

RESPIRATORY TRACT AND FOOD HYPERSENSITIVITY

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Respiratory symptom complaints are among the most frequent reasons patients seek medical attention. These symptoms typically include nasal congestion, rhinorrhea, sneezing, itching of the nose and throat, coughing, or wheezing. Numerous causes should be considered in the differential diagnosis (Table 1) of these symptoms. Of these, respiratory tract symptoms are commonly attributed to inhalant allergies, such as those observed with allergic rhinitis. In contrast, food allergy as a specific cause for respiratory tract symptoms has been less well-defined.

Other articles in this issue have highlighted the most common clinical manifestations of allergic reactions to foods. These symptoms typically involve the skin and gastrointestinal tract.⁴⁴ In addition, respiratory symptoms may result from an allergic reaction to food but are not as common as cutaneous and intestinal symptoms and rarely occur in isolation. In general, respiratory symptoms are a more worrisome group of clinical manifestations because they have been frequently observed in fatal and near-fatal reactions following food ingestion.⁴⁷

This article reviews information implicating foods and food additives as causes for specific symptoms in the upper and lower respiratory tract. A specific focus is placed on the role of food hypersensitivity in asthma, rhinitis, otitis media, and respiratory anaphylaxis. Key clinical points are discussed, as well as a reasonable diagnostic work-up for food allergy and respiratory symptoms. This information provides a practical approach to the work-up of food allergy in patients presenting with respiratory complaints.

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IMMUNOLOGY AND ALLERGY CLINICS OF NORTH AMERICA

Table 1. RESPIRATORY SYSTEM COMPLAINTS: ETIOLOGIC CATEGORIES

Infectious Illnesses
Viral upper respiratory tract infection
Sinusitis
Allergic Diseases
Allergic rhinitis (seasonal, perennial)
Asthma
Food allergy
Nonallergic Rhinitis/Vasomotor Rhinitis
Environmental Irritants
Passive tobacco smoke
Strong odors
Anatomic Abnormalities
Nasal polyps
Deviated nasal septum
Foreign body
Enlarged tonsil and adenoids
Ciliary dyskinesia
Cystic Fibrosis
Rhinitis Medicamentosa

EPIDEMIOLOGY

Vital to any discussion of the role of food allergy in respiratory symptoms is a basic understanding of the classifications of adverse food reactions. As discussed elsewhere in this issue, an adverse food reaction is any abnormal clinical response following the ingestion of a food or food additive.²⁷ These reactions are divided into two major categories. Food allergy is an immunologically mediated food reaction unrelated to any physiologic effect of the food or additive (e.g., an allergic reaction to an ingested peanut resulting in laryngeal edema, coughing, and wheezing); food intolerance is any abnormal physiologic response to a food that is not immunologically mediated (e.g., an exaggerated physiologic reaction following the ingestion of monosodium glutamate, including headache, flushing, muscle tightness, and generalized weakness). Understanding this terminology and overall classification aids in the interpretation of the scientific information reviewed in this article, implicating food allergy in respiratory tract symptoms.

Published surveys have reported that as many as 15% to 30% of households include at least one member who believes they are allergic to some food or food ingredient.^{3, 5} With this elevated public perception of food allergy, it is understandable why many associations have been made between the ingestion of certain foods and food additives and respiratory symptoms. A recent Australian survey reported that patients with asthma did not report food-related illness more frequently than

those respondents without asthma, but those reporting respiratory symptoms following food ingestion were more likely to be atopic.⁵³ Public perceptions, however, have not always been substantiated when food challenges have been used to confirm patient histories.^{6, 27, 34} This idea is true for respiratory symptoms as it is with cutaneous and gastrointestinal symptoms covered in respective articles in this issue. When the investigation focus has been on the role of allergic reactions to food and food additives in specific respiratory symptoms, the incidence in asthmatic patients has been estimated to be between 2% and 8% in children and adults.^{33, 39}

PATHOGENESIS

Immune responses mediated by specific IgE antibodies to food allergens are the most widely recognized mechanism for food-induced respiratory tract symptoms.¹⁹ 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, which are present in the airway. Subsequent allergen exposure binds these IgE antibodies, initiating the release of a vast array of mediators such as histamine, prostaglandins, and leukotrienes. This action results in vasodilatation, smooth muscle contraction, and mucus secretion,²⁹ which in turn leads to the different clinical symptoms observed in the respiratory tract.

Food allergens are water-soluble glycoproteins, with molecular weights typically less than 70 kD. These characteristics facilitate the absorption of these allergens across mucosal surfaces.³⁰ Egg, milk, peanut, soy, fish, shellfish, and tree nuts are some of the common examples of food allergens that have been implicated in respiratory reactions and have been confirmed in well-controlled, blinded food challenges.^{6, 8, 13, 46} Furthermore, investigations of patients experiencing near-fatal or fatal anaphylactic reactions following food ingestion have mainly been secondary to peanut, tree nuts, and shellfish.^{47, 57}

In addition to the common groups of food allergens mentioned previously, several different food additives, including monosodium glutamate, sulfites, and aspartame, have been implicated in adverse respiratory reactions.⁵² Although a high percentage of adults with asthma perceive that food additives contribute to worsening of their respiratory symptoms,¹ well-controlled investigations in this area have reported a prevalence rate of less than 5%.^{8, 39} The following section summarizes new information investigating the contribution of specific foods and food additives in worsening asthma symptoms.

CLINICAL BACKGROUND

Food Allergy and Respiratory Symptoms

Respiratory symptoms secondary to food allergy do not always present with the same clinical pattern. For example, these reactions can

occur suddenly and without warning if the food allergen is not routinely ingested and, in some cases, may result in generalized anaphylaxis.^{11, 47} In contrast, if the food is routinely ingested, the patient with food allergy-induced respiratory symptoms generally presents clinically with more chronic symptoms such as chronic atopic dermatitis,¹² chronic asthma,³⁸ or both of these atopic conditions. Of the various respiratory symptoms induced by food allergy, the following section focuses on investigations examining food allergy-inducing asthma and increased airway hyperreactivity.

Asthma Induced by Food Allergy

The majority of information regarding food allergy and respiratory symptoms deals with food-induced asthma. In one investigation, 300 patients with asthma (ages ranging from 7 months to 80 years) were evaluated in a pulmonary clinic.³⁹ Twenty-five patients had a history of food allergy suggested by clinical symptoms (20 had interpretable blinded food challenges), whereas skin tests or radioallergosorbent test (RAST) and wheezing were documented in six (2%) of the cases. All of the cases with confirmed food-induced wheezing were children. In another investigation, 140 children with asthma were screened by clinical history, skin testing, and RAST analyses; 32 patients were able to undergo blinded food challenges.³⁵ Of these children, 13 (9.2%) had food-induced respiratory symptoms and 8 (5.7%) had 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 et al reported that food-induced bronchospasm was present in 8.5% of 284 asthmatic children evaluated.³⁷ The majority of the allergic sensitization occurred in the first year of life and was caused by a single food, especially egg. In another study, five children with cow's milk allergy, and histories of wheezing following its ingestion, experienced bronchospasm as well as other respiratory, cutaneous, and gastrointestinal symptoms during blinded food challenges with cow's milk.²² Furthermore, Businco et al evaluated 42 children (ages ranging from 10 to 76 months) with atopic dermatitis and milk allergy.¹⁴ Eleven (27%) of these patients developed asthmatic symptoms during a positive food challenge; in six children, these asthma exacerbations were the only adverse symptom observed.

Over an 18-year period, 598 children with pulmonary disease were evaluated at the National Jewish Center for Immunology and Respiratory Medicine.⁷ Of the 410 (69%) children with a history of asthma, 279 (68%) had a history of food-induced asthma. There were positive food challenges in 168 (60%) of the 279 patients. This investigation revealed that 67 (24%) of the 279 children with a history of food-induced asthma had a documented, positive blinded food challenge that included wheez-

ing. Interestingly, only five (2%) of these patients had wheezing as their only objective adverse symptom.

A total of 320 children with atopic dermatitis undergoing blinded food challenges at Johns Hopkins Hospital were monitored for respiratory reactions.²⁴ The patients, ages 6 months to 30 years, were highly atopic, had multiple allergic sensitivities to foods, and over one half had a prior diagnosis of asthma. Food allergy was confirmed by blinded challenges in 205 (64%) of these patients; almost two thirds of these patients experienced respiratory reactions during their positive food challenges (i.e., nasal 70%, laryngeal 48%, pulmonary 27%). Overall, 34 (17%) of 205 children with positive food challenges developed wheezing as part of their reaction. Furthermore, 88 of these patients were monitored with spirometry during positive and negative food challenges. Thirteen (15%) developed lower respiratory symptoms, including wheezing; however, only six patients had a more than a 20% decrease in forced expiratory volume (FEV). Wheezing as the only manifestation of the respiratory reaction was a rare observation.

These results suggest that respiratory symptoms may be provoked in a subset of patients with asthma; The following list summarizes the role of food allergy and asthma:

- Respiratory symptoms such as wheezing, cough, and dyspnea may be provoked in a subset of patients with food allergy.
- Patients with food allergy and asthma are generally younger (i.e., in the infant and childhood age groups).
- Children with atopic dermatitis, especially those with food reactions confirmed during blinded food challenges, are a higher risk group for food-induced asthma.
- The primary observed clinical effect is not acute bronchopulmonary obstruction but chronic asthma symptoms or difficult-to-control asthma.
- Food-induced respiratory symptoms (e.g., wheezing) occurring in isolation are a rare observation.
- Food-induced allergic reactions may increase airway reactivity in patients with moderate-to-severe asthma, and may do so without inducing acute asthma symptoms.

The patients with food allergy and asthma are generally younger. Children with atopic dermatitis, especially those with food reactions confirmed during blinded food challenges, appear to have a higher risk for developing food-induced asthma. The primary observed clinical effect is not acute bronchopulmonary obstruction but chronic asthma symptoms or difficult-to-control asthma. Finally, food-induced respiratory symptoms (e.g., wheezing) rarely occur in isolation.

Respiratory Symptoms Induced by the Inhalation of Food Allergens

Patients experiencing cough and shortness of breath following the inhalation of wheat proteins while baking have been diagnosed with

baker's asthma. Affected patients usually have positive skin tests to extracted wheat proteins.²¹ Recently, allergic reactions associated with airborne fish particles have been reported in fish-allergic patients.¹⁶ The investigators evaluated children with fish allergy who reported allergic reactions upon incidental inhalation of fish odors or fumes. Of the 21 patients evaluated, 9 had either wheezing or rhinitis alone, and 3 had respiratory and cutaneous symptoms together. Methods of exposure included boiling or frying fish and simple exposure to fish.

Airway Reactivity and Asthma Induced by Food Allergy

Food allergens contributing to increases in airway reactivity, and in some cases exacerbations of asthma, have been previously investigated. Investigators have recommended using histamine inhalation challenges to assess food-induced asthma because conventional spirometry lacked the sensitivity to detect these changes.⁴⁹ Patients with histories of food-induced asthma can have significant increases in airway reactivity following food challenges, typically after 90 minutes, without a concomitant change in baseline peak flow. In contrast, a different investigation concluded that food allergy is an unlikely inducer of increased airway reactivity.⁵⁸ Eleven adults with asthma, a history of food-induced wheezing, and positive prick skin 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 to either food allergens or placebos. Unfortunately, the small number of patients investigated and the lack of environmental controls prior to the repeat methacholine challenges limit their conclusions.

In a more recent investigation, 26 children with asthma and food allergy were evaluated for changes in their airway reactivity before and after blinded food challenges.²⁶ Of the 22 positive, blinded food challenges, 12 involved chest symptoms (cough, laryngeal reactions, or wheezing). Another 10 positive food challenges included laryngeal, gastrointestinal or skin symptoms without any chest symptoms. Significant increases in airway reactivity occurred in 7 of the 12 patients who experienced chest symptoms during positive food challenges. Decreases in FEV₁ were not generally observed in these seven patients, suggesting that significant changes in airway reactivity can occur without demonstrable spirometric changes in a preceding food challenge. These data indicate that food-induced allergic reactions may increase airway reactivity in patients with moderate-to-severe asthma and may do so without inducing acute asthma symptoms.

Rhinitis Induced by Food Allergy

One of the more frequent complaints of food allergy is adverse nasal symptoms that are thought to be secondary to food ingestion. For example, many patients associate the ingestion of cow's milk and other dairy products with an increase in the production and thickness of

nasal secretions. When investigated 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.²⁴ Rhinitis typically occurs in association with other clinical manifestations (i.e., cutaneous or gastrointestinal symptoms) during allergic reactions to foods and rarely occurs in isolation.^{8, 24} Finally, rhinitis induced by food allergy is more frequently observed in infants and young children than in adults.

Serous Otitis Media Induced by Food Allergy

Serous otitis media has multiple causes, of which the most prominent is viral upper respiratory tract infections. The involvement of food allergy in recurrent serous otitis media has been proposed; however, its specific role has been overestimated.^{8, 36} More data obtained from well-controlled investigations are needed before general recommendations can be made regarding this potential connection.

Food-Induced Anaphylactic Reactions with Respiratory Symptoms

As discussed in greater detail in another article in this issue, the first symptoms often noticed in a food-induced anaphylactic reaction involve the respiratory tract.²⁶ These symptoms typically occur in the oropharynx and include pruritus, angioedema (e.g., laryngeal edema), stridor, cough, dyspnea, wheezing, and dysphonia. Moreover, the presence of asthma, especially in those patients with poorly controlled disease, is a common risk factor for serious and even fatal cases of food-induced anaphylaxis.⁴⁷

Food Additives and Respiratory Symptoms

Despite conflicting published reports regarding the effect of monosodium glutamate (MSG) on asthma symptoms,^{2, 32, 48, 51} a recent report concluded that there was limited evidence that some people with asthma are more likely to have adverse effects from MSG compared with the general population.⁴² With this background, Woods et al⁵⁴ designed a randomized, double-blind, placebo-controlled MSG-challenge protocol for identifying early and late asthmatic reactions. They were unable to demonstrate MSG-induced immediate or late asthmatic reactions in a group of 12 adult asthmatics who perceived that this food additive did negatively affect their overall asthma control. In addition, these investigators observed no significant changes in bronchial hyperresponsiveness or soluble inflammatory markers (e.g., eosinophil cationic protein, tryptase) during this investigation protocol. Finally, another recent investigation performed double-blind, placebo-controlled oral challenges with MSG in subjects who had histories of adverse reactions to this food

additive.⁵⁶ Although the participants experienced no specific upper or lower respiratory complaints, 22 (36.1%) of the 61 enrolled subjects had confirmed adverse reactions to MSG including headache, muscle tightness, numbness, general weakness, and flushing.

DIAGNOSIS

Medical History

A detailed medical history including specific questions about upper and lower respiratory signs and symptoms should be obtained in patients with a history of respiratory symptoms thought to be provoked by food ingestion. 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, and the reproducibility of the symptoms. Moreover, documentation of the specific treatment received and its response, if any, are useful. Finally, a family history positive for allergy can be a useful historical point.

Diet diaries are occasionally helpful in identifying which food is most likely responsible for an adverse reaction. Patients are asked to keep a chronologic record of all foods and known food ingredients ingested over a specified period of time and to record any symptoms they experience during this time. The diary can then be reviewed at a patient visit to determine if there is any relationship between the foods ingested and the respiratory symptoms experienced. Unfortunately, it is uncommon to detect by this method an unrecognized association between a food and a patient's respiratory symptoms.

Elimination diets can also be utilized in the diagnosis of food-induced respiratory symptoms; however, they 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. The success of an elimination diet depends on several factors: (1) the correct identification of the food allergen(s) or food additive involved, (2) the ability of the patient to maintain a diet completely free of all forms of the possible offending allergen, and (3) the assumption that other factors will not provoke similar symptoms during the study period. Satisfying all of these requirements can be very difficult, thus limiting the usefulness of an elimination diet. All efforts should be made to prevent complications from unnecessary dietary restrictions such as poor weight gain and failure to thrive.⁴³

Physical Examination

In evaluating patients with respiratory system complaints that may be induced by food allergy, the physical examination can be particularly

useful. Findings here are helpful in assessing overall nutritional status, growth parameters and any signs of allergic disease, especially atopic dermatitis. Moreover, this examination helps to rule out other conditions that may mimic food allergy. The following are categories of disorders that should be included in the differential diagnosis of respiratory symptoms that are thought to be secondary to adverse food reactions²⁷:

- Gastroesophageal reflux
- Hiatal hernia
- Tracheoesophageal fistula
- Cystic fibrosis
- Psychological reactions: vocal cord dysfunction, anorexia, bulimia

Skin Testing for Food Allergy

Skin tests (i.e., prick or puncture) are used to screen for IgE-mediated food allergies.^{4, 9, 45} These can be performed even in infants in the first few months after birth. When used in conjunction with standard criterion of interpretation, these tests give reliable clinical information in a short period of time (e.g., 15–20 minutes). If high-quality extracts are used, the 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 finding emphasizes the need to confirm the clinical history and positive skin test with a food challenge, if the history is not convincing for anaphylaxis. Intradermal skin testing with foods have questionable diagnostic benefit and should never be performed prior to a standard prick or puncture skin test. Intradermal skin testing increases the risk of inducing a systemic reaction and is less specific when compared with prick skin testing.^{9, 44}

In summary, when high-quality skin test extracts are used in conjunction with a standard criterion of interpretation, this form of testing provides reliable clinical information in the overall workup of a patient with suspected food allergy-induced respiratory reactions. Conversely, the routine use of skin testing for 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 were skin tested to common foods and aeroallergens and were compared with similar testing in 60 control patients without any respiratory disease.⁴¹ 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.

Food Challenges

Food challenges can be very useful in the diagnostic evaluation of a patient with food-induced respiratory symptoms. An excellent publica-

tion has reviewed the combined clinical experience of six centers doing food challenges.¹⁰ Of these procedures, the double-blind placebo-controlled food challenge (DBPCFC) is the best method to diagnose and confirm food allergy and other adverse food reactions.^{4, 12, 44} These challenges should be conducted in a clinic or hospital setting with available personnel and equipment for treating systemic anaphylaxis. Another article elsewhere in this issue provides a thorough overview and discussion of the essential features, uses, interpretations, and limitations of food challenge procedures.

Other Testing

Laboratory assessment of food allergy may include the measurement of food-specific IgE in the serum (e.g., IgE RAST testing, ImmunoCAP [Pharmacia Diagnostics, Uppsala, Sweden]). This measurement provides information similar to prick skin tests but is less specific.^{44, 55} A previous article discusses the reliability and clinical usefulness of these specific IgE antibody measurements to food allergens. In contrast, basophil histamine release assays, which are mainly limited to research settings, have not been shown conclusively to be a reproducible, diagnostic test for food allergy.²⁷ Finally, the diagnostic value of the following tests are not currently supported by objective scientific evidence: food-specific IgG or IgG subclass antibody concentrations, food antigen-antibody complexes, cytotoxic tests, and subcutaneous provocation and neutralization.^{15, 28}

The medical history, supplemented with an appropriate laboratory testing and well-designed food challenges, can provide useful information in the workup of patients with respiratory symptoms that may be induced by food allergy.^{24, 26, 27} A diagnosis based solely on history or skin test/RAST is not acceptable. If no specific foods are implicated in the history and if skin tests to foods are negative, further workup 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.

TREATMENT

Once a food allergy has been diagnosed and implicated as a cause for respiratory symptoms, strict avoidance of the offending food is necessary.^{8, 27, 44, 45} A properly managed elimination diet can lead to resolution of symptoms. 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 any anticipated nutritional deficiencies, such as calcium deficiency.^{17, 18, 31} Restriction diets should exclude only those foods proven to provoke food allergy.^{8, 45} After strictly avoiding the offending food for several years, many children outgrow food allergies. Allergies to peanuts, nuts, fish, and shellfish, however, tend to be lifelong. Food challenges may be repeated to determine if the patient is still clinically reactive to the suspected food allergen or if oral tolerance has developed. Presently, there is no evidence to support the use of oral or parental immunotherapy for food allergy-induced respiratory symptoms.

Educating patients and families on how to read food labels and identify common words for the allergen of concern (i.e., milk: casein and whey) is crucial. This process helps the patient to avoid ingestion of hidden ingredients.^{5, 20} In addition, children with asthma and food allergies appear more likely to suffer a severe allergic reaction or anaphylaxis if they ingest a food allergen.⁴⁷ These patients should have self-injectable epinephrine and a detailed treatment plan immediately available. Finally, the Food Allergy Network (Fairfax, Virginia: phone 800-929-4040; www.foodallergy.org) is a lay organization that has been developed to serve as a resource to patients with food allergies, their families, physicians and other caretakers.

SUMMARY

Previous studies investigating the pathogenic role of food allergy in respiratory symptoms suggest that although IgE-mediated food-induced symptoms are uncommon, they are usually observed in younger patients, especially those with a current or past history of atopic dermatitis. Moreover, food allergy may definitely be an trigger in a subset of patients with asthma. This specific cause should be considered if a patient has wheezed (or experienced anaphylactic symptoms) after ingesting a particular food(s), has atopic dermatitis or a history this disease, or has a current or past history of food allergies or positive skin tests to some foods. Finally, the workup of food allergy in asthma should also be considered in those patients with poorly controlled asthma despite the constant use of a number of medications, including prednisone.

With this in mind, practice parameters for the diagnosis and treatment of asthma have recently highlighted the potential role of food allergy in asthma in some patients.⁴⁰ Allergies to foods can induce wheezing in a subset of patients with asthma. Evaluation of food allergy should be considered in patients with chronic symptoms, especially those in the pediatric age group with a history of atopic dermatitis. A positive prick skin 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 history convincing for anaphy-

laxis following the ingestion or inhalation of a food or food additive, a presumptive diagnosis based on less stringent criteria may suffice.

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