms, non IgE cell-mediated mechanisms or a mixture of the two (3). One individual may be allergic to one or more foods, although allergic reactions are always antigen specific and directed against a specific allergen structure of a specific food. The type of symptoms, and the intensity of the reactions, vary considerably, depending on the immunological mechanisms and concomitant regulatory mechanisms of the individual. The aim of this review was to describe symptoms of food allergies by target organs and to provide an overview on advances in research of tolerance induction, risk factors and prevention of food allergies in children, with special reference to IgE mediated food allergies.

Classification of food allergies

Food allergy symptoms appear when allergens meet specific immune structures, namely antibodies or leukocytes, directed against the specific allergen in the blood stream or at border surfaces of the human body. According to European guidelines, food allergies have traditionally been divided into IgE mediated and non IgE mediated disorders (4) and these two forms may often coexist (1). IgE mediated symptoms appear rapidly after exposure to the offending allergen, when allergen specific IgE binding leads to the release of a mediator, such as histamine, from mast cells (5). Non IgE mediated symptoms typically occur after delay of a few hours or days. The immunological processes involved in non IgE mediated allergic reactions are poorly understood, but T cell activation is probably involved.

Symptoms of food allergies

In clinical practice, an approach based on the symptoms and characteristics of the patient is often the most feasible method (Figure 1). The symptoms of food allergies may be local or generalised and the same patient may present with one or more symptoms. Symptoms may affect the skin, nasal and oral mucosa, conjunctival surfaces, gastrointestinal tract or, in the most severe forms, the respiratory tract and cardiovascular organs. There are large variations in symptom severity between, and also within, patients. The occurrence of symptoms depends on the individual amount of allergen exposed and in some patients even a minor amount of allergen may cause severe anaphylaxis. Some symptoms are easy to recognise objectively, whereas others are more subjective. In addition, other allergic diseases, such as asthma and atopic eczema, are common in children with food allergies, probably due to a genetic background (6).

Skin is the organ that is most commonly affected by food allergy symptoms, with large variations in symptom characteristics (Figure 1). Skin symptoms that occur rapidly after exposure to the allergen, such as acute urticaria, angioedema, flushing and itching, are typically IgE mediated. Contact dermatitis is considered to be a delayed, cell mediated symptom (1). In contrast, worsening of atopic eczema may occur rapidly due to IgE mediated mechanisms or delayed, probably due to cell mediated mechanisms.

Gastrointestinal symptoms associated with food allergies are diverse and form a heterogeneous group of clinical phenotypes (Figure 1), whose characteristics vary according to the pathomechanisms of the specific clinical syndrome. Pathomechanisms are often poorly understood and the symptoms of different phenotypes can overlap (1). The most common rapidly occurring symptoms are abdominal pain, nausea and vomiting, which may be signs of severe allergic reactions. Itching of the mouth and throat is not usually a sign of a severe reaction, but an indication of cross-reactivity due to a pollen allergy, and these symptoms are caused by structural similarities between allergenic proteins of pollens and foods. Interpreting delayed gastrointestinal symptoms is challenging due to their subjective nature. For example, tearfulness and various abdominal symptoms are common in small children, but they are most often caused by other reasons than food allergies (7).

Immediate, IgE mediated conjunctival and respiratory symptoms can also be associated with food allergies. In contrast, chronic allergic respiratory symptoms, such as allergic rhinitis or asthma, are rarely related to food allergies. If they are present, respiratory symptoms associated with food allergies are usually seen in association with generalised allergic reactions, including anaphylaxis. Severe respiratory symptoms may be presented as inspiratory stridor, due to laryngeal swelling, or wheezing, due to small airway obstruction. Unstable asthma significantly increases the risk of airway obstruction and fatal anaphylaxis (8).

Anaphylaxis associated with food allergies is an intensive, rapidly progressing, generalised allergic reaction that is most commonly IgE mediated and may be fatal without immediate treatment (9). The first presenting symptoms may include warming of the skin, erythema and redness, tachycardia and as feeling of swelling in the throat. Symptoms may rapidly progress, with increasing angioedema and extension of urticaria, worsening of difficulty breathing and pallor. Final stages include a drop in blood pressure and cardiac arrest. Fear of life-threatening reactions caused by anaphylaxis has been shown to reduce the quality of life among children with food allergies and their families (10).

The development of oral tolerance

Despite extensive research, the exact pathomechanisms of food allergies are still unclear. However, it seems evident that either failure in the development of tolerance or the breakdown of existing tolerance is probably involved in this process (11-12). Each antigen has to be specifically identified and accepted by the immune system to enter the human body. A default result in case of food antigens is the induction of tolerance, whereas potentially pathogenic micro-organisms, such as viruses or pathogenic bacteria, should induce a protective inflammatory response. Oral tolerance can be defined as immunologic hypo-responsiveness to a prior fed antigen in subsequent contacts with the same antigen. According to the multi-phase model presented by Pabst and Mowat, cluster of differentiation (CD)103⁺ dendritic cells that initially meet food antigens at the intestinal mucosa translocate to the regional lymph nodes of the omentum (11) (Figure 2).

There these cells initiate transforming growth factor beta dependent differentiation of antigen specific forkhead box protein 3 transcription factor regulatory T cells. During the third phase these cells begin, under the influence of retinoic acid, to express proteins, namely chemokine receptor 9 and $\alpha 4\beta 7$ -integrin, which direct them back to the small intestinal mucosa, the lamina propria. The fourth phase involves an interleukin 10 associated proliferation of these antigen-specific regulatory T cells. Thereafter, some of these cells exit the lamina propria via lymphatics and are distributed throughout the body's immune system in order to maintain tolerance to that specific antigen.

Risk factors for sensitisation

Potential risk factors for allergic sensitisation are the same factors that are involved in the development of normal tolerance. In addition to genetic predisposition, early life factors such as diet, including breast feeding and when solid food are introduced, the composition of normal bacterial flora and exposure to pathogenic micro-organisms and antibiotics are particularly involved in the sensitisation process (13). An obvious initial origin of sensitisation in the body is the gastrointestinal mucosa, in which cells involved in immune defence are in direct contact with food allergens. However, an alternative hypothesis has been presented, that suggests that dermal contact of food antigens is the major route of sensitisation (14).

Sensitisation against food allergens, and the subsequent development of food allergies, has usually occurred during the first year of life. The initial contact between food allergens and the child's immune system occurs during pregnancy and minor traces of food antigens also enter the gastrointestinal tract of the child through breast milk. Larger exposure to food antigens occurs after the introduction of solid foods into the child's diet (15). A maternal avoidance diet during pregnancy or breast feeding is not an effective way to prevent food allergies in offspring (16). There is an evidence-based consensus that states that exclusive breastfeeding after six months of age does not prevent or decrease the risk of a child developing food allergies (17). However, breast milk contains a significant amount of immunologically active factors that potentially promote the development of tolerance (18). There is no doubt that breast milk plays an important role in the

maturation of the gastrointestinal tract and in the overall wellbeing of the child, including the mother-child interaction. According to the general nutritional guidelines, the timely introduction of solid foods, starting at the age of four to six months, is also important. The risk of sensitisation and subsequent development of food allergies has been reported to be lowest among the children who start solids early and whose diet is diverse during the first year of life (19-20).

The living conditions of people in the western world have undergone fundamental changes during the last few decades. One study reported that atopic eczema was rare among the children living in traditional agricultural communities (1.3%), when compared to children living on modern farms (7.6%) or those not living on a farm (12.1%) (21). These findings support the hygiene hypothesis, which suggests that early microbial exposure decreases the risk asthma or allergies developing (22). It seems probable that colonisation of the gastrointestinal tract and changes in microbiomes are significant factors that also contribute to the development of tolerance against food allergens. The latter may be related to specific bacterial classes, such as Clostridia and their metabolic products directing immune responses, especially short-chain fatty acids (23). Likewise, unfavourable changes in microbiomal composition, for example due to antibiotics, may correlate with, or even predispose, children to food allergies (23). The possible influence of manipulating microbiomes, for example by probiotics, in preventing food allergies is currently unclear. There is some scientific evidence that certain strains of probiotics might prevent atopic eczema among high-risk patients (24).

Associations between food sensitisation, food allergies and atopic eczema have been shown in both selective and population-based studies (25). For example, more difficult and more chronic eczema has been associated with a higher probability of food allergies. In infancy, food allergies are a common activating factor for atopic eczema and it has commonly been considered that the food allergy is causing the eczema. However, atopic eczema often precedes the onset of food allergies, supporting the hypothesis that atopic eczema is the risk factor for food allergies and not vice-versa (14, 25). Newborn skin pH remains higher for a couple of weeks after delivery, at about six, after which the pH decreases to about five during the subsequent weeks or months. Elevated

skin pH may indicate many adverse influences to the skin, such as decelerated repair of the skin barrier after minor injuries, decreased skin surface cohesion, susceptibility to inflammation and colonisation with pathogenic microbes such as *Stafylococcus Aureus* (26). Although homeostasis improves with age, newborn skin is especially vulnerable to the adverse influences of environmental factors.

Individual influences of risk factors

The genetic background of the child determines whether the influence of various risk or preventive factors lead to the development of tolerance, sensitisation or clinical food allergies. The influence of a specific environmental factor in the disease process may vary between individuals and this variation is called the gene-environment interaction and the regulation of gene expression or epigenetics.

A study by Hong et al noticed that breastfeeding increased the risk of sensitisation against food allergens, but only among the children carrying the specific functional gene variants of β -1 receptor of interleukin-12, toll-like receptor 9 and thymic stromal lymphopoietin (27). These gene variants participate in the development of the balance of T helper 1 and T helper 2 cells, which is important in allergies. Liu et al studied the association between umbilical blood vitamin D concentrations, food sensitisation and the risk of food allergies in a cohort of more than 600 children (28). The authors also studied if genetic background modified this association, in other words if the association between sensitisation and vitamin D concentration differed by the genetic background of a child. The results showed a significantly increased risk of sensitisation among the children with low vitamin D levels, but only among the children with favourable risk gene composition.

Skin barrier dysfunction is an important risk factor in food specific sensitisation and food allergies. One study found that children with increased transepidermal water loss after birth had an increased risk for food allergies by the age of two years, irrespective of whether they developed atopic eczema or not (42). Filaggrin is a skin epidermal protein that is associated with barrier function and strengthens and tightens the stratum corneum layer of skin, thus preventing water

evaporation and decreasing the permeability of harmful antigens through the skin (29,30). Filaggrin loss of function mutation can be found in up to half of the patients with moderate to severe atopic eczema. It has been suggested that this mutation is associated with sensitisation to food antigens through the skin, with exposure at home occurring through the hands, kitchen table or house dust (14,29). On the other hand, this association was limited to peanuts in a study from Sweden (44). Another study showed that the risk of peanut sensitisation among children with filaggrin loss of function mutation was significantly increased in a dose-dependent manner (29). These findings support the hypothesis that oral allergen exposure in early life induces tolerance, whereas skin exposure may increase the risk of sensitisation when a skin barrier defect is present (14,31,32).

Is prevention of IgE-mediated food allergy possible?

The ultimate goal of both the prevention and treatment of food allergies is to induce persistent tolerance. This may be achieved by either primary prevention, before the original sensitisation, or by secondary prevention or treatment after sensitisation. Some studies have suggested that there is an optimal time window in the maturation of the gut associated lymphoid tissue after birth to face food antigens and develop tolerance (33-34). It is possible the gastrointestinal immune system can be reprogrammed throughout life (13). Intervention studies have brought significant new knowledge on the role of early nutrition in the prevention of food allergies (35).

In a study from Australia, 49 children with moderate to severe atopic eczema who were enrolled at four months of age and received egg powder by four to eight months onwards had about a 30% lower risk of developing an egg allergy by the age of one year, when they were compared to the 37 children receiving a placebo rice powder (36). A later paper from the same team reported that the children who developed symptoms when they ate eggs had already demonstrated an abnormal T helper 2 skewed immune response against several allergenic proteins in eggs before their first egg consumption (37). In addition, having this abnormal Th2 response at the age of four months predicted the development of an egg allergy by the age of 12 months. The infants' responses weakened by age and they were not influenced by the egg powder intervention. This study shows

that introducing eggs into the infants' diet at the age of four to eight months did not increase the risk of an egg allergy, even among high-risk children. It also points out that immunological processes leading to the development of food allergies may begin before the specific food item has been introduced to the diet.

The Learning Early about Peanut Allergy study provided convincing evidence that peanut allergies could be avoided by high-risk children if peanuts were introduced into their diet at an early stage and that avoiding peanuts increased the risk (35). In this study, 640 children aged four to 11 months of age with severe atopic eczema or egg allergies were randomised to receive either peanuts or a placebo until the age of five years. The children most sensitive to peanuts were excluded from the study. The children with minor skin prick reactions, and children not sensitised to peanut, were randomised separately. At the age of five years only 1.9% of children with a negative skin prick test for peanuts who received peanuts and as many as 13.7% of those who avoided peanuts had developed a peanut allergy. The respective figures for children with minor skin prick reactions against peanuts at baseline were 10.6% in the peanut group and 35.3% in the placebo group. The results of this study led to a rapid response by an international working group, which promptly published recommendations for the early introduction of peanuts into the diets of high-risk children living in countries with a high prevalence of peanut allergies (38). Consumption of peanuts and other nuts is also increasing in Scandinavian countries and it is not thought to be appropriate to avoid these allergens just in case.

The population-based Enquiring About Tolerance study from the UK evaluated whether the introduction of allergenic foods, such as peanuts, eggs, cows' milk, fish, wheat and sesame seeds, at the age of three months would be effective in preventing food allergies by the age of three years (39). Researchers recruited 1,303 children who had been exclusively breastfed until three months of age to the study. The control group was advised to follow general UK guidelines on exclusive breastfeeding until the age of six months. In an intention-to-treat analysis, food allergies developed in 5.6% of the children in the intervention group and in 7.1% of those in the control group, but the difference was not statistically significant. The challenge of that study was that less than half of the

children were able to follow the intervention diet protocol to introduce at least five of the allergenic food items by the age of six months. The per-protocol analysis revealed that the development of food allergies was, in general, significantly less common in the intervention group (2.4%) than in the control group (7.3%) ($p=0.01$). For single food items, similar results were found for peanuts (0% versus 2.5%, $p=0.003$) and eggs (1.4% versus 5.5%, $p=0.009$), respectively. An important finding of that study was that the early introduction of solid foods did not have negative effect on breastfeeding. The percentage of mothers who were breastfeeding at the age of six months was 97% in the intervention group and 98% in the control group (40).

CONCLUSION

The organs most commonly affected by food allergies are the skin and gastrointestinal tract, but conjunctival and respiratory symptoms may also be present, especially in immediate type reactions. In the last decade, major progress has been made in understanding the symptoms and mechanisms of food allergies in children. This new information has led to major changes in prevention and treatment guidelines for food allergies. However, many there are still many unanswered question in this field and further research is essential.

FINANCE

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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List of abbreviations:

IgE Immunoglobulin E

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Figure legends

Figure 1. Food allergy related symptoms and their mechanisms. FPIES, food protein induced enterocolitis syndrome; FPE, food protein-induced enteropathy; FPIAP food protein-induced allergic proctocolitis.

Figure 1. Photograph by Petri Kulmala of his own child.

Figure 2. Simplified model for the development of oral tolerance modified from the model presented by Pabst and Mowat (11). First, the CD103⁺ dendritic cell migrate to the regional lymph node of the omentum after the initial contact with a food antigen in the M-cells of the small intestinal mucosa. Second, these cells initiate the transforming growth factor β dependent differentiation of antigen-specific FOXP3⁺ regulatory T cells. Third, retinoic acid induces the expression of proteins, chemokine receptor 9 and $\alpha 4\beta 7$ -integrin, on the surface of the antigen-specific regulatory T cells to direct these cells to the intestinal mucosa (lamina propria). The fourth phase includes the cytokine IL-10 driven local proliferation of these cells. Thereafter, some of these cells leave the lamina propria via lymphatics and spread throughout the immune system in order to maintain systemic tolerance to their specific antigen.

CD, cluster of differentiation; TGF- β , transforming growth factor β ; FOXP3, forkhead box protein 3; chemokine receptor 9; IL-10, interleukin 10.

Figure 1.

Figure 2.