

Manifestations of Inhalant Allergies Beyond the Nose

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KEYWORDS

- Allergic rhinitis • Rhinosinusitis • Asthma • Laryngitis • Conjunctivitis
- Unified airway • United airway disease

KEY POINTS

- Allergic rhinitis, rhinosinusitis, and asthma frequently occur in the same patients.
- The upper and lower airways are linked both epidemiologically and pathophysiologically.
- Allergic rhinitis is a risk factor for the development of asthma, and treatment of rhinitis has been shown to improve asthma outcomes.
- Rhinosinusitis and asthma are linked, and comorbid sinusitis and asthma is associated with more severe clinical presentation.
- Allergic laryngitis is less well-understood; however, there is evidence of an epidemiologic link.

INTRODUCTION

Allergic inflammation affects both the upper and lower airways. The relationship between allergic rhinitis and its comorbidities, including chronic rhinosinusitis (CRS) and asthma, has been well-established. Given that a large part of the otolaryngologist's practice involves the diagnosis and management of upper airway disease, including allergic rhinitis, sinusitis, and laryngitis, knowledge of the manifestations of inhalant allergies beyond the nose is critical. The otolaryngologist may be the first physician to suspect and diagnose asthma in this at-risk patient population. As otolaryngologists, we therefore must be knowledgeable regarding the signs and symptoms of lower airway disease to ensure timely diagnosis of asthma and to optimize treatment of both upper and lower airway inflammatory diseases. A thorough understanding of the close relationship between allergic rhinitis, CRS, and asthma will facilitate early identification of asthma and improve patient outcomes.¹

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THE UNIFIED AIRWAY

The “unified airway” or “united airway disease” describes the concept of viewing the upper and lower airways as a single, functional unit. This model originated from the observation that allergic inflammation in response to an allergen is not confined to a specific organ, but rather it affects the entire respiratory tract. The nose, paranasal sinuses, pharynx, larynx, trachea, and bronchi through the pulmonary alveoli are included in this unit. Upon allergen exposure, local inflammatory processes occur along with a systemic response produced by the migration of proinflammatory mediators through the circulatory system. Under this model, upper and lower airway disease, including rhinitis, sinusitis, and asthma, can be thought of as different manifestations of the same disease.²

The upper and lower respiratory tracts share histologic structures in common, including pseudostratified columnar epithelium, basement membrane, lamina propria, and goblet cells. It follows that inflammatory processes are similar along the length of the respiratory tract. However, there are several structural differences that contribute to the unique physical manifestations of allergic inflammation in distinct respiratory sites; upper airway mucosa is richly vascular, whereas lower airway bronchial mucosa is characterized by the presence of smooth muscle. Inflammation of the nasal mucosa results in vasodilation and edema, whereas inflammation of the bronchial mucosa produces smooth muscle contraction.³ The pathophysiologic link between the upper and lower airway has been demonstrated in several studies.^{4–6} Stimulation with antigen at 1 respiratory site has been shown to produce an inflammatory response at distant and distinct respiratory sites. This “inflammatory cross-talk” supports the shared immunity mechanism to explain the unified airway.

Because the inflammation associated with allergy acts both locally and systemically, upper and lower airway pathology frequently coexist. Allergic rhinitis is the most common atopic disease. Not only is allergic rhinitis associated with asthma, but the presence of allergic rhinitis itself is considered a risk factor for the development of asthma. Long-term studies have demonstrated that allergic rhinitis is a risk factor for the future development of bronchial hyperresponsiveness and/or asthma. The risk of development of asthma is 3 times higher in patients with allergic or nonallergic rhinitis.⁷ Patients with clinically severe sinonasal symptoms are at even greater risk for the development of asthma.⁸ The prevalence of asthma in patients with rhinitis has been estimated to be as high as 40%, and approximately 80% of patients with asthma also have rhinitis. Furthermore, 30% of patients with allergic rhinitis who do not have asthma demonstrate bronchial hyperresponsiveness to methacholine or histamine challenge.³ This supports the idea of “one airway, one disease.”

The clinical impact of the unified airway has also been explored. Examination of prescription data revealed that patients with both asthma and allergic rhinitis had a higher percentage of prescription medication use than those with asthma alone.¹ Several studies have shown that treatment of rhinitis in patients with asthma produces clinical benefit in terms of reduction of lower airway symptoms, emergency room visits, and hospitalizations.^{9–11}

RHINITIS AND ASTHMA

Epidemiologic Relationship and Clinical Implications

Allergic rhinitis is defined as symptomatic, immunoglobulin E (IgE)-mediated inflammation of the nasal mucosa after allergen exposure. Symptoms of allergic rhinitis include rhinorrhea, nasal congestion, obstruction, pruritus, and sneezing.¹² Asthma is a chronic respiratory disorder characterized by wheezing, coughing, chest

tightness, and shortness of breath.¹³ The epidemiologic relationship between rhinitis and asthma has been well-studied over the past several decades. Patients with allergic or nonallergic rhinitis are more likely to develop asthma than the average individual, and those with asthma are far more likely to suffer from comorbid rhinitis.

The prevalence of allergic rhinitis in the United States has been estimated to be between 15% and 40%, and this number is increasing.^{14,15} There is a strong relationship between allergic rhinitis and asthma, and the two frequently coexist in the same patient. Patients with rhinitis have a 3 times higher risk of developing asthma than an individual without rhinitis, irrespective of the presence of atopy.^{7,8} Asthma affects approximately 8% of the US population; however, the prevalence of asthma in patients with allergic rhinitis has been estimated to be as high as 40%. In contrast, up to 80% of asthmatic individuals also have allergic rhinitis.^{16,17}

Allergic rhinitis tends to precede or occur at the same time as the development of asthma. In a study of 738 college students with 23 years of follow-up, the temporal relationship between rhinitis and asthma was assessed. Of those patients who had both allergic rhinitis and asthma, 44.8% developed nasal symptoms first and 20.7% developed upper and lower airway symptoms simultaneously. In patients with nonallergic rhinitis, 38.5% developed rhinitis first and 30.8% developed rhinitis and asthma at the same time.^{7,18} In a retrospective review of 154 children with allergic rhinitis, approximately 20% of patients developed asthma within 10 years. Those with perennial allergic rhinitis were more likely to develop asthma than those with seasonal allergic rhinitis.¹⁹ Linneberg and colleagues²⁰ examined the relationship between allergic rhinitis and asthma in 734 patients with confirmed IgE antibodies to pollen, animal dander, or dust mite. Over an 8-year follow-up period, the relative risk of developing asthma in patients with allergic rhinitis to pollen was 8.2, to animal dander was 18.9, and to dust mite was 46.5. At follow-up, 100% of patients with asthma also had allergic rhinitis.

Patients with both rhinitis and asthma tend to have more severe disease, which is more difficult and costly to control.^{21–23} Large, population-based studies have demonstrated a link between the severity of both diseases. In a study of more than 25,000 asthmatic patients in the UK, those with concomitant allergic rhinitis experienced more doctor visits and were more often hospitalized for asthma. The presence of comorbid allergic rhinitis was associated with higher asthma-related drug costs.²⁴ In another study of almost 30,000 asthmatic patients in Japan, patients with concomitant allergic rhinitis were more likely to have uncontrolled asthma as defined by Global Initiative for Asthma guidelines than those without allergic rhinitis.²⁵ Conversely, Ponte and colleagues²⁶ demonstrated that poorly controlled asthma was associated with moderate to severe rhinitis.

Given the epidemiologic connection between allergic rhinitis and asthma, and the temporal relationship in which allergic rhinitis tends to precede the development of asthma, the Allergic Rhinitis and its Impact on Asthma guidelines have made several recommendations. Some recommendations were made in an attempt to prevent the development of both allergic rhinitis and asthma, including prophylactic avoidance of dust mite exposure and avoidance of occupational agent exposures, which contribute to the development atopic disease. In patients already sensitized to particular allergens, recommendations are made to avoid further exposure to indoor molds, animal dander, and occupational allergens.²⁷

The link between the inflammatory response in the upper and lower airways is further substantiated by studies suggesting that the treatment of allergic rhinitis improves asthma outcomes. Optimal management of rhinitis may improve coexisting asthma. Several studies have shown a decrease in the frequency of asthma

symptoms, improvement in lower airway function, and decrease in emergency room visits in patients using intranasal corticosteroids.^{9–11,28–30} A recent metaanalysis conducted by Lohia and colleagues³¹ examined the efficacy of intranasal corticosteroids on asthma outcomes. Data from 18 trials including a total of 2162 patients were analyzed. Nasal inhalation of corticosteroids resulted in improvement in asthma outcomes, including pulmonary function, bronchial reactivity, asthma symptom scores, asthma-specific quality of life, and rescue medication use. Crystal-Peters and colleagues³⁰ examined the rate of asthma-related emergency room visits and hospitalizations over a 1-year period. Of 4944 patients with allergic rhinitis and asthma, 3587 patients were treated for allergic rhinitis and 1357 were not. In the treated group, asthma-related hospitalizations decreased by 61%, and the incidence of 2 or more asthma-related emergency room visits decreased by 54% compared with the untreated group. These studies highlight the importance of recognizing the relationship between rhinitis and asthma, both in terms of reducing physical symptoms and in lowering health care costs.

Pathophysiologic Link

Both epidemiologic and pathophysiologic connections between rhinitis and asthma have been described. Several mechanisms have been proposed to explain the pathophysiologic link between the upper and lower airways. One proposed mechanism is that inflammatory products of the nose may be aspirated into the lower airways during an exacerbation of nasal inflammation. Although the aspiration of nasal contents may contribute to lower airway inflammation, there is significant evidence that a systemic response is involved. This mechanism is that of inflammatory cross-talk, in which local inflammation leads to upregulation of various inflammatory mediators, both locally and at distant sites within the respiratory tract. An additional proposed mechanism to explain the pathophysiologic link between the upper and lower airways is the neurogenic mechanism, in which neuronal stimulation in the nasal mucosa results in the release of neurotransmitters, which produce changes in the distal airway, including smooth muscle contraction.^{32,33}

Several studies have demonstrated that allergic rhinitis and asthma are characterized by similar inflammatory processes, including the presence of similar proinflammatory mediators in response to the presence of an allergen. In previously sensitized individuals, the process is initiated when an antigen encounters high-affinity receptors on mast cell and basophil cell membranes. This reaction not only results in a local immune response, but also in a system-wide response, enabling the inflammatory reaction to reach other target organs through the circulatory system. During the early phase, an immediate hypersensitivity reaction occurs, during which preformed mediators are released from mast cells and basophils. This phase is characterized by rhinorrhea, sneezing, pruritus, cough, wheezing, and mucous production. In the late phase, which occurs 6 to 24 hours after initial exposure, eosinophils, basophils, and their progenitor cells are released from the bone marrow into the circulatory system.³ Thus, allergic rhinitis is characterized not only by a local inflammatory response affecting the nasal airway, but also by a more diffuse involvement of the respiratory tract, even in the absence of clinical asthma.

In a study performed by Braunstahl and colleagues,⁴ the upper and lower airways of 8 nonasthmatic patients with allergic rhinitis and 8 nonallergic healthy controls were evaluated after segmental bronchial provocation. The number of eosinophils and expression of interleukin (IL)-5 and eotaxin increased in both the nasal mucosa and blood of atopic individuals after segmental bronchial provocation; these changes were not observed in healthy controls. In a later study by the same group, segmental

bronchial provocation was again undertaken to evaluate the role of mast cells and basophils in allergic inflammation of the upper and lower airway. Segmental bronchial provocation in nonasthmatic patients with allergic rhinitis resulted in a reduction in mast cells in the nasal mucosa owing to enhanced degranulation. There was a decrease in basophils in the bloodstream and an increase in basophils in the nasal and bronchial mucosa after segmental bronchial provocation in allergic patients that was not observed in nonallergic, healthy controls.⁵ Conversely, nasal provocation was shown to result in the upregulation of adhesion molecules and eosinophils in both the upper and lower airway.⁶

Several studies also support the neurogenic mechanism for unified airway or united airway disease. Inflammation in the nose can lead to upregulation of neural activity, resulting in exaggerated responses, including sneezing, pruritus, and rhinorrhea, upon allergen exposure. Neural signals generated in the nose have been shown to affect distal respiratory sites.³⁴ In the presence of neuromediators, including substance P and calcitonin gene-related peptide, histamine and bradykinin are released, leading to increased vascular permeability and edema. Additionally, cholinergic neurotransmitters produce smooth muscle contraction, resulting in bronchoconstriction.³³

RHINOSINUSITIS AND ASTHMA

Epidemiologic Relationship and Clinical Implications

Rhinosinusitis is defined as “a group of disorders characterized by inflammation of the mucosa of the nose and paranasal sinuses of at least 12 consecutive weeks.”³⁵ Rhinosinusitis is associated with various symptoms including purulent rhinorrhea, nasal obstruction, facial pain or pressure, and decreased sense of smell. CRS affects 31 million patients in the United States each year, and the prevalence continues to grow. CRS represents a major health care issue, associated with frequent doctor visits, significant cost of medications for patients, and indirect costs incurred by the patient, including lost time from work or school.³⁶ According to the National Health and Nutrition Examination Survey, approximately 14% of Americans have CRS, and CRS accounts for 91.2 million health care visits per year.^{37,38} A relationship between rhinosinusitis and asthma has been shown. The prevalence of asthma in the general population falls between 5% and 8%; however, the prevalence of asthma in patients with rhinosinusitis approaches 20%.^{39–41} The Global Allergy and Asthma Network of Excellence conducted a large population-based, epidemiologic survey of more than 52,000 adults to determine the prevalence of asthma and rhinosinusitis in 12 European countries. There was a strong association between asthma and rhinosinusitis, with an odds ratio of 3.47 at all ages. The association was even stronger in those who reported allergic rhinitis in addition to CRS, with an odds ratio of 11.85.⁴¹ Approximately 20% of patients with CRS have nasal polyps; in patients with chronic sinusitis with nasal polyps, the prevalence of asthma increases to 50%. This number is even higher in rhinosinusitis patients who ultimately undergo sinus surgery.^{36,42,43}

The clinical association between sinusitis and asthma has been investigated. Multiple studies have demonstrated that the presence of comorbid CRS and asthma is associated with worse asthma outcomes. Using the results from the GA(2)LEN survey (Global Allergy and Asthma European Network), Elk and colleagues⁴⁴ studied the impact of CRS on pulmonary measures and quality-of-life outcomes in patients with asthma. Patients with both CRS and asthma had lower quality of life scores and poorer pulmonary function measures when compared with patients with asthma alone. In another study by ten Brinke and colleagues,⁴⁵ factors associated with frequent

asthma exacerbation were investigated. In this study, severe sinonasal disease was associated with more frequent asthma exacerbations, with an odds ratio of 3.7.

The presence of asthma has been shown to be associated with worse sinus disease. In 1 study, patients with severe asthma were more likely to have severe sinonasal involvement, as measured by validated visual analog symptom scale and computed tomography (CT) scan, than those with mild to moderate asthma.⁴⁶ In another study of 89 patients with severe asthma, the degree of inflammation was assessed by CT score, pulmonary function testing, blood and sputum eosinophilia, and nitrous oxide in inhaled air. Significant associations were found between CT scan scores and peripheral blood eosinophil counts and exhaled nitric oxide levels. In this study, 84% of patients with severe asthma had an abnormal sinus CT scan.⁴⁷ A recent study of 187 patients with CRS aimed to determine whether the presence and severity of comorbid asthma impacts the clinical presentation of CRS. In this study, Lund-Mackay CT scores were significantly greater in patients with moderate or severe asthma compared with mild, intermittent, and nonasthmatic patients. The presence of allergic sensitization was highest in the moderate to severe asthma group, and the presence of nasal polyposis was significantly higher in the moderate to severe asthma group.⁴⁸

The treatment of CRS has been shown to result in an improvement in asthma severity in those individuals with both diseases, although the evidence is inconsistent. Medical treatment of sinusitis alone has been shown in some studies to improve lower airway symptoms. Several studies have demonstrated that the use of intranasal corticosteroids results in decreased bronchial hyperresponsiveness. However, a recent multicenter, randomized, double-blind, placebo-controlled trial compared outcomes in patients treated with intranasal mometasone compared with placebo. There was no statistically significant difference in outcomes including asthma quality of life, lung function, or episodes of poorly controlled asthma in adults.⁴⁹

Surgical treatment of CRS by endoscopic sinus surgery has been shown to improve both objective measures of pulmonary function and quality-of-life measures in patients with comorbid asthma. Several studies have shown decreased asthma medication use after sinus surgery. Additionally, continued medical therapy after sinus surgery has been shown to improve asthma control in long-term studies up to 6 years.^{50–53}

Pathophysiologic Link

Rhinosinusitis and asthma seem to be 2 different manifestations of a similar pathophysiologic process in which eosinophils play a critical role. Whereas CRS represents a spectrum of disease with a variety of causative factors, eosinophil-mediated inflammation is common to most forms of rhinosinusitis, even in the absence of atopy.^{36,39}

The mucosa of the respiratory tract, including the paranasal sinuses and bronchi, is composed of pseudostratified columnar epithelium. Chronic inflammation of the respiratory mucosa results in histologic changes, including basement membrane thickening, goblet cell hyperplasia, subepithelial edema, cellular infiltration, and mucous hypersecretion, which similarly affects the paranasal sinus and bronchial mucosa. In a histopathologic study performed by Dhong and colleagues,⁵⁴ the sinus mucosa of patients with and without asthma were examined. Basement membrane thickening, goblet cell hyperplasia, and eosinophil infiltration were found to be greater in the patients with sinusitis and comorbid asthma.

The inflammation of both CRS and asthma are characterized by similar inflammatory mediators and cells. Eosinophils and IL-5-producing lymphocytes are common to both disease processes. Key T-helper type 2-cell driven proinflammatory cytokines

seen in both disease processes include IL-4, IL-5, and IL-13. IL-5 is responsible for promoting eosinophil production and preventing eosinophil apoptosis. Inflammatory mediators including regulated on activation normal T cell expressed and secreted (RANTES), eotaxin, and endothelial adhesion proteins are also seen in both CRS and asthma. RANTES and eotaxin facilitate transendothelial migration of eosinophils and movement of eosinophils into epithelium. Activation of adhesion proteins including intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 leads to downstream effects, including transmigration of inflammatory cells. In the lower airway, this leads to airway narrowing and bronchospasm. With time, repeated insult results in permanent airway remodeling.¹⁴

The pathophysiologic similarities seen in CRS and asthma further support the unified airway or united airway disease model. The proposed mechanism of local and systemic inflammation via upregulation of inflammatory progenitors in the bone marrow provides a framework for the pathophysiologic similarities between CRS and asthma.

ASTHMA: EPIDEMIOLOGY AND CLINICAL PRESENTATION

Epidemiology

Asthma is a chronic lung disease characterized by bronchial hyperreactivity, resulting in episodic coughing, wheezing, chest tightness, and shortness of breath. More than 25 million children and adults suffer from asthma in the United States.^{55,56} The number of people with asthma continues to increase. In 2001, 1 in 14 individuals, or 20 million people in the United States had asthma. By 2009, 1 in 12 people, or 25 million people had asthma. The overall prevalence of asthma in the United States is 7.8%. The prevalence of asthma is higher in children than in adults, with an estimated prevalence of 8.4%, making it the most common chronic disease of childhood.^{13,57} Asthma is more likely to affect women and girls than men and boys. Increased asthma rates have disproportionately affected different ethnic groups. African American children are almost twice as likely to have asthma when compared with white children, with prevalence rates of 13.4% compared with 7.4%, respectively. African American children have experienced a disproportionately greater increase in asthma rates, an almost 50% increase between 2001 and 2009. Asthma also disproportionately affects people of different socioeconomic status, affecting 11.1% of those below the poverty level.⁵⁷ In addition to allergy, other risk factors for the development of asthma include environmental exposures, including tobacco smoke and pollution, respiratory infections, obesity, occupational exposures, and genetics.¹³

Morbidity and Mortality

Asthma is associated with significant morbidity and mortality in the United States. In 2010, the number of hospital outpatient department visits with asthma as the primary diagnosis was 1.3 million. The number of physician visits with asthma as the primary diagnosis in 2012 was 10.5 million. There were 1.6 million emergency department visits for asthma in 2013.⁵⁷ In 2015, there were a total of 3615 deaths attributable to asthma. Of that number, 219 deaths were in children and 3396 were in adults.

Asthma is not only a significant health issue, but also poses a major financial burden on society. With the increasing rates of asthma in the United States also comes increasing costs owing to medical costs, missed school or work days, hospitalizations, and early deaths. In the United States, the annual cost of asthma has increased by approximately 6% between 2002 and 2007, increasing from an estimated \$53 million to \$56 billion. Costs associated with asthma have a significant impact on

both the national and individual levels. In 2015, the prevalence of asthma in those with private insurance was 7.0% compared with 13.6% in patients with Medicaid. Approximately 40% of uninsured and 11% of insured people with asthma are unable to afford their prescription medications.^{57,58}

Clinical Presentation

Asthma is an inflammatory disorder characterized by symptoms including cough, wheezing, shortness of breath, or chest tightness. These symptoms are recurrent and are often associated with exposure to various triggers. Common triggers of asthma include inhalant allergen exposure, upper respiratory viral infection, and exposure to environmental irritants like smoke or pollution. Depending on the individual's trigger, symptoms may be worse at different times of the year or in different environments.¹³

The evaluation of a patient with asthma should include a thorough history, including history of atopic disease. Patients should be questioned about the presence of both upper and lower respiratory symptoms. Nasal symptoms including nasal congestion, rhinorrhea, hyposmia, anosmia, postnasal drip, and sneezing should be elicited. Patients should be asked about triggers of their symptoms, whether symptoms are worse in a particular location or more severe during a particular season. Because asthma is, in part, a heritable disease, it is important to gather a thorough family history of asthma and/or allergy. The diagnosis and management of asthma is discussed in detail (See John H. Krouse's article, "[Asthma Management for the Otolaryngologist](#)," in this issue for further details).

ALLERGIC RHINITIS AND OTHER COMORBIDITIES

Laryngitis

Although there has been extensive research over the past 2 decades aiming to characterize the relationship of the upper and lower airways, much of the work has focused on allergic rhinitis, sinusitis, and asthma. The role of the larynx in the unified airway is less well understood. Although there has been anecdotal evidence of the connection between allergy and vocal dysfunction, there are few controlled studies examining this.⁵⁹ The larynx is positioned between the upper and lower airways, and therefore may be considered a part of the unified airway. In acute laryngitis, diffuse inflammation involving the supraglottis, glottis, and subglottis can be seen. In contrast, chronic laryngitis is characterized by inflammatory changes primarily at the level of the vocal folds. Several studies have examined the role of allergy in both acute and chronic laryngitis. Corey and colleagues⁶⁰ described and differentiated between the 2 forms of laryngitis. In acute allergic laryngitis, upon exposure to an allergen, there is rapid edema of the lips, tongue, pharynx, and larynx. This potentially life-threatening response may be associated with cutaneous symptoms, dyspnea, and tachycardia. Chronic laryngitis has a significantly less aggressive presentation. These patients typically have mild vocal fold edema and thick mucous of the glottis and supraglottis. Chronic laryngeal inflammation can result in dysphonia, throat clearing, and cough.

Several studies have attempted to define the mechanism by which allergic laryngitis occurs.^{61,62} Two underlying processes have been proposed to result in allergic laryngitis. The first proposed mechanism suggests that impaired nasal breathing results in altered resonance characteristics of the upper airway, resulting in dysphonia in the allergic patient.⁶³ The second, more recently proposed mechanism, suggests that postnasal drip leads to laryngeal irritation and subsequent harmful behaviors including coughing and throat clearing.^{62,64} Dworkin and Stachler⁶² proposed a model for

laryngitis resulting from inhalant allergen exposure, describing 3 contributory mechanisms. First, local inflammation in the nose or sinuses produces a system-wide inflammatory response by upregulation of inflammatory mediators in the circulatory system and by local increase mucous production. Second, increased mucous produced in the upper airways is transported to the pharynx and ultimately to the larynx. Last, this mucous acts as an irritant on the pharynx and larynx, resulting in compensatory behaviors, including throat clearing and coughing. These behaviors result in histologic changes to the laryngeal mucosa.^{62,65} Finally, some suggest that allergic laryngitis results from the systemic propagation of local inflammation to involve the entire respiratory tract, that is, the unified airway.⁵⁹

Epidemiology and Clinical Implications

The association between allergic rhinitis and laryngitis has been shown in multiple studies. Simberg and colleagues⁶⁶ performed a survey in 49 allergic patients and 54 nonallergic controls in which the frequency of various vocal complaints was assessed. Patients in the allergy group had significantly more severe voice symptoms than nonallergic controls. These differences remained when controlling for asthma. In another study conducted by Millqvist and colleagues,⁶⁷ 30 patients with confirmed allergy and 30 nonallergic controls were evaluated for subjective voice dysfunction using the Voice Handicap Index, a validated questionnaire for the evaluation of voice quality. During allergy season, patients with allergy reported significantly more respiratory and voice symptoms than did controls.

The relationship was investigated further in direct provocation studies.^{68,69} Reidy and colleagues⁶⁸ developed transoral provocation using nebulized antigen. Dworkin and colleagues⁶⁹ found that when using a high concentration of antigen, patients developed vocal fold edema and erythema, increased secretions, coughing, hoarseness, and respiratory issues. These reactions lead to early termination of the study owing to safety concerns. In an attempt to control for potential confounders, including pulmonary reactions, Roth and colleagues⁷⁰ conducted a similar study using transoral provocation, but excluded those patients with airway reactivity on methacholine challenge. In this double-blind, placebo-controlled study, the effect of antigen challenge on subglottic pressure was compared with the effect from saline placebo. All patients had significant increase in subglottic pressure after antigen presentation.

The relationship between allergy and vocal dysfunction has been shown; however, further investigations must be undertaken to determine the mechanism behind allergic laryngitis. Patients with dysphonia or cough should be evaluated for comorbidities including allergic rhinitis, sinusitis, and asthma.

Conjunctivitis

Conjunctivitis is an inflammation of the conjunctiva caused by a variety of agents, including allergens. Ocular allergy represents a heterogeneous group of disorders with different pathophysiologic mechanisms, physical manifestations, and treatment responses, and includes acute allergic conjunctivitis, allergic conjunctivitis, vernal keratoconjunctivitis, and atopic conjunctivitis, among others. Allergic conjunctivitis is an inflammatory response of the conjunctiva to environmental allergen and often occurs in conjunction with allergic rhinitis.⁷¹ Signs and symptoms of conjunctivitis include conjunctival hyperemia, chemosis, itching, tearing, and/or mucoid discharge. These signs and symptoms are the result of an immune response triggered in a previously sensitized individual. Upon subsequent exposure of an individual's ocular surface to a particular allergen, allergen-specific IgE receptors on conjunctival mast cells are activated, resulting in mast cell degranulation. Inflammatory mediators, including

histamine, prostaglandins, and leukotrienes, contribute to the manifestations of ocular allergy.⁷² Allergic conjunctivitis of this type affects the tarsal conjunctiva and eyelid but spares the cornea.⁷¹

Epidemiology and Clinical Implications

Allergic conjunctivitis is common, affecting up to 40% of the population in the United States.⁷³ Between 40% and 60% of patients with atopy are affected by ocular symptoms.^{73,74} Using data from the third National Health and Nutrition Examination Survey, the prevalence of allergic conjunctivitis has been estimated. Of the 20,010 individuals surveyed, 6.4% of the population reported ocular symptoms alone, 16.5% reported nasal symptoms alone, 29.7% reported both nasal and ocular symptoms, and 47.4% were asymptomatic. In this study, 40% of surveyed individuals reported at least 1 occurrence of ocular symptoms in their lifetime. Ocular symptoms tend to be present throughout all decades of life, in contrast with isolated nasal symptoms or combined nasal and ocular symptoms.⁷³ There is a strong epidemiologic connection between allergic conjunctivitis and allergic rhinitis. The epidemiologic link between allergic conjunctivitis and rhinitis is so strong that epidemiologic studies rarely separate the clinical entities; rather, allergic rhinoconjunctivitis has been studied more thoroughly. The connection between allergic rhinitis and allergic conjunctivitis is further substantiated by studies showing that treatment of allergic rhinitis with intra-nasal steroids improves ocular symptoms as well.⁷⁵

SUMMARY

The upper and lower airways are connected both epidemiologically and pathophysiologically. Local and systemic inflammatory responses to allergen exposure have given rise to notion of the unified airway or united airway disease. Otolaryngologists encounter patients with upper airway symptoms, including nasal obstruction, nasal congestion, rhinorrhea, and sneezing in daily practice. Therefore, the otolaryngologist should familiarize himself or herself with the signs and symptoms of lower airway disease which often accompany upper airway pathology. Although the diagnosis and management of asthma is not traditionally thought to fall within the purview of an otolaryngology practice, the otolaryngologist may be the first to suspect lower airway pathology in a patient presenting with upper airway complaints. In light of the evidence that treatment of lower airway disease impacts therapeutic outcomes in upper airway disease, and vice versa, the importance of expedient diagnosis and management of asthma is clear.

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