

Risk Factors for Food Allergy

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Food allergy is a common problem that often affects young children. Numerous factors affect the development of food allergy both prenatally and postnatally. These factors are genetic and environmental. Although little can be done post-conception to alter a child's genetic risk for developing food allergy, early identification may permit alterations of the environment in which food allergy develops. Environmental factors operate both prenatally and postnatally. By understanding how these factors affect development of food allergy, it may be possible for parents to modulate the development of this difficult problem in their children.

Introduction

Numerous genetic and environmental factors affect the development of food allergy in children, both prenatally and postnatally. An understanding of how these factors affect the development of food allergies and early identification of allergies may permit alterations of the environment in which food allergy develops, enabling parents to modulate the development of this difficult problem in their children.

Genetics

The risk that a particular neonate will develop atopic symptoms during the first two decades of life is strongly related to the presence of the disease in their parents and siblings. At the phenotype level, there is a closer association between specific disorders, such as asthma or atopic dermatitis, in the child, and the same manifestations in parents or siblings than with other atopic manifestations in the family [1]. These clinical observations suggest the presence of phenotype-specific genes.

Various genes predisposing to atopy have been identified, influencing specific IgE responses to particular antigens. A linkage has been reported between a region on chromosomes 11 and 13 and asthma and allergic rhinitis [2] and with atopy in general [3]. In Amish families, a linkage between total IgE levels and several markers

in the 5q 23-31 region, which contains genes coding for interleukin (IL)-3, IL-4, IL-5, IL-9, IL-12B, and IL-12 has been found [4]. The human major histocompatibility complex (MHC) includes genes coding for human leukocyte antigen (HLA) class II molecules, which are involved in the recognition and presentation of exogenous peptides. An HLA influence on specific IgE responses to antigens has been described [5].

It has been concluded from genetic studies that both asthma and other allergic disorders are genetically heterogeneous and that each of the atopic phenotypes is probably the result of a polygenic inheritance and a complex interaction between genes and environmental factors [6]. Recently, the heritability, which is the estimated contribution of heredity versus environment to the variance of a trait, of a specific food allergy (peanut) in twins was studied [7•]. A significantly higher concordance rate was found for peanut allergy among homozygotic twins compared with dizygotic twins. The estimate of heritability for peanut allergy in this study was high, 82% to 87%, showing a strong genetic influence on the complex trait of peanut allergy. Previous studies have shown a role for HLA class II genes in the determination of this phenotype [8].

In addition, the influence of the maternal phenotype on the development of the disease in children is stronger than that of the paternal phenotype. This suggests that pregnancy may be a critical time for determining subsequent disease development [9,10].

Environment

Prenatal

Fetal exposure to food allergens occurs during gestation. Production of IgE starts as early as 11 weeks gestation [11], initially by the liver, followed by the fetal lung and spleen during the next 10 weeks. As a result, the fetus is able to mount an antigen-specific IgE response before birth [12]. Intrauterine allergen exposure is very common, especially for dietary antigens, as reflected by the large proportion of neonates who have positive proliferative responses to cow's milk [12].

The most commonly postulated pathway for allergen exposure of the fetus is transplacental. This is especially true for IgG-allergen immune complex transfer from mother to fetus [13]. Small amounts of IgG may cross the placenta early in gestation, and levels begin to rise rapidly from 20 weeks to become maximal between 32 weeks gestation

and birth [14]. However, the passage of allergens, either free or complex, to the fetus has not been demonstrated. An alternate theory proposes allergen exposure across the fetal membranes, where the maternal (deciduas) and fetal tissues are in intimate contact [15]. The passage of proteins from the maternal to the fetal side of this membrane is already known to occur [16].

The major advantage of transamniotic transfer of allergen and other factors that may regulate the ensuing response is access to the gut-associated lymphoid tissue (Peyer's patches are mature by 19 weeks gestation) [17]. The gastrointestinal tract of the fetus is exposed to amniotic fluid by fetal swallowing, which may start at 10 weeks gestation [18]. This process accounts for 70% of the daily protein turnover of amniotic fluid [19]. The interaction of the fetus with the gestation-associated environment from the amniotic fluid or nutritional factors at the placental interface may lead to fetal programming and a susceptibility to atopic disease development.

There may be a period of fetal life when the fetus is exquisitely sensitive to initiation of antigen-specific reactivity [20]. Allergen-specific responses are demonstrable from 23 weeks of gestation and birch-pollen-specific reactivity at birth is more likely if maternal exposure to birch-pollen season occurred during months 5 to 7 of pregnancy [21]. If an IgE-mediated mechanism is functional at the maternofetal interface during pregnancy, it may ultimately be the IgE-IgG ratio of the mother that has the greatest consequences for the offspring [22]. Interestingly, if the birch pollen season coincides with the last 2 months of the pregnancy, when IgG transfer across the placenta is maximal, the neonate does not show birch pollen-specific reactivity at birth, as would occur if the mother had been exposed to the birch pollen season in the preceding 3 months [23].

Postnatal

Early immunologic markers

Elevated umbilical cord IgE was thought to be a specific marker of later atopic disease, but has not proven to be a sensitive marker of subsequent disease development [24]. Raised cord-blood mononuclear cell (CBMC) proliferation responses to β -lactoglobulin has been shown to correlate with positive skin prick tests to cow's milk at 1 year of age in children with atopic eczema [25]. Allergen-specific CBMC proliferative responses tended to be higher in neonates with an immediate family history of atopy than in their low-risk counterparts [26,27].

It has been documented that neonates, in general, have reduced interferon (IFN)- γ production compared with adults [28]. However, IFN- γ production at birth is even further decreased in infants who are at risk for atopic disease [29]. Downregulated IFN- γ production by β -lactoglobulin-stimulated CBMC has been described in infants who developed cow's milk-mediated allergic disease at 1 year of age [25] and in a group of children in Japan who also later

developed atopic disease [30,31]. Children who developed atopy continued to be poor producers of IFN- γ over the first 2 years of life [27].

Several groups have reported elevated serum IgG antibodies to hen's egg proteins as predictors for subsequent sensitization to aeroallergens and to the development of allergic airway symptoms leading to asthma [28]; however, as long as we lack genetic and immunologic markers to use as potential predictors for atopic disease, primary prevention of food allergy will be difficult.

Intestinal barrier

Shortly following birth, a newborn's gastrointestinal tract is confronted with foreign proteins in the form of bacteria and food antigens. It must process and absorb ingested food, provide rapid response to various pathogens, and remain unresponsive to large quantities of foreign nutrient antigen. Both immunologic and nonimmunologic mechanisms are operative. However, immaturity of these mechanisms exists. Basal acid output in the stomach is relatively low the first month of life, increasing antigen absorption [29]. Intestinal proteolytic activity does not reach mature levels until approximately 2 years of age [30]. Intestinal microvillus membranes are immature, resulting in altered antigen binding and transport through mucosal epithelial cells [31]. Furthermore, the newborn lacks IgA and IgM in exocrine secretions and salivary IgA levels, which are absent at birth [32]. These levels remain low during the early months of life. Large quantities of ingested proteins place a tremendous burden on the immature, gut-associated lymphoid tissue. The early introduction of numerous food antigens stimulates production of IgE antibodies [33]. A prospective study demonstrated a direct linear relationship between the number of solid foods introduced into the diet by 4 months of age and the subsequent development of atopic dermatitis [34].

Other environmental factors

New risk factors have become relevant in connection with nutrition, environmental exposure, and lifestyle in connection with the observed increase in atopy. A prospective study in Germany [35] reported an increased risk for sensitization in children whose mothers smoked up to the end of pregnancy and continued to smoke after birth. A significantly increased sensitization rate regarding IgE antibodies to food proteins, particularly those to hen's egg and cow's milk, was observed during infancy. This observation may be related to the fact that, in children, the highest urinary cotinine concentrations are detected during the first years of life when the child spends most of the time close to the mother.

In a recent Swedish study [36], the prevalence of atopy in children from anthroposophic families was found to be lower than that in children from other families, which led to the conclusion that lifestyle factors associated with anthroposophy may lessen the risk of atopy in childhood.

In a study [37] comparing areas with little genetic difference, East and West Germany, a lower prevalence rate for atopy was found in the East.

Endotoxin exposure is a possible element of atopy prevention in early life [38]. Endotoxins consist of a family of molecules that are an intrinsic part of the outer membrane of gram-negative bacteria. They and other bacterial-wall components can be found abundantly in stables where pigs, cattle, and poultry are kept. Their concentrations are found highest in the stables of farming families and also in dust samples from kitchen floors and mattresses in rural areas. These findings help support the hypothesis that environmental exposure to endotoxin and other bacterial walls is an important protective determinant regarding the development of atopic diathesis.

Prenatal or perinatal bacterial infections should also be considered risk factors for modulation of atopy. Preterm birth, in many cases, is considered a result of bacterial infections during pregnancy. This is supported by the observation that premature infants with very low birth weight have a lower prevalence of atopic eczema and atopic sensitization [39]. Results of a Finnish study [40] indicated that preterm infants were more often primed by severe neonatal infections (15% blood culture verified sepsis). Their data further confirmed that prematurity is linked with a decreased long-term risk for atopic sensitization. As previous data show, microbial agents have an important effect on atopic sensitization and induction of tolerance [41,42]; the special neonatal microbial exposure of preterm infants can be assumed to have a partial role in inducing the post-natal maturation of their T-cell system more toward the T-cell line.

Another consideration is that intestinal microflora might be a major source of microbial stimulation of the immune system in early childhood. Microflora has been shown to enhance Th1-type responses [43–45]. The results of a comparative study of Estonian and Swedish children [46] demonstrated that differences exist in the intestinal microflora. In Estonia, the typical microflora includes more *Lactobacilli* and fewer *Clostridia*, which are associated with a lower prevalence of atopic disease. One recent study [47] examined the effect of adding probiotics to infant formulas. Infants with milk allergy and atopic dermatitis had milder symptoms and fewer markers of intestinal inflammation if their milk formula was fortified with *Lactobacilli*.

Recovery from natural measles infection has been shown to reduce the incidence of atopy to 50% of that seen in vaccinated children [48]. The fact that certain infections are inducing a systemic and nonspecific switch to Th1 activities could be responsible for an inhibition of the development of atopy during childhood [49–51].

Observations from Japan suggesting that positive tuberculin responses in children predict a lower incidence of asthma, lower serum IgE levels, and cytokine bias toward the Th1 type [52] were supported by animal experiments that demonstrated that the IgE response to

ovalbumin in mice could be downregulated by a previous infection with bacillus Calmette-Guérin (BCG) [53,54].

Feeding

The first allergens encountered in an individual's life are food allergens. In utero sensitization to food allergens can be inferred by several observations. Firer *et al.* [55] reported one child who developed angioedema and four neonates who developed systemic reactions within the first 72 hours of life when fed cow's milk. The route of sensitization may have been in utero, because it is known that the fetus continually swallows amniotic fluid, which contains proteins found in the maternal diet [56]. After birth, infants can become sensitized to food proteins in breast milk or commercial formulas. One study [57] examined human milk samples during the entire lactation period of 25 healthy mothers and found detectable amounts of β -lactoglobulin in 93 of 232 milk samples. Food antigens have also been detected in human milk by radioimmunologic methods [58]. The occurrence of positive prick skin tests to egg at 6 months in babies who were exclusively breast-fed may occur postnatally by dietary antigens consumed by the mother and transferred into breast milk [59].

Therefore, sensitization to food antigens has been associated even with breast-feeding. In a randomized study [60] following the development of atopic disease in babies whose mothers were receiving an exclusive diet (cow's milk and egg) starting at 28 weeks gestation, breast milk or casein hydrolysate up to the age of 3 months caused no statistical difference in the development of atopy at age 9 years. However, previous studies indicated a beneficial effect of maternal elimination diet during both pregnancy and lactation [61].

Exclusive breast-feeding and the delayed introduction of solids for at least 4 months have been thought to be of value in the reduction of the development of atopic dermatitis [62–64]. In one study [65], the rate of atopic dermatitis was significantly less in the exclusively breast-fed group than the formula-fed infants. However, if solids were added during the first 4 months of life in the breast-fed infants, there was no difference. Another study [66] examining breast-fed infants who had solids at 3 months versus no solids, significantly fewer of the no-solid group had atopic dermatitis at 1 year of age.

It has been postulated that secretory IgA (sIgA) in maternal breast milk passively protects the nursing infant by decreasing antigen entrance across the gastrointestinal mucosa at a time when the newborn's mucosal defense mechanisms are maturing [67]. Total sIgA and cow's milk-specific sIgA were measured serially in 57 mother-infant pairs who were engaged exclusively in breast-feeding for the first 6 months postnatally. All of the infants who scored high on the allergy symptom scale received breast milk with total and cow's milk-specific sIgA antibody concentrations below the median value. This finding

suggests that maternal sIgA may protect against the development of atopic disease in infants.

Prevention of Sensitization

Much controversy exists about whether an antigen avoidance diet merely postpones sensitization to food antigens until later in life, when the genetically at-risk infant begins consuming more food allergens. A prospective study [68] followed 267 infants treated prophylactically with strict avoidance of cow's milk until 1 year of age. These children were then allowed to consume cow's milk. Only 4% demonstrated specific IgE to cow's milk at 1 year of age compared with 16% of formula-fed atopic infants. Of 200 infants followed for 3 years, only two infants have subsequently developed specific cow's-milk IgE. Other studies [69–71] suggest that the use of hypoallergenic formulas may delay, or possibly prevent, some gastrointestinal food hypersensitivity and may delay the onset of atopic dermatitis in some children.

Currently, the only definitive treatment for food hypersensitivity is avoidance of any food proven to cause symptoms. Infant soy formulas may be substituted if milk allergy is present. Unfortunately, allergy to soy protein may also exist. The most important allergens in early infancy include cow's milk, soy formula, wheat, peanut protein, and egg. One approach to eliminate cow's milk allergens from the diet is the addition of predigested bovine casein or whey to create formulas that provide nitrogen as mixtures of peptides and amino acids [72]. The use of an amino acid–derived formula can further reduce antigenicity [73]. Milk substitutes often are used in high-risk infants when formula feeding or supplementation is required [74].

Currently available modified proteins are classified as hydrolyzed or extensively hydrolyzed. The hydrolysis process may release biologically achieved peptides such as immunopeptide casein fragments [75], and traces of the original protein may be detectable in the final product [76]. One Finnish study [77] indicates that substitute milk formulas can be graded according to β -lactoglobulin content, which was significantly less in extensively hydrolyzed formulas. The amount of reduction was similar to that in human milk. The lowest β -lactoglobulin concentrations were found in the synthetic amino-acid–derived formula, which has been shown to be safe for children with severe milk allergy or with hypersensitivity to multiple cow's milk proteins, soy milk, casein, and whey hydrolysates.

Conclusions

Food allergy is a common problem that often affects young children. Because the only known treatment is avoidance of the food, it may be helpful to understand the risk factors that lead to sensitization and, subsequently, to development of symptoms. Such factors include genetic influences

that cannot be altered other than by considering it when selecting potential mates prior to conception, and environmental factors that can be modified once they are understood. By understanding these risk factors, it may be possible to prevent or at least delay the development of food allergy.

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