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Food Allergy Prevention and Management in Children

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Abstract

Food allergy is a reaction mediated by immunological mechanisms that cause various symptoms in susceptible individuals while harmless in individuals who are not sensitive to the specific allergen. The reactions that take place are divided into three: IgE-mediated reactions, non-IgE-mediated reactions, and mixed-type reactions. While many types of food have the potential to cause allergen reactions, fewer foods are responsible for the most clinically severe reactions and for the majority of reported cases. Food allergy, which is increasingly common worldwide, is becoming an important public health problem. Although there are no clear epidemiological data, the prevalence of food allergy varies between 6-10% in preschool children and decreases to 2-5% in adulthood. Food allergy has long been recognized as a pediatric disease, as most cases tend to begin in childhood and disappear with growth. There is increasing evidence to support the role of early administration of potential food allergens to prevent food allergy. The management process of food allergy cases includes plans and innovative treatment strategies aimed at a personalized approach.

Keywords: Allergic reaction; Food allergy; Child; Management.

1. Introduction

1.1. Definition

Food Allergy is defined as an abnormal immune response developed in the body after allergenic food (plant/animal) is consumed. Abnormal immune response; includes IgE-mediated reactions, non-IgE-mediated reactions, and mixed-type reactions that occur rapidly due to hypersensitivity to the allergen [1]. Food allergy, which can lead to life-threatening reactions as well as impairing the quality of life; occurs due to the potential allergenic effects of more than 170 foods, mainly eggs, cow's milk, peanuts, wheat [2].

1.2. Epidemiology

Prevalence of food allergy is difficult to determine clearly because working study populations, geographic variation, method used in diagnosis, age range and other factors affect studies [3]. It is reported that while the prevalence of food allergy is higher among younger age groups, it decreases with age [4]. If explained numerically, verifiable and diagnosed food allergy prevalence for first 1 year is between 6-10%, while for adults it decreases to 2-5% [5]. The prevalence of food allergies is increasing in our country as well as around the world. To study food allergy prevalence among the pediatric age group, a study has been made in the Eastern Black Sea region with 2739 children ages range between 6-9. Food allergy prevalence verified by the children's skin prick test is 33.1%, the prevalence of food allergy confirmed by nutrient challenge test is 0.8% [6].

1.3. Diagnosis

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Food allergy can be diagnosed by various methods but the first step is history, namely anamnesis. In the skin prick test, which is the most commonly used method in diagnosis, after the nutrient extract is dripped onto the skin area, the average swelling width is measured and tests with a value of ≥ 3 mm are considered positive. Measuring IgE levels with a specific antigen, is another common method used in food allergy diagnosis. If the specific IgE level formed in the body against the allergen is ≥ 0.35 kU/L, the test is considered positive. The oral provocation tests, which can be used in both clinical studies and studies with research purposes to diagnose food allergy, is applied by starting from minimum dose of risky food that is known to not present any reaction and increasing this dose at intervals of 20 minutes on average [3,7].

1.4. Food Allergy Prevention

There are many studies looking for ways to prevent food allergy or reduce the incidence of it among the pediatric age group [7]. Various hypotheses have been developed to explain the reason for the increasing prevalence of food allergies. These hypotheses have been important for the course of current studies made to prevent food allergy. One of the hypotheses claims that low levels of vitamin D is increasing the risk of food allergy development. In a cohort study conducted with 12-month-old infants by HealthNuts in Australia, the deficiency of vitamin D was associated with proven food allergy [8]. It has been shown that vitamin D in food allergy affects various mechanisms that support immunological tolerance like dendritic cells and T regulatory cell function. Prevention programs based on properly prepared dietary supplementation of vitamin D can be beneficial to reduce the development of food allergy [9].

With growing proofs based on the epidemiologic studies, the early introduction of food for food allergy prevention has challenged the idea of avoiding the allergen. In a prospective study about early introduction of food conducted for food allergy prevention, infants who started cow's milk protein formula within the first 14 days upon life, had lower rates of IgE-mediated cow's milk allergy comparing to those who didn't start cow's milk formula. Data from the HealthNuts cohort in Australia showed that infants who started consuming eggs at 10-12 or >12 months had a significantly higher risk of egg allergy comparing to infants who were introduced earlier at 4-6 months [8]. A study examining the early introduction of peanut protein to the diet of children who have a risk of peanut allergy showed that they had an obvious protection comparing to those who avoided peanut protein. 640 infants 4-11 months of age at risk for peanut allergy (severe eczema, egg allergy or both) were randomized into a treatment group (6 g of peanut per week) and a peanut avoidance group. 0.3% of peanut protein consuming group and 17.3% of avoidance group reacted positively against peanut. This result is a widely-confirmed view that children who are at a high risk for peanut allergy may have a greater benefit from consuming peanut protein than avoiding it [7].

A controlled randomized study has been conducted to determine whether the early introduction of allergic foods to breastfed infants is protective against food allergy or not. This study has been conducted in United Kingdom with participation of 1303 infants aged 3 months who were only breastfed. Participants have been randomized into standard introduction or early introduction groups. Standard introduction group consists of only breastfed infants until they are 6 months old and early introduction group consists of infants in whom allergic foods are included in their diet at 3 months of age. Six allergic foods were presented to the participants in the early introduction group who were given skin prick test two times at the beginning: first cow's milk, then random peanut, boiled chicken egg, sesame, white fish and wheat. An open-label incremental food load containing a total of 2 g of protein from that food was applied to infants from early introduction group who had swellings at any size after their first skin prick test. At the end of analysis, allergy development against one or more of these six allergen foods was 7.1% (595 in 42) in the standard introduction group and 5.6% in the early introduction group (567 in 32). In other words, any food allergy prevalence has been found lower in the early introduction group rather than standard introduction group [10].

There is growing evidence that supports the role of early administration of potential food allergens to avoid food allergy. Even though there are questions about when to include allergens effectively and safely in the diet, strategies for early consumption versus avoidance of common food allergens are considered a promising intervention to reduce the risk of food allergies. In the general population, more studies are needed to improve information about how to prevent food allergy [11].

1.5. Food Allergy Management

Clinical management of food allergy includes a lot of treatment strategies to minimize the risk of various reactions that might occur [12].

1.5.1. Elimination diet

Elimination diet, is the removal of the food which contains allergen from diet for more than one week after the responsible allergen is determined in patients with food allergy. A decrease with the symptoms caused by allergen is expected during the period when elimination diet, which is also called elimination/purification process, is applied. When the source of food allergy can't be determined, gradual elimination diets are applied. The first stage in the elimination diet is the removal of foods at high risk for food allergy (dairy products, wheat, oilseeds, seafood, egg, soy) from the diet. If allergic symptoms are still observed after the application, the second stage is started. In the second stage, there are less food that is allowed to consume. If no sensitivity will be observed in the patient for the food allowed to consume in the second stage, symptoms will disappear on the fifth or sixth day of the diet. If there are still observed symptoms, the application is continued by limiting nutritional content [13]. Elimination diets can be associated with increased anxiety and nutritional deficiencies among patients and families. Therefore, liberalizing the diet to consume safe foods that can be tolerated by the patient is very important for increasing the quality of life [14]. In the elimination diets applied, in addition to food allergen, foods containing this allergen should be avoided. For example, if a person is allergic to eggs, he or she should avoid all foods containing eggs (13). At the point where foods contain hidden allergens, food label comes into play. In many parts of the world, all the main food allergens added to recipe must be listed in the food labels. Many packaged foods have a precautionary allergen labelling (PAL) such as "may contain traces of, may contain". But most of the patients do not consider PAL. Existing proofs show that most foods with PAL do not contain enough allergen to trigger reactions in presence of an undeniable risk, whereas foods without PAL contain enough allergen to trigger reactions [15]. Consumers are confused by the food labels that can accurately describe more than 50% of the terms related to a certain allergen. Thus, for people with allergies and their family members "Not suitable" is considered to be the most effective label among the others to deter the purchase of a product [14]. PAL can be used as an important risk management tool in food allergy if its reliability is proven with clear and consistent information about any allergen inclusion and risk of reactions [15].

1.5.2. Cow's milk substitutes

Products that can be used instead of cow's milk for growth and development in infants and young children with cow's milk allergy should be added to the patient's diet. Such formulas must meet the general requirements until the transition to complementary foods in infants under 6 months. Older children may also need these substitutes to ensure adequate caloric intake. Highly hydrolyzed formula, amino acid-based formula, and soy-based formulas are among the long-term and beneficial management strategies. Highly hydrolyzed cow's milk formulas are the first choice to replace cow's milk [12]. Because of the tastelessness of hydrolyzed cow's milk formulas has been associated with low intake of formula in infants fed with this type of formula, particularly in the first year of life, and associated growth problems [9]. Amino acid-based formulas, which are the only completely non-allergenic formulas, can be used in patients who do not respond to highly hydrolyzed cow's milk formulas. Soy formulas cannot be recommended for infants under 6 months of age, given the nutritional assessment of phytate and phytoestrogen content, which reduces the absorption of minerals and trace elements [12].

There is less data about other mammalian milks. Goat milk and sheep milk contain proteins very similar to those found in cow's milk [12]. Diagnosis and Rationale for Action against Cow's Milk Allergy guidelines state that milk allergens cross-reacts in various species of mammals [9]. For this reason, sheep and goat milk is not recommended for patients with cow milk's allergy because of cross-reactivity. Camel, donkey or mare's milk has been shown to be less cross-reactive than goat's milk. It is recommended to choose an appropriate cow's milk substitute by carefully evaluating the age of the patient with cow's milk allergy, coexistence of gastrointestinal symptoms, anaphylactic reaction history, nutritional requirements and economic status [12].

1.6. Education and risk assessment

Risk assessment and education in people at risk of severe reactions play an important role during food allergy management process. The education program offered to people with food allergies should include an individualized management plan that takes into account the many factors that may affect the identification and treatment of reactions. These factors are; the age of the person with food allergy, literacy of the patient and family, type of food allergy, comorbidities and medical support. Within the scope of the training, patient-specific avoidance strategies at home and outside, interpretation of warning signals, use of self-injectable adrenaline, when and how to treat reactions should be explained to the other party. School nurses, teachers, and nursery staff should be trained on food allergy by family physicians and dietitians, within a multidisciplinary clinical approach [12].

1.6.1. Immunotherapy

As a method used in the treatment of food allergy, immunotherapy aims to provide a continuous unresponsiveness to food allergens or increase the threshold value required for the formation of a food induced allergic reaction. Immunotherapy causes various changes in the immune system such as stimulation of Foxp3+Treg cells that produce IL-10 and TGF- β , increase of IL-10 secreting regulatory B cells (Breg) and regulation that reduces Th2 inflammation. Immunotherapy can be administered in different ways, including oral (OIT), sublingual (SLIT) and epicutaneous (EPIT). Epicutaneous immunotherapy is applied by sticking special adhesive devices containing food allergen to the skin surface [7].

In OIT, it is aimed to give the food allergen orally starting from the lowest doses and to provide food allergen tolerance in the following processes. In OIT, allergen and any non-allergen food are mixed in low doses and an insensitivity is provided in the individual over time. Later, the rate of the allergen in the content is increased in accordance with the individual's tolerance. It is followed by 3 phases: the initial phase, the increase or loading phase, and the protection (continuation) phase. The time elapsed between phases varies depending on the individual's tolerance or allergic response. Since the side effects and reactions to be observed after the addition of allergen in the person with food allergy are not completely known, the process must be performed in a hospital environment and with the right treatment protocols [13]. A study has been made by Yeung and his friends in 2012 with in total 196 children (106 treatment and 90 control) to assess OIT method in milk allergy. It was reported that in the general treatment group, 62 of the children could tolerate 200 mL of milk, while in the control group this rate was 8%. It was concluded from the study that successful desensitization to cow's milk was achieved in children, but long-term tolerance was not achieved. According to this review, it has been proven that oral immunotherapy is an effective method to induce desensitization in milk allergy [14]. In a study made by Vickery and his friends in 2017, children were separated in two groups and one of the groups was given daily 300 mg and the other one was given daily 3000 mg of peanut protein orally. At the end of three years, it was determined that allergic reactions related to this allergen decreased in children and this decrease was more significant in children in the 3000 mg group ($p < 0.05$) [13]. OIT is considered to be the most effective immunotherapy method since it elicits a greater tolerogenic active immune response comparing to other immunotherapy options [7].

SLIT follows a protocol in which an allergen is administered sublingually in tablet-drop or food form with gradually increasing doses and then consumed. There are reasons for preferring the treatment because the tolerance of the oral mucosa to inflammatory reactions is high and long-term SLIT reduces the IgE level while increasing the IgG level. This method is considered to be a safer method comparing to OIT since its application is made by lower doses. By applying the gradually increasing amounts of allergen food under the tongue in the first stage, insensitivity to the food is ensured. After reaching the highest dose, with a stable allergen amount, protection phase is continued for a while. In a study observing the effect of SLIT treatment against peanut allergy, 40 individuals were given peanut powder (maximum 10 grams) in increasing doses for 3 years. After the intermediate phase given for 8 weeks, it has been observed that tolerance to the allergen is achieved in approximately 98.0% of individuals after re-exposure to the allergen and long term SLIT application is beneficial in peanut allergy [13]. In a study conducted to examine the effect of SLIT treatment in peach allergy, Pru p3 extract, an important allergen of peach, was placed sublingually. After 6 months of treatment, it has been reported that individuals tolerate higher doses of peach, have a smaller bump size in the skin prick test, and an increased level of specific IgG4 [14].

1.6.2. Pharmacological treatment

Pharmacological strategies that can be applied during food allergy management process, is a treatment option that can be used to prevent worsening or the reappearance of the symptoms. Adrenaline applied after the consumption of allergen food is very important to prevent fatal consequences of anaphylactic reactions, hypotension, shock and other allergic symptoms (urticaria, bronchospasm, edema, gastrointestinal symptoms, etc.). For that reason, it is a specific remedy that can be used as a rescue tool in patients with food allergies. In case of itching and hives, while antihistamines that block specific H1 receptor may also be beneficial, H2 receptor blockers can also be used in the treatment of gastrointestinal symptoms. Personalized pharmacologic treatments are omalizumab containing monoclonal anti-IgE antibody, dupilumab containing anti-interleukin-4Ra, reslizumab containing anti-IL-5 monoclonal antibody and mepolizumab are therapeutic tools used in food allergy. Omalizumab prevents clinical manifestations by binding the Fc region of IgE antibodies and blocking the binding of IgE to Fc γ RI on mast cells and basophils [7].

Complementary and alternative medicines are other alternatives used in the management process of food allergies. Almost 8.4% of Japanese children use complementary and alternative medicines when managing food allergies. Among these medicines herbal tea is used the most (22%), followed by Chinese herbal medicine (18.5%) and lactic acid bacteria (16%). Many studies on this management option has focused on food allergy herbal formula 2 (FAHF-2), which is a type

of a Chinese herbal medicine. Studies have shown the reliability and tolerability of FAHF-2, while presenting data on its immunomodulatory effect. However, none of the studies analyzed the clinical effect of this formulation [14].

Many people with IgE-mediated food allergy are recommended to carry an epinephrine auto-injector (EAI) in case of being exposed to the allergen accidentally. Almost 50% of cases with food allergies don't carry an epinephrine auto-injector with them. Similarly, most of the patients do not have enough knowledge about how to use the epinephrine auto-injector. Repeated instructions may develop individual's epinephrine auto-injector using skill [14].

1.6.3. Nutrition and nutritional supplements

Food allergy appears when there is a disruption in standard tolerance mechanisms. Disruption of tolerance causes adverse immune response reactions against normally harmless food allergen such as cow's milk, eggs, peanut or shellfish. Nutrition plays a key role in the protection, development and optimal functioning of immune cells. Nutritional factors are crucial in maintaining the proper functioning of the immune system by influencing the nature of an immune response [9].

It is unknown whether a "healthy diet" (20% protein, 50% carbohydrate, 30% fat) has an effect on prevention and management of food allergy or not. Today, the Mediterranean diet is used as a representative measure for healthy diet. A reviewing article containing summarized studies of the effects of the Mediterranean diet on allergy prevention demonstrated that, the Mediterranean diet in one study showed a possible increased risk of the infant developing allergic disease, in another study it reduced wheezing and in another study it had no effect on allergy prevention. Although Mediterranean-style eating habits show promising effects by reducing the seen symptoms of asthma/wheezing, it does not have any effect on other allergic symptoms. Therefore, more studies are needed on well described healthy eating criteria to examine its effect on allergy prevention [9].

Children with food hypersensitivity have an increased amount of mastocytes, eosinophils, and neutrophils in their digestive system. Constant exposure to the allergen, may cause chronic inflammatory changes in the mucous membrane and increase in the reactive oxygen species (ROS). Excess ROS must be neutralized by the components of antioxidative barrier. Zinc is an essential trace element and needed for various cellular functions. Zinc is a co-factor of many enzymes, including superoxide dismutase (SOD), which plays an important role in maintaining the oxidative-antioxidative balance. A study of 134 children aged 1-36 months with food allergies demonstrated that these children have a weaker antioxidative barrier due to significantly lower zinc concentrations [9].

The effects of vitamin D on the innate and adaptive immune system have been investigated and expanded. The active vitamin form, which is 1,25(OH)₂ calcitriol, has effects on epithelial cells, T cells, B cells, macrophages and dendritic cells. Vitamin D stimulates innate immune reactions by increasing the production of antimicrobial proteins like cathelicidin. This action plays a role in protecting the mucosal integrity by stimulating connectivity genes. However, the potential effect of vitamin D on the Th1/Th2 adaptive immune response is related to food allergy. Almost all cells of the adaptive immune system express the receptor of vitamin D and this makes them sensitive to the vitamins. Especially considering a potential role for vitamins in food allergy, vitamin D has been shown to affect various mechanisms that support immunological tolerance, such as T regulatory cell function and induction of tolerogenic dendritic cells [9].

Essential fatty acids are important immunomodulators. α -linolenic acid (ALA), an N-3 polyunsaturated fatty acid (PUFA), is converted to eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in the mammalian body, which are then converted into anti-inflammatory preservatives. Studies in this area showed that dietary PUFA supplementation during infancy does not affect the prevalence in food allergy development. However, essential fatty acids, including n-3 PUFAs, can be consumed as part of the normal diet through breast milk, formula and food, or as supplements at any stage of the life cycle, due to their potential role in preventing and treating allergic diseases with proven immunomodulatory effects [9].

1.6.4. Microbiota

The gut microbiota has influences on balancing between allergic sensitivity and immunological tolerance in the gut in several ways. Microbiota is the center to maintain the tolerance state against food antigens. Microorganisms that shape both immune system and also colonize the guts and the skin, affect the maturation of immune system and food tolerance. Sensitivity against food allergy is influenced by both commensal microbiota and also its metabolites. Therefore, environmental factors through the composition of the microbiota is affecting the risk of food allergy. Clostridia species from the human gut microbiota reduce allergic responses and inhibit the development of food allergy by inducing Treg cell formation that suppresses Th2-induced responses or inhibiting systemic absorption of major food allergens. The composition of the gut microbiota may lead to the development of resistance or susceptibility to food allergy in the

individual. Allergic infants have a gut microbiome dominated by Firmicutes phylum, Ruminococcaceae, and Lachnospiraceae. The abundance of Clostridiales species Anaerostipescaecae is associated with the expression of regulatory genes in the intestinal epithelium. Therefore, especially Clostridiastrains exert protective effects against food allergy by inducing Foxp3+Treg lymphocytes. Bacteroidales and Clostridiales strains inhibit food allergy by inducing both GATA-3 Treg cells and RORgamma-t1 Treg cells that suppress IgE [5].

The immunomodulating and antiallergic effects of the gut microbiota are mediated by metabolites produced from dietary fiber fermentation that regulate the pool of intestinal Treg cells. It has been suggested that fiber-rich diets may affect the balance between different strains of commensal bacteria in the gut microbiota [5]. Short-chain fatty acids (SCFA) from metabolites produced from dietary fiber fermentation and bacterial metabolites produced in the human gut play an active role in regulating the immune system in the body. SCFAs increase the regulatory effect of dendritic cells, leading to stimulation of Treg cells. SCFAs can be produced by bacteria after the digestion of dietary fibers. It has been shown that infants on a diet high in fruits and vegetables have a lower risk of food allergies by the age of 2, which may be related to increased dietary fiber intake. Dietary intake of polyunsaturated fatty acids, a factor that may also increase the production of SCFAs by bacteria, has been shown to be inversely associated with childhood atopy susceptibility [1].

The effects of modifiable prebiotics, probiotics and synbiotics on the intestinal microbiota have been the subject of many studies [2]. The Atopic Disease Prevention Guidelines (GLAD) concluded that prebiotic supplementation in infants is likely to reduce the risk of recurrent wheezing and the development of food allergy due to its effect on the microbiome. Probiotics are live microorganisms that are claimed to be therapeutic and preventive for allergic diseases by affecting phagocytosis and the production of proinflammatory cytokines. New guidelines published by the World Allergy Organization (WAO) suggested that probiotics should be recommended to infants and mothers at high risk of allergic disease. The researchers say that this protective effect may be due to the effect of the probiotic on T regulatory cells. When several studies examined dietary management in infants with cow's milk allergy, infants fed a hydrolyzed casein-based formula (eHCF) fortified with the *Lactobacillus rhamnosus* GG (LGG) probiotic showed a higher tolerance gain to allergens compared to those fed a hydrolyzed casein-based formula without any supplement. Researchers say that this protective effect may be due to effect of the probiotic on T regulatory cells. Such a difference may be due to the possible effect of eHCF + LGG on the bacterial community structure on the infant's intestinal surface. More scientific approval is needed to include probiotics and prebiotics in therapeutic approaches [9].

1.7. The role of dietitian

The main goals in the management of food allergy in children prevent the occurrence of acute and chronic symptoms by avoiding foods that might cause allergic reactions, while maintaining optimal growth with an appropriate, healthy and nutritionally balanced diet, under the guidance of a dietitian. Since the cornerstone of food allergy management is avoiding the allergens that causes reactions, patients need to know safely how to notice allergic reactions and how to treat them and also they need to know which allergens should be avoided. For this to happen, various health professionals are needed to be informed. Dietitians can train families and individuals on purposefully identifying responsible foods, interpreting ingredient lists, reading food labels, including risks of cross-contamination, and recommendations for alternative products that meet the child's nutritional needs. During the era of elimination diets, parents need support and advice on appropriate substitutes so that vital nutrients are included in their child's diet and do not jeopardize growth and development. During this process, guidance of a dietitian or a health professional experienced on food allergies is essential [9,13].

2. Conclusion

Food allergy, causes a significant health burden at both the individual and population level worldwide. The increase observed in the incidence of the disease has brought food allergies to a level that has a significant impact on the quality of life of children and their families. While in the past the prevention of food allergy was largely focused on allergen avoidance, there is now interventional evidence to suggest that early introduction of potential allergens may be beneficial in allergy prevention. In line with the latest guidelines published for the prevention of food allergies, it is recommended that allergic foods should not be delayed when complementary foods are introduced and should be included in the diet at the earlier stages of life. More studies are needed to be done to prevent or reduce the incidence of food allergy in pediatric age group.

Personalized strategies must be applied during the process of food allergy management. These strategies must include the prevalence of food allergies in specific countries, eating habits of families and doctor and dietitian support. People with cow's milk allergy, must be attentive about enough nutrient intake when choosing an appropriate hypoallergenic

formula. There are studies on the effect of healthy nutrition and micro-macro nutrients on food allergy. Researching nutrients and other aspects of food preparation in detail is essential to better understand how they can affect the immune system and thus allergy outcomes, and to advise to those who have food allergies.

Studies suggest that for food allergy, immunotherapy applied by various methods might be helpful to increase tolerance. Oral immunotherapy may be useful for IgE mediated food allergy, however it has an important risk of a local and systematic reaction. Generally, specific immunotherapy needs to be done clinically under the supervision of an allergist with expertise in the field. As a long term strategy, more researchers are needed on whether immunotherapy can be presented in daily clinical application or not.

Efforts should be made to establish adequate diagnosis facilities for all patients with food allergies in the world. An elimination diet based on allergy test must be controlled until an obvious improvement in the symptoms is achieved. When preparing an elimination diet based on food allergy test, nutritional integrity of the diet must be examined vigorously.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest.

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