

Food Allergy and the Respiratory Tract

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Previous studies have confirmed that IgE-mediated, food allergy-induced respiratory tract symptoms occur, typically accompanied by cutaneous or gastrointestinal symptoms. The possibility that respiratory tract symptoms are food allergy induced should be considered in patients who have a current or past history of one or more of the following: atopic dermatitis, wheezing (or experiencing anaphylactic symptoms) after ingesting a particular food or foods, and confirmed food allergy. Moreover, the work-up of food allergy in asthma should be considered in patients in whom asthma is poorly controlled despite persistent use of appropriate asthma medications. A definitive diagnosis of food allergy should be based on clinical history, appropriate laboratory testing, and, when indicated, well-controlled oral food challenges. Treatment is based on establishing a safe elimination diet and an emergency plan for managing reactions caused by accidental ingestion.

Introduction

The most common clinical manifestations of allergic reactions to foods involve the skin and gastrointestinal tract [1]. In addition, upper and lower respiratory tract symptoms may result from an allergic reaction to food. These symptoms are not as common and usually are accompanied by cutaneous or gastrointestinal symptoms. Respiratory symptoms, especially asthmatic reactions, secondary to food allergy reactions are worrisome because they have been observed frequently in fatal and near-fatal reactions following food ingestion [2].

A wide variety of respiratory symptoms have been attributed to food allergy, including nasal congestion, rhinorrhea, sneezing, itching of the nose and throat, coughing, and wheezing. Approximately 6% of asthmatic children have food-induced lower airway symptoms. In the evaluation of patients with these clinical symptoms, numerous causes, not only food allergy, must be considered in the differential diagnosis (Table 1). Food allergy as a specific cause of respiratory tract symptoms has been

less well defined compared with viral upper respiratory tract infections, allergic rhinitis, and sinusitis.

This review discusses information implicating foods as a cause of respiratory tract symptoms. A specific focus is placed on the role of food allergy in asthma, rhinitis, otitis media, and respiratory anaphylaxis. Circumstances in which food allergy should be considered as a cause of respiratory tract symptoms are highlighted. Key clinical studies in this area are reviewed and contrasted. This information should provide a practical approach to the work-up of patients presenting with respiratory tract symptoms and food allergy.

Epidemiology

Critical to any discussion of food allergy is a basic understanding of the classification of adverse food reactions. An adverse food reaction is any abnormal clinical response following ingestion of a food or food additive [3]. These reactions are divided into two major categories. First, food allergy is an immunologically mediated food reaction unrelated to any physiologic effect of the food or additive (eg, an IgE-mediated or allergic reaction to an ingested peanut resulting in laryngeal edema, coughing, and wheezing). Second, food intolerance is any abnormal physiologic response to a food that is not immunologically mediated (eg, an exaggerated physiologic reaction following ingestion of monosodium glutamate [MSG] including headache, flushing, muscle tightness, and generalized weakness).

The true prevalence of food allergy-induced respiratory tract symptoms has been difficult to ascertain. There is an elevated public perception of food allergy-induced asthma [4], and it is understandable why many associations have been made between ingestion of certain foods and food additives and respiratory tract symptoms. Public perceptions, however, have not always been substantiated when food challenges have been used to confirm patient histories [5,6]. When the focus has been on the role of food allergy reactions and the respiratory tract, the incidence in asthmatic patients has been estimated to be between 2% and 8% in children and adults [7,8]. Although a high percentage of asthmatic adults perceive that food additives worsen their respiratory symptoms [9], well-controlled studies in this area have reported a prevalence of less than 5% [7,10]. Finally, an Australian survey noted that 17% of 669 adult respondents reported food-induced respiratory symp-

Table 1. Respiratory tract symptoms: differential diagnostic categories

Infectious illnesses
Viral upper respiratory tract infections
Recurrent otitis media/eustachian tube dysfunction
Sinusitis
Allergic diseases
Allergic rhinitis (seasonal, perennial)
Asthma
Food allergy
Nonallergic rhinitis
Passive tobacco smoke
Strong odors
Weather changes
Anatomic abnormalities
Nasal polyps
Deviated nasal septum
Foreign body
Enlarged tonsil and adenoids
Ciliary dyskinesia
Cystic fibrosis
Rhinitis medicamentosa

toms [11]. Asthmatic patients did not report food-related illness more frequently than did nonasthmatic patients, but those reporting respiratory symptoms following food ingestion were more likely to be atopic.

Pathogenesis

Immune responses mediated by specific IgE antibodies to food allergens are the most widely recognized mechanisms for food-induced respiratory tract symptoms [12••]. Atopic patients produce IgE antibodies to specific epitopes in the food allergen. These antibodies bind to high-affinity IgE receptors on basophils and tissue mast cells throughout the body, including the upper and lower respiratory tract. Subsequent allergen exposure binds these IgE antibodies, initiating the release of a vast array of mediators such as histamine, prostaglandins, and leukotrienes. This results in vasodilatation, smooth muscle contraction, and mucus secretion, which in turn lead to the different clinical symptoms observed in the respiratory tract.

Egg, milk, peanut, soy, fish, shellfish, and tree nuts are some of the common food allergens that have been implicated in respiratory reactions and have been confirmed in well-controlled, blinded food challenges [5,10,13•,14]. Studies of patients experiencing near-fatal or fatal anaphylactic reactions following food ingestion have shown that these reactions are mainly secondary to peanut, tree nuts, and shellfish [2,15]. Several different food additives, including MSG, sulfites, and aspartame, have been implicated in adverse respiratory reactions [16]. Also, as described in *Respiratory symptoms induced by inhalation of food allergens* below, asthmatic responses may occur due to direct inhalation of aerosolized particles containing allergenic food.

Clinical Background: Food Allergy–Induced Symptoms

Asthma

The majority of information regarding food allergy and respiratory tract symptoms deals with food-induced asthma. In one study, 300 consecutive asthmatic patients (aged 7 months to 80 years) were evaluated in a pulmonary clinic [7]. Twenty-five patients had a history of food allergy suggested by clinical symptoms, skin tests, or radioallergen sorbent test (RAST). Food-induced wheezing was documented in 6 (2%) of the patients; all of these were children aged 4 to 17 years.

In another study, 140 asthmatic children (aged 2 to 9 years) were screened using clinical history and food-specific IgE antibody testing [17]. Of these children, 32 underwent blinded food challenges: 13 (9.3%) had food-induced respiratory symptoms, and eight (5.7%) had specific asthmatic reactions documented during food challenges. Only one patient had asthma as the sole symptom during a positive food challenge. Interestingly, the patients with food allergy and asthma were generally younger and had a past medical history of atopic dermatitis.

Oehling and Baena Cagnani [18] reported that food-induced bronchospasm was present in 8.5% of 284 asthmatic children evaluated. The majority of the allergic sensitization occurred in the 1st year of life and was caused by a single food, especially egg. Finally, Businco *et al.* [19] evaluated 42 children (aged 10 to 76 months) with atopic dermatitis and milk allergy. Eleven (26%) of these patients developed asthmatic symptoms during a positive food challenge; in six children, asthma exacerbation was the only adverse symptom observed.

The prevalence of food-related wheezing appears to be highest in younger patients with atopic disease. Hill *et al.* [20] in Australia studied 100 children (mean age 16 months) who had clinical histories of adverse reactions to cow's milk. The children were separated into three distinct groups based on symptoms. The first group consisted of 27 infants who reacted acutely to cow's milk ingestion (29% had lower airway responses on oral challenges) and had cow's milk-specific IgE antibodies. The second group consisted of 53 infants with primarily non-IgE-mediated gastrointestinal reactions to cow's milk challenges; only 4% of this group experienced lower airway symptoms. The third group consisted of 20 patients with late-onset reactions to oral challenges with cow's milk; the majority of these patients had chronic asthma or atopic dermatitis, and 50% had wheezing after the milk challenges. Another study from Turkey confirmed that food allergy can elicit asthma in children aged less than 6 years, but the incidence is low (4%), even with major food allergens such as egg and cow's milk [21].

Over two consecutive decades, 598 children with pulmonary disease were evaluated at the National Jewish Center for Immunology and Respiratory Medicine [22]. Of the 410 (69%) children with a history of asthma, 279 (68%)

had a history of food-induced asthma. Of the 279 patients, 168 (60%) had a positive food challenge and 67 (24%) had a positive blinded food challenge that included wheezing. The following foods were responsible for these reactions: peanut (19 patients), cow's milk (18), egg (13), tree nuts (10), soy (two), wheat (two), other legumes (two), and turkey (one). Interestingly, only five (2%) of these patients had wheezing as their only objective adverse symptom.

A total of 320 patients (aged 6 months to 30 years) with atopic dermatitis undergoing blinded food challenges at Johns Hopkins Hospital were monitored for respiratory reactions [23]. The patients were highly atopic, had multiple allergic sensitivities to foods, and more than half had a prior diagnosis of asthma. Food allergy was confirmed by blinded challenges in 205 (64%) of these patients; almost two thirds experienced respiratory reactions during positive food challenges (nasal, 70%; laryngeal, 48%; pulmonary, 27%). Overall, 34 (17%) of these 205 patients developed wheezing as part of their reaction. Furthermore, 88 (43%) of these patients were monitored with pulmonary function testing during positive and negative food challenges. Thirteen (15%) of the 88 patients developed lower respiratory symptoms, including wheezing, but only six (7%) of the patients had a greater than 20% decrease in forced expiratory volume in 1 second (FEV₁). As documented in the studies cited earlier, wheezing as the sole manifestation of respiratory reaction was rare.

These results suggest that respiratory symptoms may be provoked in a subset of asthmatic patients. Table 2 summarizes the major considerations for implicating the specific role of food allergy in respiratory tract symptoms. Table 3 compares the prevalence of food allergy-induced asthmatic reactions.

Respiratory symptoms induced by inhalation of food allergens

Occupational exposure to airborne food allergens also can result in chronic asthma. For example, baker's asthma is caused by occupational exposure to airborne cereal grain dust. Patients with this disorder experience cough and shortness of breath following inhalation of wheat proteins while baking. Affected patients usually have positive skin tests to extracted wheat proteins [24].

Also, allergic reactions associated with airborne fish particles have been reported in patients with fish allergy [25]. These researchers evaluated children who reported allergic reactions upon incidental inhalation of fish odors or fumes. Of 21 patients evaluated, nine had wheezing or rhinitis alone, and three had respiratory and cutaneous symptoms together. Methods of exposure included boiling or frying fish and simple exposure to fish. Finally, Sicherer *et al.* [26•] recently reported that peanut-allergic patients may experience adverse respiratory reactions when exposed to peanut dust on airline flights serving peanut snacks.

Airway hyperresponsiveness

Food allergens contributing to increases in airway reactivity, and in some cases exacerbations of asthma, have been previously studied. In one study, 26 asthmatic children with food allergy were evaluated for changes in airway reactivity before and after blinded food challenges [27]. Of 22 positive blinded food challenges, 12 involved chest symptoms (cough, laryngeal reactions, or wheezing), and 10 involved laryngeal, gastrointestinal, or skin symptoms without any chest symptoms. Significant increases in airway reactivity occurred in seven of the 12 patients who experienced chest symptoms during positive food challenges. Decreases in FEV₁ generally were not observed in these seven patients, suggesting that significant changes in airway reactivity can occur without demonstrable pulmonary-function changes. These data indicate that food-induced allergic reactions may increase airway reactivity in a subset of patients with moderate to severe asthma and may do so without inducing acute asthma symptoms.

In contrast, another study concluded that food allergy is an unlikely cause of increased airway reactivity [28]. Eleven asthmatic adults with a history of food-induced wheezing and positive skin prick tests to the suspected foods were evaluated. An equal number of patients had increased airway reactivity, as determined by methacholine inhalation challenges, after blinded food challenges with either food allergen or placebo. Unfortunately, the small number of patients and the lack of environmental controls prior to the repeated methacholine challenges limit the conclusions that can be drawn.

Rhinitis

Adverse nasal symptoms may be attributed to food ingestion. For example, many patients associate ingestion of cow's milk and other dairy products with increased production and thickness of nasal secretions. When studied in large numbers of patients, nasal symptoms, especially rhinitis, accounted for 70% of the respiratory symptoms observed in children undergoing double-blind, placebo-controlled food challenges [23]. Rhinitis typically is associated with other clinical manifestations (*ie*, cutaneous and gastrointestinal symptoms) during allergic reactions to foods and rarely occurs in isolation [10,23]. Food allergy-induced rhinitis is observed more frequently in infants and young children than in adults.

Serous otitis media

Serous otitis media has multiple causes; the most prominent is viral upper respiratory tract infection. Allergic inflammation in the nasal mucosa may cause eustachian tube dysfunction and subsequent otitis media with effusion. Food allergy has been proposed as a cause of recurrent serous otitis media; however, this association has been overestimated and controversial [10,29]. Respiratory atopy (*eg*, allergic rhinitis and allergic asthma) may be a more

Table 2. Role of food allergy in respiratory tract symptoms

Food-induced respiratory tract symptoms typically are accompanied by cutaneous or gastrointestinal symptoms and rarely occur in isolation.

Children with atopic dermatitis, especially those with food reactions confirmed during blinded food challenges, are at increased risk of food-induced asthma.

Respiratory tract symptoms such as cough, wheezing, shortness of breath, and chest tightness may be provoked in a subset of patients with food allergy.

Infants and children are more likely to have food allergy and asthma than are other age groups.

The primary observed clinical symptom is not acute bronchopulmonary obstruction but chronic or difficult-to-control asthma.

Food-induced allergic reactions may increase airway reactivity in patients with moderate to severe asthma, sometimes without inducing acute asthma symptoms.

Table 3. Estimated prevalence of food allergy-induced asthmatic reactions

Clinical condition	Estimated prevalence, %
Cow's milk allergy (infants)	29
Asthma and a history of food-induced wheezing	24
Moderate to severe atopic dermatitis	11
Asthma	6
Food allergy without asthma	5

important predisposing factor than is food allergy alone [30]. In contrast, another report cautiously suggests that in a subset of infants with recurrent otitis media, IgG complexes with food antigens, particularly cow's milk proteins, may contribute to the middle ear inflammation in this disorder [31]. More data obtained from well-controlled studies are needed before general recommendations can be made regarding this association.

Anaphylactic reactions involving the respiratory tract

Anaphylactic reactions involving the respiratory tract typically include pruritus in the oropharynx, angioedema (*eg*, laryngeal edema), stridor, cough, dyspnea, wheezing, and dysphonia. In a survey of six fatal and seven near-fatal anaphylactic reactions following food ingestion, asthma and respiratory symptoms were part of the clinical presentation in all patients. The foods responsible for these serious reactions were peanut, tree nuts, egg, and cow's milk. A recent report summarized acute allergic reactions to peanut and tree nuts in 122 atopic children: 52% had lower respiratory tract symptoms as part of their overall reaction [32]. In summary, the presence of asthma and a short list of common foods are significant risk factors for serious and even fatal cases of food-induced anaphylaxis [2,33].

Food additives and respiratory symptoms

Despite public perceptions, there is conflicting evidence that some asthmatic patients are more likely to have adverse effects from MSG compared with the general population [34]. Woods *et al.* [35••] designed a randomized, double-blind, placebo-controlled MSG-challenge protocol for identifying immediate and late asthmatic reactions. They were unable to demonstrate MSG-induced immediate or late asthmatic reactions in a group

of 12 asthmatic adults who perceived that MSG negatively affected their overall asthma control. Also, no significant changes in bronchial hyperresponsiveness or soluble inflammatory markers (*eg*, eosinophil cationic protein and tryptase) were observed.

Other researchers recently performed double-blind, placebo-controlled oral challenges with MSG in 61 patients who had histories of adverse reactions to MSG [36]. Although the patients experienced no specific upper or lower respiratory symptoms, adverse reactions to MSG, including headache, muscle tightness, numbness, general weakness, and flushing, were confirmed in 22 (36.1%). Sulfite-containing foods (*eg*, dried fruits and wines) also have been shown to cause bronchospasm and severe asthmatic attacks in sensitive asthmatic patients [1].

Diagnosis

Medical history supplemented with appropriate laboratory testing and well-designed food challenges can provide useful information in the work-up of patients with respiratory symptoms that may be induced by food-allergy [3,23,27]. A diagnosis based solely on history or a skin test or RAST is not acceptable. If no specific foods are implicated in the history, and if skin tests to foods are negative, further work-up for IgE-mediated allergy is not indicated. With positive skin tests or respiratory symptoms associated with specific foods, an elimination diet may be instituted for 7 to 14 days. If symptoms persist, food is not likely to be the problem, except in some cases of atopic dermatitis or chronic asthma. Symptoms recurring after a regular diet is resumed should be evaluated with a properly designed food challenge.

Medical history

A comprehensive, detailed medical history should be obtained from patients suspected of having food allergy-induced respiratory tract symptoms. The history should include questions about the timing of the reaction in relation to food ingestion, the minimum quantity of food required to cause symptoms, specific upper and lower respiratory signs and symptoms, and the reproducibility of the symptoms. A family history of allergy or asthma can be a useful historical point. When there is a history of unexplained sudden asthma exacerbation, details about preceding food ingestion should be elicited. History of a severe or anaphylactic reaction following ingestion of a food may be sufficient to indicate a causal relationship. Finally, documentation of the specific treatment received and its response, if any, are useful.

Although diet diaries are used occasionally to identify which food is the likely cause of an adverse reaction, an unrecognized association between a food and a patient's respiratory symptoms is not often detected by this method. Elimination diets also have been used to diagnose food-induced respiratory symptoms but are rarely diagnostic of food allergy, particularly in chronic disorders such as atopic dermatitis or asthma. Their success depends on identifying the correct allergen and completely eliminating it in all forms from the diet. If a certain food or group of foods are suspected of provoking the adverse reaction, they are completely eliminated from the diet, typically for 7 to 14 days. All efforts should be made to prevent complications, such as poor weight gain and failure to thrive, resulting from unnecessary dietary restrictions [37].

Physical examination

Physical examination findings are helpful for assessing overall nutritional status, growth parameters, and signs of allergic disease, especially atopic dermatitis. Moderate or severe atopic dermatitis or corticosteroid-dependent asthma predict a higher risk of food-induced asthma. Moreover, this examination will help rule out other conditions that may mimic food allergy. Table 1 highlights categories of disorders that should be included in the differential diagnosis of respiratory symptoms that are thought to be secondary to adverse food reactions [38].

Skin testing

Skin tests (*eg*, prick and puncture) are used to screen for IgE-mediated food allergy [1]. These can be performed even on infants in the first few months after birth. When used in conjunction with a standard criterion of interpretation, these tests give reliable clinical information in a short period (15 to 20 minutes). If high-quality extracts are used, skin testing is an excellent method of excluding IgE-mediated food allergies; the negative predictive accuracy is greater than 95%. Conversely, the positive predictive accuracy is generally less than 50%, limiting the clinical interpretation of positive skin tests. This emphasizes the need to confirm clinical history

and positive skin tests with a food challenge if the history is not convincing for anaphylaxis. With some commercial food extracts (*eg*, fruits and vegetables), degradation of the food proteins increases the rate of false-negative skin tests. Therefore, fresh extracts are more reliable and should be used. Intradermal skin testing with foods increases the risk of inducing a systemic reaction and is less specific compared with the skin prick test [1,39]. It is of questionable diagnostic benefit and should never be performed prior to performing a standard prick or puncture skin test.

Routine skin testing with foods in patients presenting with asthma is not practical. Of children evaluated in a tertiary-care hospital emergency room, 97 patients with asthma or bronchiolitis underwent skin testing with common foods and aeroallergens [40]. The results were compared with results of similar testing in 60 control patients without any respiratory disease. In infants and young children with wheezing, the prevalence of IgE antibodies to food allergens was low. Most IgE responses among wheezing children were to aeroallergens.

Other testing

Laboratory assessment of food allergy may include the measurement of food-specific IgE in the serum (*eg*, RAST). When highly sensitive assays are used, the sensitivity and specificity are similar to that of skin tests [1,41,42]. In contrast, basophil histamine release assays, which are limited mainly to research settings, have not been shown conclusively to be reproducible, diagnostic tests for food allergy [3]. The diagnostic value of the following tests currently is not supported by objective scientific evidence: food-specific IgG or IgG subclass antibody concentrations, food antigen-antibody complexes, cytotoxic food tests, and subcutaneous provocation and neutralization [43,44].

Food challenges

When there is clinical suspicion of a food-induced respiratory tract reaction and the test for specific IgE antibody to the food is positive, an elimination diet may be implemented to see if clinical symptoms resolve. Confirming this association, however, can be very difficult, and food challenges can be a useful and reliable diagnostic tool. An excellent publication reviewed the combined clinical experience of six centers that performed food challenges [45]. Of these procedures, the double-blind, placebo-controlled food challenge is the best method to diagnose and confirm food allergy and other adverse food reactions [1,12••]. These challenges should be conducted in a clinic or hospital setting with available personnel and equipment for treating systemic anaphylaxis. If clinical history does not suggest a high risk of severe reaction, an oral food challenge can be performed in the office setting. A recent publication by Sicherer [12••] summarizes the major considerations in performing supervised food challenges.

Treatment

Once a food allergy has been confirmed as a cause of respiratory tract symptoms, strict avoidance of the offending food is necessary [1,3,10]. A properly managed elimination diet can resolve clinical symptoms such as chronic asthma. Appropriate nutritional counseling is important to ensure that an elimination diet is well-balanced, to provide appropriate substitutes for foods that are eliminated from the diet, and to avoid anticipated nutritional deficiencies such as calcium deficiency [46–48]. Growth parameters should be monitored closely, especially in infants and children on elimination diets. Woods *et al.* [49] were unable to prove that ingestion of dairy products induced bronchoconstriction in a group of asthmatic adults. They recommended that asthmatic patients should not unnecessarily restrict their dairy intake, which can lead to nutritional deficiencies. Elimination diets should exclude only those foods proven to provoke food allergy [1,10].

Implementing an elimination diet may sound simple, but the complete removal of a food allergen requires diligence and careful attention to detail. For example, in a cow's milk-free diet, patients must be educated to not only avoid all milk products, but also to read food ingredient labels for key words that may indicate the presence of cow's milk proteins (*eg*, casein, whey, lactalbumin, lactoglobulin, and caramel color). This process helps the patient avoid ingestion of hidden ingredients [50,51]. Organizations such as the Food Allergy Network (Fairfax, VA; <http://www.food-allergy.org/>) and the International Food Informational Council (Washington, DC; <http://www.ificinfo.health.org/>) are excellent resources for patients with food allergies, their families, physicians, and other caregivers. The Food Allergy Network provides a service to alert families when contamination or mislabeling occurs in commercial food products.

An emergency plan should be written to help patients manage clinical symptoms caused by accidental ingestion of a relevant food allergen. For children, the plan should be given to appropriate school personnel. Self-injectable epinephrine and antihistamines must be on hand to treat allergic reactions after accidental ingestion. Epinephrine is the drug of choice to treat acute, severe reactions and to allow time to seek immediate medical attention.

Conclusions

Previous studies of the pathogenic role of food allergy in respiratory tract symptoms suggest that IgE-mediated, food-induced symptoms, which are uncommon, usually are observed in younger patients, especially in those with a current or past history of atopic dermatitis. Moreover, food allergy definitely may be a trigger in a subset of asthmatic patients. This possibility should be considered if a patient has wheezed (or experienced anaphylactic symptoms) after ingesting a particular food or foods, has atopic

dermatitis or a history of this disease, has a current or past history of food allergies, or has a positive skin test to some foods. Finally, the work-up of food allergy in asthma should be considered in patients in whom asthma is poorly controlled despite persistent use of appropriate asthma medications including oral corticosteroids.

With this in mind, practice parameters for the diagnosis and treatment of asthma recently have highlighted the potential role of food allergy in some patients [52]. Allergies to foods can induce wheezing in a subset of asthmatic patients. Evaluation of food allergy should be considered in patients with chronic symptoms, especially children with a history of atopic dermatitis. A positive skin prick test to suspected foods may suggest specific food allergens that require further study. A definitive diagnosis of food allergy should be based on a double-blind, placebo-controlled oral challenge. Under certain circumstances, such as a convincing history of anaphylaxis following ingestion or inhalation of a food or food additive, a presumptive diagnosis based on less stringent criteria may suffice.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

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