

# Food allergy in children

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## SUMMARY

Food allergy represents a highly up-to-date and continually increasing problem of modern man. Although being present in all ages, it most often occurs in children aged up to three years. Sensitization most often occurs by a direct way, but it is also possible to be caused by mother's milk, and even transplacentally. Predisposition of inadequate immune response to antigen stimulation, reagenic or nonreagenic, is of non-selective character so that food allergy is often multiple and to a high rate associated with inhalation and/or contact hypersensitivity. Also, due to antigen closeness of some kinds of food, cross-reactive allergic reaction is also frequent, as is the case with peanuts, legumes and tree nuts or cow's, sheep's and goat's milk. Most frequent nutritive allergens responsible for over 90% of adverse reactions of this type are proteins of cow's milk, eggs, peanuts, tree nuts, wheat, soy, fish, shellfish, crustaceans, and cephalopods. Allergy intolerance of food antigens is characterized by a very wide spectrum of clinical manifestations. Highly severe systemic reactions, sometimes fatal, are also possible. The diagnosis of food allergy is based on a detailed personal and family medical history, complete clinical examination, and corresponding laboratory and other examinations adapted to the type of hypersensitivity and the character of patient's complaints, and therapy on the elimination diet. A positive effect of elimination diet also significantly contributes to the diagnosis. Although most children "outgrow" their allergies, allergy to peanuts, tree nuts, fish, shellfish, crustaceans, and cephalopods are generally life-long allergies.

**Keywords:** food allergy; children; prevention; treatment

## INTRODUCTION

Food allergy represents an up-to-date and continually increasing medical problem [1-4]. It is considerably more pronounced in the developed compared to developing countries [5, 6]. It is seen in 2-8% of children, mostly infants and small children [4, 5, 7, 8, 9]. The disorder is mainly of transitory character and primarily develops in genetically predisposed infants, particularly those in the first six months after birth and non-breast milk fed [5, 10, 11, 12]. The additional risk factors involve hereditary IgA deficit, formula feeding or supplementation in the first days after birth, non-adopted cow's milk diet of infants, too early or too late introductions of solids, vitamin D deficiency, cesarean section birth, as well as frequent gastrointestinal infections in the earliest age [4, 5, 10, 13, 14, 15]. Sensitization most frequently develops by a direct route, but it is also possible to occur due to mother's milk, and even transplacentally [1, 14, 16-19]. Predisposition of inadequate immune response to antigen stimulation is of non-selective character, therefore nutritive allergy is often multiple and in a high rate associated with hypersensitivity due to inhalation and/or contact [20, 21]. Also, due to antigenic closeness of some food types, cross-reactive allergic reaction is also frequent, as is the case with cow's, sheep's and goat's milk, peanuts, legumes, and tree nuts [6, 20]. The

most common food allergens responsible for about 90% of adverse reactions of this type are the proteins of cow's milk, eggs, peanuts, tree nuts (walnuts, hazelnuts, almonds, etc.), soy, wheat flour, fish and marine mollusks, crustaceans and cephalopods (shells, crabs, squids) [1]. Significant allergens include berries and citrus fruit, honey, sesame seeds, but also many other foods and their additives [4, 22]. According to the data from the USA and Western Europe, the leading causes of food allergy in childhood are cow's milk proteins (2.0-3.5%), eggs (1.3-3.2%) peanuts (0.6-1.3%), fish (0.4-0.6%) and tree nuts (0.2%) [1, 20, 23].

Allergy to food proteins occurs as the result of a defect or insufficiency of T-cell suppression and initiation of one or more hypersensitive immune reactions occurring as the response to antigen stimulation [24]. According to the classification by Coombs and Gell, allergic reactions are differentiated into the following four basic types: IgE-mediated or reagenic (I), cytotoxic (II), immunocomplex (III), and T-cellular (IV) [21].

## CLINICAL MANIFESTATIONS AND DIAGNOSTICS

Food allergy is characterized by a wide spectrum of clinical manifestations (Table 1) [1, 3, 20, 23]. Most severe IgE-mediated systemic

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**Table 1.** Basic manifestations of allergy to food proteins

Type of allergy	Manifestations
Cutaneous	Urticaria, Quincke's edema, perioral erythema, atopic dermatitis
Gastrointestinal	Gastroesophageal reflux, eosinophilic esophagitis, gastritis and enteritis, abdominal colics, protein-sensitive enteropathy, enterocolitis induced by food proteins, proctitis/proctocolitis, chronic constipation
Respiratory	Rhinitis, laryngeal stridor, obstructive bronchitis, pulmonary hemosiderosis (Heiner syndrome)
Systemic	Anaphylactic shock
Other	Otitis media, hyperactivity, insomnia, arthritis

reactions, sometimes lethal, are also possible [3, 21, 23]. Although peanuts are responsible for anaphylactic shock to food in over 50% of cases, it should be kept in mind that it can be also provoked by other highly allergenic foods, including those outside of that list. According to the rapidity of manifestation, i.e. type of hypersensitivity, adverse events can be early (reaginic) or late (nonreaginic) type [23]. After ingestion of allergens, reaginic changes manifest themselves within a couple of minutes to two hours, while nonreaginic ones appear later, usually after 36–48 hours, even with a delay of up to one week [1, 23]. Although most frequently occurring during the first few minutes after allergen intake, the occurrence of severe reaginic reactions, including anaphylactic shock, is possible even after several more hours. In addition, nonreaginic reactions, particularly T-cells, can remain non-manifested even after one to two weeks after exposure. Cutaneous and gastrointestinal complaints are seen in most patients, while symptoms of other systems are less frequent [21]. If viewed from the pathogenic aspect, reaginic type of hypersensitivity is more frequent than nonreaginic, as well as combined compared to isolated [21].

Allergy to cow's milk proteins represents the most frequent clinical entity within the frame of the so called "protein-sensitive syndrome" that occurs in early childhood [1, 20, 23]. Clinical expression is dominated by cutaneous changes (eczema, perioral erythema, urticaria, Quincke's edema) and allergic proctocolitis [20, 23, 25, 26, 27]. Besides eczema, allergic proctitis/proctocolitis is the earliest type of allergy to cow's milk proteins [20, 25, 26]. Gastroesophageal reflux, constipation and abdominal colic belong in the frequent manifestations of allergies to cow's milk antigens, while others are far less frequent or exceptionally rare [25, 28]. The only sign of allergy to cow's milk proteins can sometimes be a refusal of milk products or sideropenic anemia resistant to oral application of iron. Although much rarer, allergy to cow's milk proteins can be also seen in later childhood [1, 20, 23, 29]. Additionally, it should be kept in mind that identical adverse reactions, parallel with cow's milk proteins or separately, can also be caused by antigens of other foods.

Allergic proctocolitis/proctitis is the result of type IV hypersensitivity [3, 21]. It usually occurs within the first three months after birth. Sensitization occurs through breast milk in 60% of cases, while 50–65% of patients are

sensitized by the proteins of cow's milk [19, 21, 29, 30, 31]. It is characterized by chronic mucoid-hemorrhagic diarrhea, usually without child's failure to thrive [21, 25, 30]. In a smaller number of patients rectal bleeding is not associated with diarrhea. Cases with a longer-lasting disease develop sideropenic anemia [25].

Protein-sensitive enteropathy represents a severe clinical type of allergy to cow's milk proteins, but rarely to other foods (wheat flour, soy, eggs, rice, chicken) [20, 25, 29]. It occurs during the first months after birth as the consequence of type IV hypersensitivity [25]. It is manifested by chronic nonhemorrhagic diarrhea, failure to thrive, and sideropenic anemia [25]. In cases not treated in a timely manner, malabsorption syndrome with global malnutrition, and sometimes exudative enteropathy, develop [25]. By histological examination of small bowel mucosa, infiltrative or infiltrative-destructive enteropathy identical to that of celiac disease is registered [25, 32].

Enterocolitic syndrome induced by food proteins usually occurs during the first months after birth, mostly within the first three months, but it is not rare even later than that [3, 29]. In children of the youngest age the basis of disorder forms the nonreaginic type of hypersensitivity to cow's milk proteins and soy, and in older children to protein components of wheat, rye and oat flour, eggs, chicken, turkey, peanuts, fish, and other foods [1, 3, 21, 29]. It is manifested by allergen-induced vomiting, irritability, abdominal distention, and nonhemorrhagic or hemorrhagic diarrhea. As it primarily affects young infants, it is often complicated by dehydration and in untimely recognized cases failure to thrive and sideropenic anemia [1, 21, 29].

The diagnosis of allergy to food proteins is based on a detailed personal and family history, complete clinical checkup and adequate laboratory and other examinations adapted to the type of hypersensitivity and the character of patient's complaints [1, 3, 21, 23]. In all patients with chronic diarrhea it is necessary to exclude other causes, while in those with milk intolerance, the deficit of lactase activity as well [1, 20, 33]. Also, in infants with chronic diarrhea, celiac disease with early clinical expression should be kept in mind [34]. In order to confirm reaginic hypersensitivity to food proteins it is necessary to carry out a skin test and/or determine the serum level of specific IgE antibodies [1, 3, 23, 25]. The finding of a larger number of eosinophils in the peripheral blood smear is also of a supportive diagnostic significance. For a reliable confirmation of allergic proctocolitis, protein-sensitive enteropathy, and eosinophilic esophagitis it is necessary to perform endoscopy with biopsy and pathohistological examination of mucosa samples [1, 3]. Withdrawal of complaints after elimination diet is an essential contribution to the diagnosis [1, 3, 20].

## PREVENTION

In the prevention of food allergy, exclusive breastfeeding plays a key role during the first four to six months after birth, as well as the continuation of breastfeeding up to the end of the first year and even longer, while other

procedures done with this goal, such as elimination of highly allergenic foods during pregnancy and lactation and introduction of nondairy foods only after completed six months are not justified [1, 2, 3, 23, 35-39]. According to the up-to-date researches, this also refers to the prophylactic-therapeutic application of probiotics, prebiotics, and  $\omega$ -3 long-chain polyunsaturated fatty acids [3, 23]. Also, according to the current standpoints, after completed six months, neither specific elimination procedure decreases the risk of allergy [37, 39]. There are also opinions based on relevant studies that such approach is not only senseless but also counterproductive [2, 38, 40]. Breastfeeding, during the introduction of complementary/solid foods started four to six months after birth and in high-risk infants, i.e. in those with proven allergy in one or more first-degree relatives, is of exceptional significance in the development of antigenic tolerance [2, 38]. For high-risk infants who cannot be exclusively breast-fed, in order to prevent sensitization to cow's milk protein or soy, infant formula based on a protein hydrolysate, primarily extensive, is recommended until the age of four to six months [2, 23, 37, 39].

## TREATMENT

Elimination diet constitutes the basis of the therapy for allergy on food proteins [1, 3, 23]. In addition, in more severe cases it is necessary to use antihistaminic and in the most severe ones adrenaline, glucocorticoids, inhalation beta-agonists, and other measures [3, 21, 23]. In a child sensitized through the mother's milk, a corresponding elimination diet is advised to the mother [1, 39]. Artificially fed infants allergic to cow's milk proteins are applied infant formula based on extensive protein hydrolysate [1, 3, 20, 23, 41]. Due to a high rate of sensitization (30–50%), soy milk is not advised for infants allergic to cow's milk proteins, particularly for those younger than six months

and with nonreaginic type of hypersensitivity [1, 3, 20, 23]. Besides abovementioned products, there are also formulas based on free amino acids. However, they are primarily intended for feeding children sensitized to extensive protein hydrolysates [1, 3, 20, 23, 25]. Due to numerous nutritional deficiencies, as well as the high risk of cross and subsequent sensitization, goat's and sheep's milk are not used in the dietary treatment of allergy to cow's milk proteins [1, 3, 20].

## PROGNOSIS

As already mentioned, food allergy, accept for peanuts, tree nuts, fish, shells, crabs and squids, which is life-long in 80–90% of cases, mostly represents a temporary occurrence [4]. Thus, for example, 80–95% of children with cow's milk proteins, soy, eggs, and wheat flour allergy out-grow it by the age of five years [20, 21]. As about 50% of infants develop tolerance for cow's milk proteins by completed 12 months of age, this time is considered optimal for tolerance provocation [1]. However, if the child had a more severe type of reaginic hypersensitivity, tolerance provocation for cow's milk with the confirmed absence of specific IgE antibodies in serum can only be done after 12–18 months of elimination diet [1]. If food antigen tolerance has not been established, the provocation is repeated every 6–12 months [1, 20]. Due to the risk of severe allergic reactions, including anaphylactic shock, it is suggested that this procedure should not be performed under out-of-hospital conditions [1]. In cases of allergy to food antigens by type of anaphylactic shock, tolerance provocation is contraindicated [1].

Finally, it should be pointed out that a considerable number of patients with reaginic type of hypersensitivity to cow's milk proteins and other foods can develop asthma and allergic rhinitis in later childhood [23, 42-45].

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### КРАТАК САДРЖАЈ

Алергија на храну је веома актуелан проблем савременог човека који се непрестано увећава. Иако се јавља у свим животним добима, најчешће погађа децу узраста до три године. Сензибилизација најчешће настаје директним путем, али је могућа и посредством мајчиног млека, па чак и преко постељице. Склоност неодговарајућој имунској реакцији, реагинској или нереагинској, на антигенску стимулацију је неселективног типа, те је нутритивна алергија често мултипла и у високом степену удружена с инхалационом и/или контактном хиперсензитивношћу. Такође, због антигенске блискости неких врста хране, честа је и унакрсна алергијска реакција, као што је то случај с кикирикијем, легуминозама и језграстим воћем или крављим, овчјим и козјим млеком. Најчешћи нутритивни алергени, одговорни за више од 90% нежељених реакција овога типа, јесу протеини крављег

млека, јаја, кикирикија, језграстог воћа, соје, пшеничног брашна, рибе и морских мекушаца, зглавкара и цефалопода. Алергијску нетолеранцију антигена хране одликује веома широк спектар клиничких манифестација. Могуће су и веома тешке системске реакције, некад и фаталне. Дијагноза алергије на храну се заснива на детаљној личној и породичној анамнези, комплетном клиничком прегледу и одговарајућим лабораторијским и другим испитивањима прилагођеним типу хиперсензитивности и природи тегоба испитаника, док се терапија заснива на елиминационој дијети. Значајан допринос дијагнози има и позитиван ефекат елиминационе дијете. Мада је алергија на храну код деце у већини случајева пролазна, на неке од намирница, као што су кикирики, језграсто воће, риба и морски плодови, она је најчешће доживотна.

**Кључне речи:** алергија на храну; деца; превенција; лечење

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