

Genetic and environmental risk factors for the development of food allergy

Bengt Björkstén

Purpose of review

To review recent clinical and experimental studies of genetic and environmental risk factors for the development of food allergy.

Recent findings

It may be true, although it is yet to be shown, that food allergies in early childhood are becoming more common and that the causes are the same as for later-developing respiratory allergies. The mother not only transfers 50% of her genes to her baby, but she is also the exclusive environment during gestation and continues to be a major environmental factor while breast-feeding her infant. Non-genetic maternal influences increasing the likelihood of food allergy include Caesarian section and high maternal age. Allergy to sesame seems to be increasing in children. This is possibly a consequence of increased use in processed foods. The search for dietary risk factors is not limited to allergenic foods, but may include other nutrients, for example excessive intake of vitamins. Two meta-analyses have seriously questioned the use of special infant formulas for allergy prevention. Novel prevention strategies, such as probiotic bacteria, have yet to be documented further.

Summary

The causes of food allergy are still unknown and no particular genes associated particularly with food allergy have been identified, although there is a strong association in general between genetic susceptibility to food allergy and that to IgE-mediated allergy. There are still no measures for general recommendation in order to prevent food allergy and no genes have been linked conclusively to disease. Further research concentrating on food allergy is obviously needed.

Keywords

children, food allergy, genetics, nutrients epidemiology

Introduction

The aim of previous research into the causes of allergic diseases, including food allergy, was mostly to identify potential risk factors in the environment and to identify the 'allergy gene'. No major environmental risk factors have been identified, however, and nor are there any reliable methods available which identify those individuals who will develop allergic disease. Over the past 10 years, focus has therefore more been directed against protective factors which could enhance the development of tolerance to allergens. Hypothetically, such factors were previously encountered early in life, but are now lost in modern affluent societies. In particular, the role of childhood infections has been discussed, but so far these studies have not been conclusive.

It is generally assumed that food allergy and respiratory allergies have more or less the same causes both with regard to genetics and environmental factors. This is probably true to a considerable degree, but it is clearly not total, and nor has the relationship been shown conclusively. This review summarizes some of the recently published research related to genetic and environmental factors that might affect the development of food allergy.

Epidemiological aspects

Clinical allergy, including food allergy, is the result of an interaction between exposure of a genetically susceptible individual to an allergen and various environmental modifying factors. It is almost generally accepted that there is a pronounced increase in the incidence and prevalence of allergic diseases in many countries, at least during the last 40–50 years and probably well before that. The assumption is based on numerous epidemiological studies concerning respiratory allergies. The epidemiology of food allergy is much less clear-cut, however, and there are still no studies confirming an increase in the prevalence of food allergy in either adults or children.

It is also generally accepted that the development of asthma and other allergic diseases is influenced strongly by genetic components. So far however the major genes associated with allergy in general or with a particular form of allergy, such as that to foods, have not been identified.

Initially, the search for environmental factors was more or less limited to identifying risk factors, but recent research has shifted the attention from triggers of sensitization and

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Institute of Environmental Medicine, Karolinska Institutet, S 171 77 Stockholm, Sweden

Correspondence to Bengt Björkstén, MD, PhD, Professor of Allergy Prevention and Pediatrics, Institute of Environmental Medicine, Karolinska Institutet, S 171 77 Stockholm, Sweden
E-mail: bengt.bjorksten@cfa.ki.se

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Abbreviations

AAP American Academy of Pediatrics
CTLA cytotoxic T-lymphocyte-associated antigen

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factors provoking allergic disease towards factors that may programme the initial susceptibility to allergic diseases. This shift in focus from why do people develop allergy?, to why are we not all allergic?, is largely a consequence of increased understanding of how immunity develops after birth. Allergic diseases are now seen by many as a result of a prolonged period after birth with an immature immune system and as a consequence of decreased immune stimulation. Current search for risk factors emphasizes the absence in modern society of factors that might stimulate the immune system, allowing it to develop protective responses and to establish appropriate control of these responses.

In the search for environmental risk factors and protective factors, however, one should bear in mind that these are not necessarily the same for respiratory allergies and food allergy or intolerance.

Microbiota and immune function

The gut flora is the quantitatively most important source of microbial stimulation and may provide a primary signal for driving the postnatal maturation of the immune system and the induction of a balanced immunity [1]. As microorganisms have been present through the evolution of humans, this has taken place in close interaction with the microbial environment. There is mounting evidence that commensal microbes acquired during the early postnatal period are required for the development of tolerance, not only to themselves, but also to other antigens [1]. This seems to be particularly true for antigens encountered in the gastrointestinal mucosa. For example, Th2-mediated immune responses are not susceptible to oral tolerance induction in germ-free mice and oral tolerance is only induced after the introduction of components of the normal microflora [2].

T cells play an important role in the pathogenesis of allergy. T-cell receptor engagement by antigenic peptides presented to major histocompatibility complex (MHC) class II molecules and activation of costimulatory molecules are crucial in the regulation of T-cell immune responses. Costimulatory molecules are responsible for second signals that induce T-cell activation and proliferation. The positive signals induced by some molecules are counterbalanced by other members of the costimulatory family, including cytotoxic T-lymphocyte-associated antigen (CTLA)-4. The hypothesis that CTLA-4 is involved in suppressing the induction and progression to food proteins was tested in an oral peanut-sensitization mouse model [3]. Anti-CTLA-4 treatment resulted in enhanced sensitization to peanut protein characterized by profound elevation of specific IgE production and clinical reaction upon an oral challenge. CTLA-4 signalling thus seems to play a pivotal role in regulating the intensity of food-allergic responses. These observations

are in line with other studies reporting an association between CTLA-4 molecules and respiratory allergy.

Genetic aspects

Extensive studies in recent years have identified an association between allergy and various genes. So far, however, no major genes have been identified that would be associated with more than a fraction of the allergic patients, and nor are there any genes that have been strongly associated with a particular expression of allergy, for example food allergy.

Over the past year, at least two studies have addressed a possible relationship between certain genes and manifestations of food allergy. The first gene of interest was a gene polymorphism in the promotor region for CD14, which is the receptor for lipopolysaccharide. This region is of interest in light of the so-called hygiene hypothesis, according to which microbial stimulation is essential for the normal development of immune regulation and oral tolerance, as a genetically determined reduced sensitivity to lipopolysaccharide would increase the propensity for IgE antibody formation. The study [4] comprised 175 asthmatic and 77 food-allergic patients of varying age. There was a significant association between one of the alleles in the region, the -159T allele, and the presence of food allergy and, surprisingly, non-atopic asthma, but not atopic asthma. This would indicate that immune regulation in food allergy and respiratory allergy may not be identical.

The relationship between human leukocyte antigens (HLAs) and nut allergy was investigated in a study comprising 84 with a clinical history [5]. The frequency of HLA-B*07 and DRB1*11 was increased as compared to atopic, but not tree-allergic, controls. The findings, although statistically significant, would appear to be of limited clinical significance and do not throw any major light on the pathophysiology of food allergy. The search for genes strongly associated with food allergy continues.

The mother as part of the environment

The mother not only transfers 50% of her genes to her baby, but she is also the exclusive environment for the first 9 months and after birth continues to be a major environmental factor, particularly while breast-feeding her infant. The impact of perinatal factors on the development of food allergy was analysed in two recent prospective studies. A Norwegian birth-cohort study comprising 2803 infants, mode of delivery, maternal or infant use of antibiotics and information on potential confounders were obtained prospectively from parental reports and the National Birth Registry [6]. Parentally perceived reactions to egg, fish or nuts, as well as objectively confirmed reactions to egg at the age of 2.5 years, were selected as outcome variables. Among children

whose mothers were allergic, birth through Caesarean section was associated with a 7-fold-increased risk of parentally perceived reactions to egg, fish or nuts (odds ratio 7.0, confidence interval 1.8–28) and there was a 4-fold increased risk of confirmed egg allergy (odds ratio 4.1, confidence interval 0.9–19) in a logistic regression analysis, adjusting for pregnancy complications, birth weight, gestational length and socio-economic factors. The association between Caesarian section and food allergy was not significant in children of non-allergic mothers; nor was maternal or infant use of antibiotics associated with an increased risk of food allergy.

The second study comprised a German birth cohort of healthy term neonates with a family history of allergy, which was followed for the first year of life with regard to the development of atopic dermatitis and IgE antibodies to foods [7]. In that study, Caesarian section was associated with an increased risk of sensitization to food allergens (adjusted odds ratio 2.1, 95% confidence interval 1.2–3.8) as compared to vaginally born babies. No association with maternal allergy was reported in this study.

The two studies confirm the results of several previous studies that birth by Caesarian section is an independent risk factor for allergy development, including food allergy. The reasons for the association are unknown, however. A possible or even likely explanation could be that it is a consequence of altered microbial colonization of the neonate. Studies in recent years have shown differences in the composition of the gut microbiota between allergic and non-allergic children in the neonatal period, i.e. before they have developed any clinical symptoms of food allergy [8]. Furthermore, it is well established that the neonatal microbial colonization of the gut differs between babies born vaginally and after Caesarian section, being delayed in the latter.

High maternal age is another possible risk factor for food allergy as indicated by an American case–control study, reporting mothers of food-allergic children to have almost three times greater odds of being over 30 years at the time of delivery than mothers of non-allergic children [9]. The diagnosis of food allergy was based on a history of acute allergic reaction associated with the intake of one or more foods to which they had mounted an IgE response, documented by a positive skin-prick test and/or RAST (allergen-specific IgE antibody test). The findings support previous reports of maternal age as a risk factor for childhood hay fever and atopic dermatitis. The explanation for the association is unknown.

Exposure to allergenic foods

It is now more or less generally accepted that allergen avoidance during infancy is not associated with any major

reduction in the incidence of respiratory allergies. On the contrary, several studies over the past 6 years have suggested that the opposite may be true. Several previous studies have suggested, however, that the avoidance of cow's milk and egg during the first 6–12 months of life does reduce the incidence of food allergy and atopic eczema/dermatitis syndrome (AEDS; the proposed name for atopic dermatitis) in infants, although there is little effect on subsequently developing allergic manifestations, which are predominantly manifest in the respiratory tract. Osborn and Sinn [10] performed a Cochrane Systematic Review analysing the outcome of randomized or quasi-randomized trials in which hydrolysed infant formulas were compared to human-milk or cow's milk formulas. In all, 18 studies met the inclusion criteria. The authors concluded that there is no evidence to support feeding with a hydrolysed formula for the prevention of allergy in exclusively breast-fed infants. Such formulas should not be offered to infants for the prevention of allergy or food intolerance in preference to breast milk. Furthermore, there was no evidence of benefit from the use of hydrolysed formula in preference to cow's milk for early feeding in the majority of babies. In infants at high risk of allergy, however, such as babies with a strong family history of allergy, there is some evidence that prolonged supplementation of hydrolysed formula as opposed to cow's milk formula reduces the risk of subsequently developing food allergy. It should be pointed out that the modest effects were limited to food allergy and no protection has been shown against allergies in general. Furthermore, the incremental costs of hydrolysed formulas and the effects of these costs if borne by the parents on compliance have not been investigated in any trial. If a hydrolysed formula is considered for allergy prevention, then an extensively hydrolysed rather than partially hydrolysed product should be considered. This is obviously also recommended in the treatment of confirmed allergy to cow's milk.

Soy formulas are sometimes recommended for prevention of allergy and food intolerance under the (false) assumption that they are less antigenic than cow's milk products. A Cochrane Systematic Review, in which five eligible studies were identified and analysed, revealed no significant difference in the cumulative incidence of allergy, nor of any specific allergy or food intolerance in infancy or childhood [11••]. Thus, soy formulas have no role in the prevention of food allergy and they may in fact be contraindicated since children tend to outgrow soy allergy less readily than allergy to cow's milk proteins.

Despite the above systematic reviews, the potential of allergy prevention by food-allergen avoidance is still debated and there is no consensus among clinical researchers in the field. The American Academy of Pediatrics (AAP), and jointly the European Society

for Pediatric Allergology and Clinical Immunology (ESPACI) and the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) have published recommendations for the prevention and treatment of food allergy. Their recommendations were scrutinized recently by Zeiger [12]. While the three associations agree on the treatment of food allergy – avoidance of feeding the offending food to the baby, including an avoidance diet to breast-feeding mothers, and the use of extensively hydrolysed infant formulas, there is not total agreement on possible preventive measures. Thus the AAP, but not the European associations, recommends the elimination of particularly allergenic foods from the diet of breast-feeding mothers. Furthermore, the AAP recommends the exclusion of cow's milk until 12 months of age and eggs until 2 years, while the European recommendations are limited to exclusion for the first 4 months of life. The associations also agree on the recommendation to consider extensively hydrolysed formula for bottle-fed infants with a strong family history of allergy. Only the latter suggestion is reasonably well supported by controlled studies. The problem remains, however, in clinical praxis, how to define infants with a high risk for allergy, as there are currently no means for identification that are acceptable in terms of sensitivity and specificity.

Other nutrients

The ingestion of foods containing sesame seeds or oil has spread to developed countries in recent years. In that light, a study reporting sesame to be a major cause of IgE-mediated food-allergic reactions in Israeli infants and young children is of interest [13]. The study clearly confirms that sesame is a potential strong allergen, which may cause food allergy early in life. The authors speculate that since sesame products have become fashionable in Westernized countries, early exposure may cause this allergen to become a major cause of severe food allergic reactions, similar to peanut. The future will tell whether this will become true.

It is known that dietary vitamins have immunomodulatory effects, at least *in vitro*. This has encouraged an analysis of cohort data from a large study comprising over 8000 children [14]. The overall incidence of food allergy was 4.9% up to 3 years of age. A high level of parental education, income and a history of breast-feeding were found to be risk factors for food allergy in univariate analyses, while premature birth was protective. The most interesting observation in that study, however, was that in multivariate analysis intake of multivitamin preparations during the first 6 months of life was associated with a higher risk for food allergies in exclusively formula-fed children (odds ratio 1.63, 95% confidence interval 1.21–2.20). Similarly, vitamin use at 3 years of age was associated with an increased risk for food allergies of a similar

magnitude, both in previously breast-fed and exclusively bottle-fed children.

Infections

According to the so-called hygiene hypothesis, infections encountered early in life at a time when the immune system is maturing would protect against subsequently developing allergies, including food allergy in early childhood. The hypothesis was based on circumstantial epidemiological evidence and limited to hay fever. There is little firm support, however, that respiratory-tract infections would be protective and indeed it was slightly surprising since it is well known from clinical experience that respiratory-tract infections trigger asthma and other respiratory allergies. In a large Danish study, Benn *et al.* [15•] studied the impact of respiratory infections during the first 6 months on the development of atopic dermatitis, i.e. an allergic manifestation that is often triggered by food. Carefully controlling for other variables, the authors could show that each respiratory-tract infection was associated with a small but statistically significant risk of atopic dermatitis (odds ratio 1.08, 95% confidence interval 1.04–1.13). The risk of atopic dermatitis decreased with each additional exposure to three or more siblings, day care, pet ownership and farm residence – risk factors that have been confirmed in many previous studies and often assume to indicate a protective role of infections. The findings challenge the hypothesis that early infections protect against allergic diseases. The protective effect of number of siblings, day care, pet ownership and farm residence remained after controlling for clinically apparent infectious diseases, suggesting that the effect is established early in life independently of this parameter.

In that study, various environmental factors were suggested to be associated with an increased number of infections were confirmed to be protective: many (older) siblings and early day-care attendance. Thus, the protective effects of these exposures, which have been confirmed in many previous studies, are not due to respiratory-tract infections, but to other, unknown influences.

Conclusion

It may be true, although yet to be shown, that food allergies in early childhood are becoming more common and that the causes are the same as for later-developing respiratory allergies. Maternal influences on the development of food allergy are not limited to transfer of genetically determined susceptibility, but also include environmental influences such as mode of delivery and age. As two meta-analyses that have seriously questioned the use of special infant formulas for allergy prevention and novel prevention strategies, such as probiotic bacteria, have yet to be documented further, there are

still no measures for general recommendation in order to prevent food allergy. Further research concentrating on food allergy is obviously needed.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

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The study challenges the hypothesis that early infections protect against allergic diseases and suggests that previously reported protective effects of siblings, day care, pet ownership and farm residence are all independent of infections.