Prevention of food allergies: to eat or to hydrate?

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Abstract

In Western countries, food allergy (FA) is one of the most common chronic diseases in childhood with an increasing prevalence of food-related anaphylactic reactions. Food allergy is associated with a significant health and socioeconomic burden. It is important not only to consider the different impacts of food allergies, but also to try to mitigate this growing epidemic through primary prevention. After focusing on the epidemiology and the multifactorial etiology, this review will give an overview of the current prevention strategies, consisting of dietary recommendations during pregnancy, breastfeeding and infancy, as well as prevention by epicutaneous sensitization.

Introduction

In 2017, 30% of the world's population suffered from allergies. Without preventive measures, the World Health Organization (WHO), predicts that 50% of the population will be affected by allergies by 2050. The atopic march is a representation of the progression of allergic disease with age in patients with a genetic predisposition to atopy and contributing environmental factors (1). Atopic dermatitis (AD) and food allergy (FA) are the first manifestations of the atopic march followed by asthma and allergic rhinitis (AR). Some of the allergic conditions, such as allergic rhinitis and asthma, showed a strong increase in incidence while in the last decade there is a worrying increase in the frequency of FA with a parallel increase in the prevalence of food-induced anaphylaxis (2-7).

Several studies show a large discrepancy between self-/parent-reported and diagnosed FA, using double-blind placebo-controlled oral food challenge (DBPCFC) (4-6). FA is a growing health concern with a high prevalence of 10% in Western countries, with the highest prevalence in infants and young children (7,8). There is also an increasing prevalence in rapidly developing countries (9). In Belgium there are few accurate data on the prevalence of FA and anaphylaxis. In 2009, the Health Council published a prevalence of FA of 6-8% in children under 3 years of age and 2-3% in adults (10). The 2018 Sciensano Health Survey reported that 9% of the population suffered from a food allergy or -intolerance but only 5,2% were diagnosed by a physician (11). The Allergo-Vigilance® network (RAV) analyzed the fatal/near-fatal anaphylaxis cases from 2002 to 2021 in France, Belgium, and Luxembourg (12). Of the 3510 anaphylaxis cases, 70 patients had grade 4 anaphylaxis of which 25 patients died. Food was the main allergen (60%) and in the group of children younger than 16 years the responsible allergens were peanut (24%), cashew nut (13,7%), milk (8,9%), hazelnut (4,3%) and hen's egg (4,1%).

In addition to the increasing prevalence, there are other important reasons to pay more attention to the primary prevention of FA. First, there is an increase in complexity, with nearly 40% of children suffering from multiple FAs (13). Second, the psychosocial burden should not be underestimated. FA can affect the individual's health and the quality of life of patients and their families. Previous studies have shown that quality of life is worse in patients with multiple FAs or allergy to an allergen that is difficult to avoid (e.g., egg/cow's milk) or a history of severe food allergic reactions (4). Third, studies in several countries have shown an increase in emergency department visits and hospitalizations due to food-induced anaphylaxis, resulting in a significant economic burden (4). In Europe, the average annual household costs are much higher in households with a food-allergic child compared to those without a food-allergic child. Finally, the current management of FA consists of allergen avoidance and treatment of acute allergic reactions, requiring patients to carry a permanent emergency kit due to the risk of reactions by accidental ingestion. Currently, there are more and more specialized centers around the world that are establishing oral food immunotherapy protocols with the main goal of increasing the reactogenic threshold, improving the child's quality of life and trying to induce tolerance. The problems of food allergen immunotherapy are that it is allergen-specific, time-consuming and associated with adverse reactions that limit tolerability (14).

Based on the above arguments, it is important that all health professionals pay attention to the primary prevention of FA. This review provides an overview of current measures for the primary prevention of FA in infants and young children.

Overview of the underlying hypotheses of FA to make prevention measures effective.

Hygiene hypothesis

In 1989, Strachan proposed the hygiene theory as possible explanation for the increasing epidemiology of eczema, asthma, and allergies (15). In this study, hay fever and eczema were less frequent in children from larger families, most likely due to a higher incidence of early childhood infections. Several studies have shown that several other factors, such as birth by cesarean section, antibiotics, anti-acids, exposure to pets, etc., can have an impact on the microbiome (16). Reduced diversity of microbial exposure or dysbiosis leads to a Th1/Th2 cell imbalance that is skewed toward a Th2 cell-mediated inflammatory response and is thus predetermined for FA.

Dual allergen exposure hypothesis

For many years, it was thought that gastrointestinal exposure to allergens led to sensitization to food allergens. In contrast, the dual

allergen exposure hypothesis suggests that sensitization occurs via the non-oral route. This hypothesis is based on the observation that many patients react to the first oral exposure to peanut. Epicutaneous exposure to food allergens induces a potent type 2 immune response and can lead to systemic food allergic reactions on subsequent oral exposure (17). The article by du Toit et al. provides a good overview of the preclinical and clinical data on epicutaneous sensitization (18). It emphasizes that AD is an important risk factor for FA. In another study, du Toit et al. observed that early introduction of peanut in infancy in Israel resulted in a lower prevalence of peanut allergy compared to a similar population in the United Kingdom where peanut was avoided (19). The Learning Early About Peanut Allergy (LEAP) clinical trial showed that introducing peanut in an age-appropriate manner between 4 and 6 months of age significantly reduced the incidence of peanut allergy in high-risk children (20).

In addition, there are studies showing that the respiratory tract is an alternative route of sensitization leading to FA (21).

Therefore, oral exposure to food allergens early in life leads to tolerance as opposed to epicutaneous and inhaled allergen exposure leading to FA. Therefore, it is important to achieve oral tolerance prior to skin or airway exposure to prevent the development of FA.

Vitamin D hypothesis

Vitamin D deficiency has been suggested as a contributing factor to FA. Further studies are needed to support this hypothesis because of inconclusive results due to methodological limitations (16,18).

Overview of the recommendations to prevent FA

The goal of primary prevention of FA is to prevent the development of allergic IgE sensitization and associated symptoms, while secondary prevention focuses on interrupting the development of FA in IgE-sensitized patients. The window of opportunity for primary prevention is early infancy, as the first manifestations of FA usually occur in infancy. It is important to apply early preventive measures to all infants regardless of family history or atopy, otherwise 10-15% of children may be missed. (16)

This review will focus on the modifiable factors such as dietary and cutaneous factors. The non-modifiable factors such as genetics, race and sex will not be discussed in detail.

A. Dietary factors

1. MATERNAL DIET

Women, who are pregnant or breastfeeding, should eat a healthy, balanced diet without restricting the consumption of specific allergenic foods (22). There is no reduction in the prevalence of FA if women avoid potential food allergens during pregnancy or breastfeeding. In contrast, it can be harmful due to insufficient intake of vital nutrients and fibers.

2. BREASTFEEDING AND INFANT FORMULA

The 2003 WHO guidelines recommend exclusive breastfeeding for the first 6 months of life based on its nutritional value and protective effects for both mother and child against a number of health outcomes (23). To date, there is no evidence that breastfeeding reduces the risk of food allergy or cow's milk protein allergy (CMPA) (22).

The EAACI Task Force proposes avoiding cow's milk supplementation in the first week of life, as this leads to a large reduction in CMPA in early childhood (21). If necessary, temporary association of donor breast milk, advanced hydrolysate cow's milk formula, rice protein formula or even amino acid formula can be used, depending on clinical, cultural and economic factors.

On the contrary, several observational studies have shown that early and persistent daily introduction of cow's milk into the infant's diet from the first days of life is associated with a reduced risk of CMPA. For this reason, Sabouraud-Leclerc et al. suggest a daily supplementation of 10 ml of first milk until diversification in exclusively breastfed children at risk of atopic diseases, after discussion with the family (16).

If formula feeding is preferred, it is important to use a non-hydrolyzed first age formula, as hypoallergenic (HA) formulas may not reduce the risk of CMPA and FA (16, 22). Soy protein formula is unlikely to protect against CMPA and should not be introduced in the first 6 months because of potential harm (high concentration of phytate, aluminum, and phytoestrogens) (22).

3. INFANT'S DIET (SOLID FOOD)

In the last two decades, there has been a paradigm shift from food allergen avoidance to early consumption of potentially allergenic foods in infancy to prevent the development of FA (24). Several observational studies have shown that delayed introduction of food allergens may be associated with an increased risk of FA (16,20,25).

The EAACI Task Force recommends the introduction of half a well-cooked egg, not raw or uncooked pasteurized egg, twice a week as part of complementary feeding between 4 and 6 months of age, as the consumption of 2 grams of egg white protein per week may prevent egg allergy. This recommendation is mainly based on the results of the Prevention of Egg allergy with Tiny Amount Intake (PETIT) study (22,23,24). In populations with a high prevalence of peanut allergy, the introduction of peanut in an age-appropriate form as part of complementary feeding between 4 and 6 months of age is recommended based on the results of the LEAP and its follow-up (LEAP-on) study (20,22,23). It is important that the introduced allergen is consumed regularly, i.e. several times per week, to avoid the development of an allergy. Early introduction of potential food allergens, such as egg and peanut, does not have a negative effect on breastfeeding or fruit and vegetable consumption, nor does it have a nutritional effect, except for a higher fat intake with early introduction of peanut, but still in the normal range (16,23,25). There are currently no recommendations for early introduction of peanut in countries with a low prevalence of peanut allergy, or for early introduction of tree nuts or wheat (16,22,23). Evidence for early introduction of fish (before 9 months of age) to prevent allergic sensitization, rhinitis and asthma is limited. Fish can be introduced after 6 months of age because of the important nutrients and omega-3 fatty acids in fish (24).

Thus, the window of opportunity to introduce food tolerance is around 4-6 months of age, especially for highly allergenic foods and highly atopic infants (16). A medical evaluation by an allergist in infants with severe AD and/or FA before introducing common food allergens into the diet remains important. This assessment needs to be done within a reasonable timeframe so that long delays do not increase the risk of sensitization.

Finally, attention should be paid to dietary diversity in the first year of life for all children as it may be associated with a reduced risk of developing allergic diseases such as asthma, AD, allergic rhinitis, food sensitization or FA (24,26). Dietary diversity is the number of different foods, food groups of food allergens eaten over time, taking into account the eating habits of each family. Tolerance development will be stimulated if there is more exposure to food allergens in the diverse diet during the first year of life. On the other hand, dietary diversity may play a role in allergy prevention by increasing the intake of nutrients (omega-3 fatty acids and non-digestible fiber) and modifying the gut microbiome (24).

4. DIETARY SUPPLEMENTS

Currently, according to the EAACI guidelines, there is no recommendation for or against vitamin or fish oil supplementation in healthy pregnant and/or breastfeeding women and/or infants due to inconclusive results in various studies for the prevention of FA, mainly due to methodological limitations (16, 22). Similarly, there is insufficient evidence to support supplementation with prebiotics, probiotics, and symbiotics in healthy pregnant and/or lactating women and/or infants to prevent FA (16, 22). Because these supplements do not cause harm in healthy women and infants, health care professionals should consider the pros and cons for each individual patient (22).

B. Cutaneous factors

AD is a risk factor for the development of FA. The risk of FA increases with the early onset, severity, and duration of AD. In addition to the genetic predisposition (filaggrin loss-of-function mutations, , corneodesmosin gene mutations) to AD, the skin is continuously exposed to environmental factors, including natural (e.g., food, aeroallergens, viruses, bacteria, fungi) and artificial (e.g., detergents, high pH creams, lotions) triggers (17). These factors can lead to skin barrier dysfunction, epicutaneous damage and allergic sensitization in patients with a genetic predisposition to allergic diseases.

In addition, the skin microbiome plays an important role in epicutaneous sensitization, with *Staphylococcus aureus* colonization being a risk factor for AD. It is associated with the severity and worsening of AD and consequently with an increased risk of food sensitization and allergy (17,26).

Because of the strong association between epicutaneous sensitization and FA, it has been suggested that improving the skin barrier of infants and thus reducing the duration and severity of AD may prevent the development of FA. This can be achieved either by improving the barrier through hydration with emollients or moisturizers, or by reducing potential damage to the skin barrier by avoiding potentially harmful substances or irritants. The Cochrane systemic review by Kelleher et al. showed moderate evidence that skin care interventions such as emollients during the first year of life in healthy infants are probably not effective in preventing AD and increase the risk of skin infections. They were unable to draw firm conclusions about FA (27). The recent systematic review by Zhong et al. published that prophylactic and continuous application of emollients in early infancy may prevent AD, especially in high-risk patients (28). The development of AD during the first 32 weeks of life could be prevented by daily application of a moisturizer in the STOP-AD randomized controlled trial by Chaoimh et al. In contrast, there was no significant effect of emollients on the prevention of allergic sensitization (29). If emollients can delay AD, the window of opportunity to induce oral tolerance by early introduction of allergenic foods increases. Currently, there is no recommendation for the standard use of emollients in infants with or without atopy risk. Further research is needed in this regard, with particular attention to the patient population that would benefit, the composition of emollients, the duration of preventive use, etc.

On the other hand, AD is also an inflammatory process. Therefore, targeting inflammation by early and adequate treatment with topical steroids may reduce the severity of AD and prevent food sensitization and allergy. It has been shown that the severity of AD, as measured by the Scoring Atopic Dermatitis (SCORAD), correlates with food sensitization (16). Therefore, anti-staphylococcal treatment is important because *Staphylococcus aureus* dysbiosis may lead to uncontrolled inflammation (16,26). The retrospective cohort study by Miyaji et al. showed that proactive topical treatment in infants with moderate-severe AD was associated with an almost twofold reduction in FA by 24 months if topical treatment was started before 4 months of age versus after 4 months of age (30). Therefore, it is important to treat all infants with AD early and appropriately with emollients and topical corticoids to restore the skin barrier. A trilipid-based emollient would be more effective in reducing transepidermal water loss (TEWL) than a paraffin/alcohol/petroleum-based emollient. The composition of the trilipid-based emollient consists of a 3:1:1 ratio of ceramides, cholesterol and free fatty acids, mimicking the skin's natural lipid composition. The PEBBLES pilot study by Lowe et al. found that twice-daily prophylactic use of the tri-lipid emollient EpiCeramTM during the first six months of life was associated with a reduced incidence of AD and food sensitization at 12 months of age (31).

A third possible preventive measure is to limit the presence of allergens in the infant's environment, as skin barrier dysfunction in infants with AD facilitates the penetration of food allergens from topical application or from the environment. The use of skin creams containing peanut protein is associated with peanut allergy (17,26). There is also an association between repeated use of oat extract containing emollients and the prevalence of oat allergy in children with AD. Studies have shown that the consumption of almonds and peanuts in the home is highly correlated with the concentration of almonds and peanuts in the dust of an infant's bedding and play area, even if the infant does not eat almonds or peanuts (16,17,26).

Conclusion

The epidemic of FA is a growing global public health problem. In recent years, many studies have supported the dual allergen exposure hypothesis: cutaneous or inhalational exposure to allergens may promote IgE-mediated allergy, while early ingestion of allergenic foods may lead to oral tolerance. Thus, there has been a paradigm shift from food allergen avoidance to early consumption of potentially allergenic foods in infancy to prevent the development of FA. Between 4 and 6 months of age, it is important to introduce half a well-cooked small egg to prevent egg allergy, and in populations with a high prevalence of peanut allergy, a heaped teaspoon of diluted peanut butter (2 grams of peanut protein) to prevent peanut allergy. The allergen must be consumed regularly throughout childhood to prevent allergy. Further studies are needed to investigate the effect of early introduction of other potential food allergens. On the other hand, the risk of FA increases with the early onset, severity and duration of AD. Currently, there is no recommendation for the use of emollients in infants with or without atopy risk. More research is needed. However, there is evidence that early and appropriate treatment of all infants with AD with emollients and topical corticoids to restore the skin barrier may reduce the severity of AD and prevent food sensitization and allergy. Dietary protein-based emollients should be avoided, and indirect contact of the infant's skin with peanuts and tree nuts should be avoided (e.g., washing hands before touching the infant) if the infant has not previously ingested them.

Conflict of interest

The author has no conflicts of interest to declare with regard to the topic discussed in this manuscript.

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