

Relevance of inhalational exposure to food allergens

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Purpose of review

This review discusses the inhalational route as a clinically important route of exposure to food allergens.

Recent findings

In childhood, we have recently demonstrated that food allergens can induce both early and late phase bronchial reactions within blinded, placebo-controlled challenges. Additionally, clinically important levels of food allergens have been measured in environmental air samples.

Summary

It is well known that the ingestion of food allergens frequently causes respiratory symptoms and that the mechanism of death in fatal anaphylaxis is usually profound bronchospasm. The mechanism by which ingested food allergens induce bronchial reactions is unclear. There are many case reports of bronchial reactions to aerosolized food allergens. Within the food industry the problems have been examined more systematically. From such work it is possible to gain an impression of the potential prevalence of the problem. With 10% of adult asthma being occupational and 10% of occupational asthma being induced by aerosolized food, inhalational exposure to food allergens plays a major role in at least 1% of adult asthma. For a patient with co-existent food allergy and asthma it is important that both dietary and environmental avoidance be practised. The similar pathophysiology of allergic and occupational asthma and the ability of inhaled food allergens to cause the latter raises the question as to whether aerosolized food could play a role in the pathogenesis of childhood asthma.

Keywords

food allergens, asthma, occupational asthma, aerosolized allergens

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Introduction

Foods generally behave as allergens when they are eaten or come into contact with the skin. Their ability to become aerosolized and cause bronchial reaction through an inhalational route is less well appreciated. Most severe allergic reactions predominately involve respiratory compromise [1,2]. In this review, we will look at the problems of respiratory reactions to ingested and inhaled foods.

Respiratory reactions associated with allergic reactions to ingested food

Many investigators have examined the extent to which allergic reactions to food involve the lower respiratory tract. For example, in one study, 100 children with IgE and non-IgE mediated milk allergy (mean age 16 months) were challenged with milk [3]. A fifth developed lower respiratory tract symptoms during the challenge. In a larger study, 320 children and young adults (6 months to 30 years) with atopic dermatitis and possible food allergy underwent placebo-controlled, blinded food challenges. Food allergy was confirmed in 205 (64%), with a quarter experiencing lower airway problems during the food challenge [4]. These respiratory reactions were typical early phase responses seen within 2 h of exposure [4].

The mechanism of food induced asthma is unclear. There are a few possibilities. First, small particles of food may be inhaled into the airway during mastication. Alternatively, food may enter the airway as a result of gastro-oesophageal reflux which often co-exists with asthma [5]. In either of these ways, food allergens could directly stimulate airway mast cells inducing a lower airway reaction. Second, potentially allergenic proteins may also be able to reach the lungs via the circulation after absorption from the gut. A final possibility is that allergenic protein may act indirectly on the lower respiratory tract via inflammatory mediators released from the skin or gastrointestinal tract. These mechanisms required further elucidation.

Respiratory reactions associated with aerosolized food

Respiratory reactions to aerosolized food have been described with occupational, environmental and domestic exposures to allergenic foods.

Aerosolized food as a cause of asthma

There are many examples in the literature of bronchial reactions associated with aerosolized food proteins. A

series of 12 patients with respiratory symptoms in response to contact with aerosolized fish has been presented by one group [6]. Similar reports have been presented by other groups [7,8]. It would seem from such reports that fish protein can readily become aerosolized through boiling, frying or simply by being exposed to the atmosphere. Taylor *et al.* [9] have investigated this further by quantifying the amount of fish allergen within environmental samples from a fish market. Using a competitive IgE immunoassay, they were able to measure levels of fish allergen of 2–25 ng/m³. The factors that determine how readily different foods become aerosolized have not been studied, although historically it seems that cooking, particularly steaming, plays an important role.

There are also self-reports of allergic reactions to peanuts on commercial airliners [10]. Of 3704 individuals registered on a national peanut and tree nut allergy register, 14 (0.4%) had experienced a reaction with only inhalational exposure on a commercial airliner (though direct contact could not be completely ruled out). In support of this mode of exposure, it has been reported in abstract form that peanut allergen has been detected in the filter system of commercial airlines [11]. Many airlines have now stopped including peanuts and tree nuts within snacks.

A number of other foods have additionally been implicated in causing allergic reactions via the inhalational route. These include milk [12], green bean [13,14], lentils [15], buckwheat [16], egg [17] and seafood [18]. Many of these are important problems in the food industry.

Occupational asthma in the food industry

Occupational exposure to aerosolized food can lead to the development of asthma in adult life. It is estimated that a tenth of adult asthma is related to occupational exposure [19]. A prime example is baker's asthma [20•]. There is now convincing evidence that this is caused by occupational exposure to airborne cereal grain or amylase, with the prevalence of symptoms being related to the level of exposure to aerosolized grain allergen within longitudinal cohorts [21•,22]. Workers with this problem cough and wheeze only in association with exposure to aerosolized wheat proteins and have positive skin prick or serum specific IgE to wheat proteins. A second example is the group of egg proteins. Occupational asthma due to aerosolized egg protein has been reported in confectionery workers and egg processors [23,24•,25,26]. Other examples include soy, cocoa, garlic and buckwheat [19].

Occupational asthma causes a significant medical and economic burden and it has been suggested that 9–15%

of adult asthma may be due to occupational factors [27]. There are unfortunately few large cross-sectional studies looking at the full extent of the problem. The data available come mainly from voluntary surveillance schemes such as SWORD (surveillance of work-related and occupational respiratory disease) in the UK. From such reports, it has been estimated that the food industry accounts for 10% of occupational asthma with over 200 cases per million employed [28]. Data reported by occupational physicians suggest that the annual risk of a baker developing baker's asthma is between 0.3 and 4.1%. This represents a considerable risk over a lifetime as a baker [21•,29].

It is intriguing that the majority of adults affected by food-induced occupational asthma can ingest the allergen without symptoms [20•]. This discrepancy may be due to localized production of specific IgE in the respiratory mucosa. Such a mechanism has been described in the case of grass pollen allergy [30]. Another possible explanation is that food allergens generally have certain physico-chemical characteristics such as being resistant to heat, acid and proteolytic enzymes [31–34]. Food allergens that cause occupational asthma may become denatured before they reach the alimentary tract. This question is also important in childhood as many children are sensitized to food allergens although few have clinical reactions to them on ingestion [35]. This raises the important possibility that children who are sensitized to a food allergen but do not react clinically after ingesting the food could possibly develop a mucosal response in the upper or lower airway after inhalational exposure. There are no studies that have examined this possibility.

Environmental aerosolized food allergen exposure

Foods have also been found to behave as more general environmental aeroallergens beyond the work environment and have been responsible for community outbreaks of asthma. Barcelona was affected by episodic epidemics of asthma during the 1970s and 1980s. Cases were clustered around the port area. Exacerbations were sudden in onset and often very severe with fatalities being reported. The cause of the problems was investigated using a case-control approach. Epidemics were linked to days when soya was being unloaded at the port. In support of this hypothesis, 74% of cases had specific IgE to soya compared with only 45% of controls [36]. Similar asthma epidemics related to aerosolized soya have also been described at Cartagena [37].

Bronchial challenges with aerosolized foods

Recently we have investigated a group of 12 children who presented with food allergy to our clinic over a 2-year period [38••]. All had proven IgE-mediated food allergy. Additionally, they suffered from asthma that

seemed to worsen on inhalational exposure to the food to which they reacted. The implicated foods were fish, milk, chickpeas, buckwheat or eggs. Although the children were practising dietary avoidance, the families continued to cook with the foods and the children continued to have asthma symptoms. Nine children consented to a bronchial challenge. Five developed objective asthmatic signs and lung function changes on bronchial food challenge. Two children also developed late phase responses. When the families of these children stopped cooking the food in the house, there was a considerable reduction in both their child's symptoms and inhaled steroid requirements.

Early and late phase bronchial reactions have also been seen in the setting of food induced occupational asthma [39]. These observations emphasize that food allergens can behave as inhalational occupational and domestic allergens. Therefore, it is critical that affected individuals avoid both oral and inhaled exposure.

Is there a role for food allergy in the pathogenesis of allergic asthma?

Given the ability of food allergens to behave as inhalant allergens, the question of whether food allergy could play a role in the pathogenesis of asthma deserves consideration. In childhood the expression of atopy progresses with age [40]. This 'allergic march' starts initially with eczema and food allergies, allergic asthma and rhinitis appearing later in childhood. This clinical picture is mirrored in terms of sensitization, with infants being predominantly sensitized to foods whereas school age children are predominantly sensitized to aeroallergen [41]. Importantly, sensitization to foods, particularly egg, is predictive of both sensitization to inhalant allergens [41] and subsequent development of asthma in childhood [42] and adult life [43]. There are two potential explanations for this temporal shift in the pattern of sensitization and clinical allergy to food and inhalant allergens. Food and inhalant allergy may both be manifestations of the same process seen at different points in the maturation of the immune system. Alternatively, sensitization to food allergens itself may have a causal role in the development of sensitization to inhalants and the subsequent development of asthma.

There are several lines of evidence that would seem to support this second hypothesis. First, it is likely that children are exposed to high levels of aerosolized food allergens within the home. As previously mentioned, fish allergen has been found in measurable quantities in air samples taken from a fish market [9]. There has been a marked reduction in the ventilation of western homes over the last 50 years, trapping aeroallergens within the domestic environment [44]. Infants now spend much of their time indoors, especially in the kitchen when food is

being prepared [45]. Second, many foods that commonly cause allergy in children and adults (for example egg, milk, wheat, and fish) frequently cause occupational asthma in adults [7,12,20,46,47]. Occupational asthma is characterized by the same pathological changes that are seen in allergic asthma with eosinophilic inflammation and subepithelial fibrosis [48]. Third, in numerous animal models of asthma, bronchial inflammation and airway hyper-responsiveness can be induced by inhaled food allergens like ovalbumin [49,50]. Finally, eosinophilic infiltration and remodelling has already been seen in the airways of young children prior to asthma being diagnosed [51]. Given this evidence, it is plausible that inhalation of food allergen in young infants with food allergies could lead to mast cell degranulation and the influx of further inflammatory cells such as eosinophils and lymphocytes, increased IL-4, IL-5 and IL-13 production and subsequent airway remodelling. Such an inflammatory milieu might potentiate further sensitization to inhaled aeroallergens such as house dust mite. This hypothesis could explain the progression from food allergy in early infancy to aeroallergen sensitization and asthma in later childhood. While this hypothesis is highly speculative, there are sufficient data to warrant further research in the area. Thus in adult asthmatics with inhalant allergies, investigators have found allergen specific T lymphocytes in bronchoalveolar lavage fluid [52,53]. There are also examples of allergen specific T cells to food proteins isolated from the skin of children with eczema and food allergies [54,55]. There have been no studies undertaken to investigate whether there are specific T cells that respond to food allergens present in the airways of wheezy infants and children with food allergies.

It is unclear whether the progressive sequences of infantile eczema, food allergies, and subsequent development of allergic respiratory disease are causally related to each other. Many atopic children progress through these different clinical phenotypes. There are considerable data linking eczema and food allergies. Thus cow's milk protein intolerance and egg allergy are associated with eczema. Studies looking at children undergoing double-blind, placebo-controlled food challenges have demonstrated exacerbations of eczema in a significant proportion of children [56]. As mentioned above, allergen specific T cells to foods have been found in the skin of children with eczema [54,55]. More recently we have suggested a reverse causal relationship, namely that eczema leads to food allergy [57]. We have shown an association between the topical exposure to peanut oil in infants with eczema and the subsequent development of peanut allergy. If indeed eczema can lead to food allergy and food allergy can contribute to the development of asthma, this might explain in part the progression of atopic disease in childhood from eczema through to food allergies and subsequent respiratory allergies.

Clinical implications of inhalational exposure to food allergens

Inhalational exposure as a cause of bronchial allergic reactions to foods is not well recognized. The extent of this problem is unclear as epidemiological studies have not addressed the issue. We are therefore left trying to quantify the problem through a series of case reports and case series. One Internet-based survey has systematically asked individuals with anaphylaxis to food whether they reacted with just inhalational exposure; 5.9% responded positively [58]. These data need to be confirmed in future studies in which the diagnosis of food allergy is proven by a double-blind placebo-controlled food challenge. The ability of food allergens to behave as aeroallergens has two important clinical implications. First, dietary avoidance alone may be insufficient to prevent further allergic reactions. Second, exposure to even low concentrations of aerosolized food allergen may be responsible for persisting symptoms of chronic asthma, necessitating the need for complete environmental avoidance in individuals with food allergy and poorly controlled asthma.

Conclusion

Inhalational exposure to food allergens seems to be an important cause of symptoms in a number of children and adults with food allergy. The exact prevalence of the problem is unclear as population-based studies are lacking. Studies suggest, however, that aerosolized food has a major role in the aetiology of occupational asthma. When food allergens are thought to play a role, it is important to identify the problem and take steps to avoid direct and indirect exposure. This may lead to a significant improvement in a patient's asthma control. The ability of aerosolized food allergens to induce respiratory symptoms raises the question of whether this form of allergen exposure is involved in the pathogenesis of childhood asthma. The extent to which inhaled food allergens are triggers in exacerbations of asthma also deserves further study both in children with food allergy and the numerous others who are sensitized to a food but have no oral symptoms.

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