

Role of food allergy in asthma in childhood

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Atopy is the major predisposing factor for asthma identified up to now, and allergen exposure, particularly indoor allergens, is considered as a causal factor for asthma. Food allergy is frequently underestimated in association with asthma, however food allergy has been shown to trigger or exacerbate broncho-obstruction in 2 to 8.5% of children with asthma. There is also evidence that double-blind placebo-controlled oral challenge is able to increase unspecific bronchial hyperresponsiveness. Sensitization to food can occur early in life involving T cell response, mainly of the Th2 phenotype, but also IgE-mediated hypersensitivity. Moreover, it has been shown that sensitization to food allergens early in life is a risk factor for sensitization to inhalent allergens and respiratory symptoms later on. Epidemiological studies suggest that changes in the dietary composition, such as trans-fatty acids, could be involved in the increase of asthma prevalence. The introduction of formula during the first trimester of life increases the risk of having asthma. The diagnosis of food allergy associated with asthma is not easy, nevertheless is important for allergists, pulmonologists and paediatricians to consider food allergy in children with respiratory symptoms, especially when asthma symptoms start early in life and when they are associated with other manifestations of food allergy. Children sensitized to cow's milk proteins and also having atopic eczema are at higher risk for asthma. Since avoidance of the offending food is the first step in the management of children with asthma associated with food allergy, a careful identification should be done in order to avoid unnecessary elimination of foods. *Curr Opin Allergy Clin Immunol* 1:145–149. © 2001 Lippincott Williams & Wilkins.

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Abbreviations

AD	atopic dermatitis
CRM	citrus red mite
Th	T helper

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Introduction

The increase in asthma and allergic disease among children is a matter of worldwide concern [1•]. This increase seems to be not only a result of improvements in screening and diagnosis, but also changes in environmental factors, including changes in dietary habits with the introduction and exposure to new dietary compounds that may be allergenic [2•].

The association of food allergy and the clinical expression of allergic diseases has always been difficult to establish, especially in asthma, when some investigators deny its existence and others tend to overestimate it.

Although food allergy has been shown to cause asthma, particularly in children, epidemiological studies precisely examining its prevalence in population-based studies are lacking because of the complexity of such studies. Therefore, at present, the prevalence of asthma as a result of food allergy can only be estimated from prospective studies performed within the asthmatic population [3].

Although foods suspected as causal factors of asthma constitute a very long list, several studies have confirmed that those foods and additives that actually produce wheezing and other symptoms during double-blind placebo controlled challenge are remarkably few. Among these foods, egg, peanut, milk, nuts, soy, fish, shellfish and wheat have been identified. The first three in the list comprise nearly 80% of the total (Table 1) [2•]. However, peanut is a very important inducer of food allergy in some countries, so much so that it is now the principal food allergy in children over the age of 3 years [4].

Fish is the second most common cause of food allergies after egg, in countries in which fish is a large part of the daily diet [5].

Evidence of cross-reaction between food allergens and inhalant allergens has mainly been reported in cases of pollen hypersensitivity with fruit and vegetable allergy [6]. Several causes of cross-reactivity between pollens and vegetable food have been elucidated [7]. More recently, progress has been made in the identification of cross-reactive allergens in latex and food [8].

A large list of drugs, chemicals and additives has been implicated as factors that may induce asthma symptoms in susceptible individuals. Between 2000 and 20 000

Table 1. Clinical symptoms, according to five predominant food allergens, in 544 children with food allergy

Symptoms	Egg	Peanut	Milk	Mustard	Cod
Atopic dermatitis	209	89	34	21	8
Urticaria, angioedema	61	61	18	21	17
Asthma	13	28	4	2	7
Gastrointestinal	4	4	5	1	0

Results are expressed as no. of patients.

substances are added to food on a regular basis to enhance flavour and colour or to prevent spoilage. Whereas many of these have been reported to cause various adverse reactions, such as urticaria, angioedema, and hyperreactivity, there are relatively few communications in patients with asthma. Some substances that affect the lung, such as monosodium glutamate [9], tartrazine [10], sulphites or sulphiting agents [11], food-borne toxins as well as histamine, alkaloids, paraquat, polychlorinated biphenyls, sweet potato toxins, Spanish toxic oil, paralytic shellfish toxin, red tide toxin, botulism, carrageenan [12], have been reported.

Pathogenesis of food-induced asthma

The increase in the prevalence of allergic diseases is not yet understood, although it appears to be associated with a westernized lifestyle and occurs in regions with increasing prosperity. It has been argued that the increasing prevalence of atopic disorders could be caused both by increased susceptibility and environmental toxicity, and it has been suggested that changes in diet may play an important role in determining the increasing incidence of immunological susceptibility [13]. Recently, it has been suggested that changes in the fatty acid omega 3–omega 6 composition in the diet may increase the risk of allergic diseases in those children who maintain the T helper (Th) type 2 lymphocyte phenotype after birth, and therefore the predisposition to become atopic. There is now some epidemiological support for dietary antioxidant vitamins being a risk factor for asthma in adults, and also some evidence for the intake of oily fish having a preventive effect in children [1••]. Trans fatty acids have been a typical part of the 'western' diet, and the hypothesis that they may play a part in the development of childhood asthma and allergies seems worth pursuing [14].

An alternative explanation of the increase in asthma susceptibility is that the change in CD4 lymphocyte phenotype from Th2 to Th1 and the expression of Th2 cytokines, IL-4 and IL-13 among others, now occurs less frequently in wealthier societies because children no longer suffer from the infections that used to promote this change [1••]. This hypothesis has been called the 'hygiene hypothesis' [15].

An early onset of IgE-mediated food allergy associated with severe atopic dermatitis (AD) indicated the presence of a Th2-dominant lymphocyte pattern, with a cytokine profile facilitating an IgE response to environmental antigens. It is not surprising, therefore, that an early manifestation of IgE-mediated food allergy is accompanied by a very high risk of sensitization to airborne allergens and a high risk of developing asthma and allergic rhinitis [16•].

There may be a significant number of routes of exposure in individuals. Those who have gastrointestinal tract hypersensitivity to food allergens and are unable to deal with the absorption of food allergens suffer presumed allergic reactions at distant sites. Another mechanism involves the specialized entry of luminal antigens into the gastrointestinal tract, utilizing a specialized epithelial cell termed a membranous epithelial cell or M cell. Once food allergen or food allergen fragments are subepithelial, either via M cells or through transport by the epithelium itself, it is free to interact with allergen-specific T cells as well as IgE-bearing B cells. Localized mast cells triggered via an IgE food allergen bridge may lead to more intact absorption of allergen by chemical mediators modifying mucosal permeability [17].

Food-induced asthma may also be triggered by the inhalation of volatile food antigens, directly stimulating airway mast cells, especially in highly allergic individuals or in cases of occupational allergy.

All other non-immunological adverse reactions should be classified as food intolerance. This is the case with sulphite or aspirin-induced asthma. There are, however, many non-specific mechanisms that may aggravate respiratory symptoms caused by food allergy, such as exercise, cold drinks, aspirin or the concomitant intake of alcohol [3].

The asthmatic airway is particularly sensitive to the effect of sulphur dioxide, probably by the direct stimulation of irritant cholinergic receptors. In those anaphylactic reactions associated with the ingestion of foods containing sulphites in a bound form, a sulphite oxidase deficiency has been implicated [18,19]. This mechanism is very similar to that induced by monosodium glutamate; however, other possible explanations have been suggested, such as the augmentation of reflex activity in the lung or the induction of bronchoconstriction by the synthesis and release of hormonal factors from the hypothalamic-pituitary region [9].

Soybean can also induce asthma symptoms by non-IgE mechanisms, which may explain the presence of an irritant-positive prick test in the absence of specific IgE [20]. With regard to milk allergy-induced asthma, there

is little scientific evidence to suggest that the ingestion of milk causes an increase in mucus production in the respiratory tract. In the few studies that have been conducted there has been no deterioration in asthma status after the ingestion of dairy products [21].

The mucous aspiration of gastric contents into the airways in patients with gastroesophageal reflux has also been mentioned from a mechanistic point of view. Aspirate food allergens could sensitize T cells in the peribronchial lymphoid tissue and induce the production of food-specific IgE antibodies that bind to the airway mast cells. Subsequent oral challenge with these food allergens might then induce IgE-dependent mediator release from mast cells as well as T cell and eosinophil activation, thus contributing to airway inflammation and reactive airway disease [22,23].

Epidemiological aspects

The majority of food-induced asthma cases are observed in early infancy, and are then often related to cows milk hypersensitivity, in which asthma has been noted in 7–29% of cases. Cows milk protein is among the first dietary antigen infants encounter. Allergy to cows milk protein affects between 2–7.5% [24] and 8.45% of infants [25•]. The estimated prevalence of cows milk allergy in an unselected population is 2.2–5.9% [26].

The associations between asthma and atopic eczema, and perhaps food allergy, must be emphasized. Many children with severe chronic asthma suffer from severe eczema in early infancy [24]. It has been stated that eczema in children has a very good prognosis; nevertheless, it is associated with an increased risk of developing respiratory allergy. This risk is especially high in children with an early onset of food allergy [27•].

In those children with AD having an IgE-mediated allergic reaction to cows milk, asthma was frequent [3]. Another study [28] demonstrated that the combination of AD and food allergy at 12 months of age was a risk factor for asthma-like symptoms, but also that this risk decreased at 24 months. Early adverse food reactions, before 36 months of age, increased the risk of developing asthma by 82% [27•]. All the studies support the theory that early food allergy, alone or in conjunction with atopic eczema, is a strong risk factor for having asthma later in life.

In areas where mugwort and birch pollen are rare, food allergy only represents a minor cause of perennial asthma. Low prevalence rates have also been found by other authors using double-blind placebo-controlled challenge [16•,29•,30]. However, when these pollen species are prevalent, allergy to cross-reactive food epitopes, such as celery or fruits may be more important.

Citrus red mite (CRM) is the most important allergen in citrus farmers with asthma and rhinitis, in which a causative allergen has not been identified [31]. However, there is no difference in the prevalence of asthma between children with and without sensitization to CRM. It has been shown that bronchial responsiveness is increased in CRM-sensitive children even if they have no asthmatic symptoms [32]. In farming areas, CRM should be included in the skin test battery for screening [31].

Peanuts are the predominant allergen in children over the age of 3 years in some studies from the USA and UK [2•,4]. The prevalence of this allergy in children in general is 1.3%. However, the incidence of this allergy has increased tremendously; it has doubled over the past 10 years. The most recent studies give a mean age of detection of 24 months. Peanut hypersensitivity is generally a long-term problem, showing no tendency to decrease over time.

Allergy to fish is common in fish-eating populations and in fish-processing communities. The prevalence of immediate-type fish allergy is higher when the consumption of fish plays a greater part in the community's diet. In Norway, the prevalence of fish allergy reaches 1/1000 of the general population, in Sweden it represents 39% of the paediatric population [5].

Others investigators were unable to confirm this prevalence in a population-based study [19], although the report did not include a properly designed blind challenge. The incidence of sulphite sensitivity in the paediatric population is unknown [18].

The prevalence of a positive skin test to soy is 15.3% in the group of individuals with asthma. There may be an association between the level and duration of exposure to inhaled soybean and sensitization to soybean aero-allergen [20].

Sensitization to foods

The induction of antigen-specific immunological hyporesponsiveness in the normal reactors occurring after previous oral (enteral) food antigen exposure plays a major role in the presentation of food allergy. The induction and maintenance of systemic immunological hyporesponsiveness (oral tolerance) depend on the genetic background and social environmental factors, the nature, dose, and frequency of administration of the antigen and various adjuvant or covert factors.

Antigen administration in a dose that would induce tolerance in adults leads to sensitization in neonates. The results of the study [16•] support the hypothesis that minute amounts of food antigens induce tolerance

rather than sensitization even in infants with an hereditary risk of atopy.

Moreover the restriction of dietary constituents in the lactating mother or in the newborn could diminish the exposure to food antigens. The benefit of the restriction of food antigen has diminished the prevalence of food-related allergy in the first months and years of life, but such benefit diminishes or disappears entirely during long-term follow-up, and there has been no protection against asthma and allergic rhinitis [33]. These interactions can induce allergic sensitization and subsequently lead to local inflammation resulting in clinical symptoms of atopic disease.

Conclusion

Several studies have demonstrated that early and long-lasting sensitization to food and inhalant allergens must be regarded as a risk factor in the development of clinical manifestations of allergic disease later in life [34,35]. Allergic sensitization is frequently asymptomatic, but sensitization is generally considered the first step in developing atopic disease [28].

Children introduced to formula before 3 months of age have a significantly greater incidence of asthma at 4 years of age. Early introduction to formula increased the risk of any atopic disease. In a family history of atopy, introduction to formula within the first 3 months increased the risk of asthma (odds ratio 1.8; 95% confidence interval 1.2–2.6; $P < 0.01$) [36]. Moreover, infants with a long-lasting sensitization to food allergen have a 5.5-fold higher risk of developing asthma than only transiently food-sensitized children [7].

Infants with egg allergy or evidence of IgE antibody to egg protein have a markedly increased risk of developing asthma compared with infants with no evidence of IgE sensitization. Studies suggested that food sensitization is an uncommon event. However, it would seem prudent to avoid exposing young infants at high risk of atopic disorders to food allergen that probably causes life-long sensitization (e.g. peanuts, nuts, fish, shellfish) for the first 2–3 years of life. Mothers of high-risk infants should probably avoid peanuts, nuts, fish and shellfish while breast-feeding [16*].

Pollen allergy has frequently been found among peach-allergic patients (odds 4:1); therefore, pollenosis might be considered a risk factor in the development of peach allergy. Despite this fact, the results of the study provide evidence that peach allergy is linked to special pollen sensitization. The peach allergy patients in our study frequently reacted to several pollens, grasses, weeds, trees, even when some of the species had never been encountered in our area. A total of 81% of peach-allergic

patients had allergic respiratory disease and were allergic to pollen. We would suggest, therefore, that patients showing sensitization to most taxonomically unrelated pollens be questioned about fruit allergy, and that the finding should be kept in mind when pollen allergy infants and (peach)-allergic patients are evaluated [37]. CRM was also a very common sensitization allergy in children living around citrus farmers, but the prevalence of asthma is not different between children with sensitization to CRM and those without it [38].

A clinical history of food allergy may be associated with latent respiratory allergy. When both respiratory and food allergy appear in the clinical history of allergy individuals, avoidance of both sources may be considered to be a good therapeutic measure; desensitization to one of the allergenic proteins may also result in desensitization to the other [6].

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