

Risk Factors for the Development of Food Allergy

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Both genetic and environmental factors seem to predispose to the development of food allergy. A most notable factor is diet, particularly during infancy. Possible other factors include maternal diet during pregnancy and lactation, birth by cesarean section, exposure to tobacco smoke, multivitamin supplementation, and intake of antacids. It is important to identify and control such risk factors to reduce the development of food allergy.

Introduction

Food allergy is estimated to affect 3% to 4% of the general population in the United States, with a higher prevalence (6%) in children [1]. Food allergy is associated with significant impact on both the child and the family, hence interventions to prevent food allergy would be very rewarding. Genetic and environmental factors, including prenatal and postnatal, have been shown to constitute risk factors for food allergy (Table 1).

Genetic Risk Factors for Food Allergy

Several studies have demonstrated a role for heredity in the development of production of immunoglobulin (Ig) E [2,3] and of atopy in general [4,5•]. There seems to be some evidence, though inconclusive, for inheritance of sensitivity to specific allergens (eg, ragweed) [6] as well as the development of asthma [7]. This article focuses on the factors specific for food allergy.

Twin study

A study of 58 pairs of twins, with at least one having a peanut allergy, showed a concordance rate of 64% among monozygotic sets compared to only 6.8% in dizygotic sets

[8]. Such an observation suggests a role for genetics in determining the sensitivity to a specific food allergen, and deserves further investigation.

Allele association and food allergy

A study by Blanco et al. [9] suggested a genetic association between latex-food allergy and certain HLA alleles, namely DQB1 0201, DRB1 0301, and DRB1 0901. In another study, polymorphism in the CD14 gene (C to T transition occurring at position -159) was associated with food allergy [10]. CD14 is part of a pattern-recognition receptor complex that binds to lipopolysaccharide. This study showed a fivefold higher incidence of the TT genotype in food-allergic subjects compared to nonatopic controls, lending further support to a role of genetics in the development of food allergy.

Environmental Risk Factors for Food Allergy

The development of allergy is greatly influenced by environmental factors, which can be prenatal (intrauterine) or postnatal.

Prenatal factors

Some children seem to have been born already sensitized to certain foods. Food allergens have been shown to cross the human placenta [11••] in concentrations that can stimulate the fetal lymphocytes [12], and the infant can be born already highly sensitized [13].

Only a few studies have evaluated the effect of maternal diet during pregnancy on allergy development in the newborn. In a prospective study by Falth-Magnusson and Kjellman [14], 212 pregnant women were enrolled; 104 were asked to exclude egg and milk from their diet from week 28 until delivery, while the other 108 had a normal diet. The offspring were evaluated by parental questionnaires, physical examination, skin prick testing, and total IgE level. By 18 months of age, no statistically significant difference in the incidence of allergy to milk or egg was noted in the infants of the two groups. In a follow-up of these children at 3 and 5 years of age, there was still no difference noted between the two groups [15].

Table 1. Possible risk factors for food allergy

Genetic risk factors
Atopic constitution
Food-specific predisposition (HLA allele associations, CD14 polymorphisms)
Environmental risk factors
Prenatal
Maternal diet during pregnancy
Postnatal
Cesarean section delivery
Maternal diet during lactation
Infant diet (breastfeeding, formulas, solid foods)
Multivitamin supplementation
Antacid intake
Exposure to tobacco smoke

Postnatal factors

Cesarean section delivery

In a cohort study of 2803 children followed to age 2.5 years, Eggesbo et al. [16] noted that delivery by cesarean section was associated with a higher incidence of confirmed allergy to egg. The difference was statistically significant in the children of allergic mothers (odds ratio [OR] 4.1). Laubereau et al. [17] studied 865 full-term infants for the development of food sensitization according to delivery method. At 12 months of age, they were tested for sensitization as determined by positive serum IgE antibodies to five food allergens (alpha-lactalbumin, beta-lactaglobulin, casein, soy bean, and ovalbumin). The rate of sensitization to at least one of those allergens in children born by C-section was 17% compared to 9% in those delivered vaginally. This difference may be attributed to the enhanced development of helper T cell subtype 2 (Th2) lymphocytes in infants born by C-section. On the other hand, infants born vaginally are colonized with the flora of the maternal birth canal, which in turn favors the development of Th1 over Th2 cells.

Maternal diet during lactation

Multiple studies have demonstrated the passage of food proteins, such as cow's milk and egg, from the maternal circulation to breast milk [18,19]. Hattevig et al. [20] noted that when mothers avoided certain foods during the first 3 months of lactation, there was a statistically significant reduction in their infants' sensitization to those foods. Several studies showed that avoidance of highly allergenic foods during lactation led to a reduction of eczema incidence but not of other allergic diseases [21–23].

Breastfeeding

Saarinén and Kajosaari [24] reported a lower prevalence of food allergy during early childhood in infants who were

breastfed for at least 1 month. Another study by Saarinén et al. [25] showed a protective effect of breastfeeding against the development of food allergy for up to 3 years of age in infants with a family history of atopy. In a multifactorial disease like allergy, it should not be expected that investigations of one factor would have the same outcome in all studies. In addition, some studies have been flawed because of small sample size, lack of randomization, blinding regarding intervention, and brief duration of breastfeeding. With the currently available information, it would be prudent to recommend exclusive breastfeeding as one of the favorable protective factors against food allergy during infancy. The favorable effect may be moderate and limited to, or more conspicuous in, infants at high risk of atopy. Also, other interventions may be needed, such as combining breastfeeding with avoidance of solid food for the first 4 months for maximal benefit [26].

Formula feeding

Because breastfeeding is not always possible for all infants, formulas have been evaluated for their prophylactic effect on the development of food allergy and their therapeutic efficacy. Hypoallergenic formulas, such as extensively hydrolyzed bovine casein (eg Alimentum, Nutramigen, Pregestimil), have been tolerated by more than 90% of patients allergic to cow's milk [27–29].

Regarding prevention, three studies have shown that both extensively hydrolyzed and partially hydrolyzed formulas significantly reduce the incidence of allergy compared to conventional cow's milk formula [30–32]. However, extensively hydrolyzed formulas seem to be more advantageous over partially hydrolyzed formulas [33]. Because partially hydrolyzed formulas (eg, Good Start Supreme, Nestlé S.A., Vevey, Switzerland) are less expensive and more palatable, they may be a first choice for prevention. The preventive effect of extensively hydrolyzed formulas on food allergy in high-risk infants appears to be enhanced when both cow's milk and solid foods are avoided during the first 4 months of life [34,35]. Amino acid formulas (eg, Neocate, Elecare, and L-Elemental) are composed of synthesized free amino acids. They were found to be well tolerated by almost all children with allergies to cow's milk or other foods [36,37].

Infant diet factors

The timing of introduction of potential food allergens into the diet has been suggested as a factor in the development of food allergy. Cow's milk is the most consumed food by nonbreastfed infants and seems to be the most common food allergen at this age. Cow's milk allergy (CMA) is more common in formula-fed infants than in breastfed infants [38]. Also, supplemented feedings can affect the development of allergy. Saarinén et al. [39] followed breastfed infants for 18 to 34 months, and studied them according to supplemental feeding they received in the newborn nurseries. The incidence of CMA was 2.4%

when supplementation was with cow's milk formula, 1.5% when supplemented with extensively hydrolyzed whey formula, and 1.7% when supplemented with pasteurized human milk. The risk of allergy by early introduction of food proteins is enhanced because of the immaturity (histologic, enzymatic, and immunologic) of the gastrointestinal mucosa during early life [40,41].

Early exposure to peanut protein also has been investigated by Lack et al. [42] in their work on the development of peanut allergy in infants. They noted that application of skin creams containing peanut oil during the first 6 months of life occurred in 84% of preschool children who had peanut allergy, 53% of those with eczema, and 59% of normal controls. This suggests that even skin contact of minute quantities of food protein with the inflamed skin of infants can cause sensitization.

In addition to early topical exposure to peanut-containing products, the form in which peanut is consumed in the diet may affect its allergenicity. Peanut allergenicity is reduced by frying or boiling and is retained, or perhaps increased, by roasting. Differences in methods of peanut preparation probably influence the prevalence of peanut allergy in various populations [43].

To minimize the risk of food allergy, certain precautions have been recommended for infant diets. Food recommendations, particularly for high-risk infants from atopic families, include breastfeeding and avoidance of solid foods and cow's milk for at least 4 to 6 months [44]. If the child is not breastfed, a formula with reduced allergenicity, particularly an extensively hydrolyzed formula or an elemental formula, should be used for at least 4 to 6 months [40,45••]. A consensus document by Fiocchi et al. [46••], along with recommendations by the American Academy of Pediatrics [44] and the World Health Organization [47], support exclusive breastfeeding for at least 4 to 6 months.

Multivitamin supplementation

Multivitamin supplementation is common in young children, with more than 50% of toddlers in the United States taking vitamins [48]. In a questionnaire study of a cohort from the National Center for Health Statistics, Milner et al. [49] noted that the intake of multivitamins during infancy and early childhood was associated with an increased incidence of food allergy, particularly in those who were formula-fed. In vitro studies showed that the development of T helper-naïve cells may be skewed to Th1 cells by the addition of vitamins B₆, C, or E [50,51] or to Th2 cells by vitamins D or A [52]. Further studies are needed to confirm a clinical association.

Antacids

One of the factors involved in the development of food allergy can be the transport of incompletely digested proteins across the gastrointestinal mucosa. Untersmayr et al. [53] evaluated 152 adult patients from a gastrointesti-

nal clinic without a history of allergy or atopy who were given histamine-2 (H₂)-blockers or proton pump inhibitors for 3 months. IgE antibodies to several foods were drawn before and after 3 months of treatment. At the end of therapy, total IgE levels were substantially higher than before antacid treatment (median 146 vs 46 KU/L). On the other hand, no significant change was noted in the total IgE level in the control group. Also, 10% of patients who received antacids had a boost in preexisting food-specific IgE antibodies and 15% developed de novo IgE sensitization to foods. Five months after antacid therapy was discontinued, skin prick tests to foods showed more positive results in the treated group than in the controls. These findings suggest that interference with food digestion by antacid intake facilitates sensitization to food. The use of antacids has been on the rise worldwide, and they are being used increasingly in young children suspected of having gastroesophageal reflux, which might be one of the causes of the increasing prevalence of food allergy.

Tobacco smoke

Tobacco smoke exposure is another factor that has been evaluated in the development of food allergy in children. In an observational birth cohort study that followed 342 children, environmental tobacco smoke was assessed through a questionnaire and measurement of urinary cotinine levels [54]. Specific IgE to four foods—cow's milk, hen's egg, soybean, and wheat—were measured at ages 1, 2, and 3 years. By 3 years of age, exposure to maternal tobacco smoke was associated with a higher risk of sensitization to at least one of the four tested foods (OR 2.3; 95% CI 1.1–4.6). This study indicates that exposure to maternal tobacco smoke during the first 3 years of life may enhance sensitization to food.

Conclusions

Genetic and environmental risk factors appear to have roles in the development of food allergy. Perhaps the most important currently accepted approach to prevent food allergy, particularly in infants from atopic families, is exclusive breastfeeding for 4 to 6 months and the use of a hypoallergenic formula for supplementation or as a substitute. It also would be prudent to delay introduction of solid foods for at least 4 to 6 months, and to introduce selected foods gradually. Highly allergenic foods, such as peanut, tree nuts, fish, and shellfish, may not be introduced until 1 or 2 years of age. There is some evidence that the elimination of highly allergenic foods from the lactating mother's diet might be useful. Regarding other possible risk factors, avoidance of environmental tobacco smoke would be most commendable, not only for the prevention of food allergy development, but also for several obvious benefits. Because food allergy has a significant impact on children and their families, it would be prudent to identify and control its risk factors.

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