

Allergic rhinitis and asthma: Epidemiology and common pathophysiology

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ABSTRACT

Allergic rhinitis and asthma are common diseases that frequently occur together. This concept has been referred to in the literature as united airway disease. Epidemiological studies have shown that the majority of patients with asthma have concomitant rhinitis and the presence of rhinitis is an increased risk factor for development of asthma. Patients with asthma and rhinitis share common physiology including heightened bronchial hyperresponsiveness and heightened reactivity to a variety of stimuli. Immunopathology of allergic rhinitis is also similar with the predominance of T-helper type 2 inflammation and tissue eosinophilia. Although several mechanisms have been proposed to explain the united airway theory, some of the best lines of evidence suggest that local airway inflammation can result in a systemic inflammatory response. Pharmacotherapeutic studies have shown that the treatment of rhinitis can improve asthma and vice versa. Nevertheless, systemic approaches such as immunotherapy lead to better outcomes for treating both disease states simultaneously. This article will focus on the data supporting the common epidemiology, shared pathophysiology, and therapeutic interventions aimed at allergic rhinitis and asthma as united airway diseases.

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The concept that allergic rhinitis and asthma frequently coexist is not new. Recently, this concept has been termed the united airway disease. Support for this concept is based on several epidemiological studies, similar pathophysiology, and interactions between the upper and lower airway. This article will focus on the data supporting the common epidemiology and shared pathophysiology of allergic rhinitis and asthma.

EPIDEMIOLOGY OF RHINITIS AND ASTHMA

Allergic rhinitis is a very common chronic disease in the United States. The prevalence of allergic rhinitis ranges between 5 and 22%.¹ Asthma is also a common disease affecting 5–16% of people worldwide.² Although ~19–38% of patients with allergic rhinitis have concomitant asthma, a much higher frequency of patients with asthma have concomitant allergic rhinitis.³

Togias and colleagues reviewed several databases of the Johns Hopkins Asthma and Allergy Center to determine the prevalence of rhinitis symptoms in patients with asthma.⁴ In these well-characterized groups, between 85 and 95% of patients with asthma had allergic rhinitis. Other investigators have evaluated the prevalence of allergic rhinitis and asthma in general popu-

lations. A survey of a London general practice of 7702 adults was reported in 1991.⁵ Almost 3000 subjects returned a usable survey and a minimum prevalence of rhinitis was found to be 24%. Of this sample, 466 subjects were then interviewed in person and there was 95% agreement with a diagnosis of rhinitis by physical interview compared with the questionnaire. Subjects with perennial rhinitis had a 3.12 odds ratio (OR) of asthma and the combination of perennial and seasonal rhinitis had a 4.48 OR for asthma. The classic study from the Settapanes studying Brown University students has also shed light on allergic rhinitis as a risk for asthma. In the original study from 1963, of 1836 students, asthma was present in 5.3%; 23 years later 6% had asthma.⁶ Among prior students who had allergic rhinitis, 10.5% developed new-onset asthma compared with only 3.6% who did not have allergic rhinitis. This difference was statistically significant, indicating allergic rhinitis as a risk for development of new asthma.

The prevalence of asthma and allergic rhinitis has also been evaluated in a Finnish twin cohort evaluated from 1975 to 1990.⁷ Allergic rhinitis was typically diagnosed before asthma and there was a threefold risk of developing asthma with a diagnosis of allergic rhinitis. Another study from Italy reported on the natural history of respiratory allergy in 99 patients who were followed for 10 years.⁸ The study found that of those patients who had rhinitis alone, 31.8% evolved to develop concomitant asthma. They also found, somewhat interestingly, that 50% of patients who presented only with asthma developed concomitant rhinitis, suggesting that the evolution of asthma and rhinitis is bidirectional.

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Although many studies have focused on allergic rhinitis and the risk of asthma, this has also been shown with nonallergic rhinitis. Results from the European Community Respiratory Health Survey found that subjects with nonallergic rhinitis had an 11.6 OR for an independent risk of asthma.⁹ Another study from Denmark showed that children with nonallergic rhinitis have a similar risk of asthma as those with allergic rhinitis.¹⁰ Nonallergic triggers may also increase the likelihood of asthma. A study evaluating nonallergic triggers using the irritant index questionnaire found that for subjects with both allergic and nonallergic rhinitis, having a high burden of irritant triggers increased the prevalence of asthma.¹¹ Finally, even a family history of rhinitis has been associated with an increased risk of asthma and a family history of asthma has been associated with an increased risk of rhinitis.¹² In summary, there are numerous lines of epidemiological studies associating a higher prevalence of rhinitis in asthma, whether allergic or nonallergic, and that the presence of rhinitis increases the risk for development of asthma.

SHARED PHYSIOLOGY OF ASTHMA AND RHINITIS

Patients with asthma and allergic rhinitis share several different physiological features. One of these is enhanced bronchial hyperresponsiveness (BHR). Patients with both perennial and seasonal allergic rhinitis have heightened BHR but it is greater in those with perennial allergic rhinitis.¹³ Interestingly, 46% of nonallergic rhinitis with eosinophilia patients also have BHR. BHR is much greater in patients with asthma than in patients with rhinitis, up to 25-fold greater. One explanation for this is that the wall thickness of asthma patients is increased and this increase in wall thickness can translate into markedly higher increases in airway resistance with a similar magnitude of smooth muscle contraction.¹⁴

Patients with rhinitis and asthma also have heightened reactivity to a variety of stimuli including methacholine, histamine, dry air, hypertonic saline, capsaicin, leukotriene D₄, and allergen. In the nose these stimuli result in sneezing, nasal congestion, rhinorrhea, and nasal itch, whereas in the bronchi these stimuli can result in cough, bronchospasm, and mucus secretion.

In addition to enhanced BHR, patients with allergic rhinitis may have more robust responses to bronchodilators. An interesting study by Ciprandi *et al.* studied a group of 375 patients with moderate-to-severe persistent allergic rhinitis and their response to bronchodilators.¹⁵ Patients were excluded if they had any history of asthma or the presence of asthma symptoms including cough, wheezing, dyspnea, and shortness of breath. Compared with nonallergic controls, patients

Table 1 Pathophysiological comparison of rhinitis and asthma

Similarities in Rhinitis and Asthma	Differences in Rhinitis and Asthma
Cellular Eosinophils, mast cells, and Th2 cells	Asthma Epithelial shedding Smooth muscle
Mediators Histamine, cysteinyl leukotrienes, Th2 cytokines, chemokines, and adhesion molecules	Rhinitis Venous sinusoids
Airway remodeling	
<i>Th2 = T-helper type 2.</i>	

with allergic rhinitis had a significant increase in forced expiratory volume in 1 second (FEV₁) after bronchodilator. In fact, two-thirds of rhinitis patients had reversibility $\geq 12\%$.

SHARED PATHOPHYSIOLOGY OF ALLERGIC RHINITIS AND ASTHMA

In addition to shared physiology in patients with allergic rhinitis and asthma, there are also common pathophysiological elements (Table 1). The immunopathology of allergic rhinitis and asthma are quite similar in regard to their cellular influx of eosinophils, mast cells, and T-helper type 2 (Th2) cells. A similar array of mediators can also be found in the lavage of patients with allergic rhinitis and asthma. Although structural changes of airway remodeling are well known in asthma, they may also occur in allergic rhinitis. Chaney *et al.* studied nasal and bronchial biopsy specimens from 15 untreated allergic asthmatic patients with perennial rhinitis, 6 steroid-dependent asthmatic patients, and 6 control subjects.¹⁶ In both bronchial as well as nasal biopsy specimens, the reticular basement membrane thickness was greater in asthma patients than in control subjects.

There are also differences in the pathophysiology of allergic rhinitis and asthma (Table 1). In asthma there is increased epithelial shedding and the presence of smooth muscles in the airway. In contrast, the nose contains venous sinusoids, and vascular engorgement (as opposed to bronchospasm) results in the obstruction of the upper airway.

PROPOSED MECHANISMS OF THE UNITED AIRWAY THEORY

Although there clearly is evidence from an epidemiological standpoint as well as similar physiological reactions to a variety of stimuli in patients with asthma

and allergic rhinitis, the mechanisms explaining this are not entirely clear. Several proposed mechanisms have been put forth to explain the united airway theory. One explanation is the so-called nasal-bronchial reflex. This phenomenon has been observed in animals; however, it is controversial as to its existence in humans.³ Another theory suggests that in patients with rhinitis, subsequent nasal congestion leads to mouth breathing. Mouth breathing, in turn, can result in inhalation of cooler and drier air, which can cause bronchoconstriction, as would be the case in patients with exercise-induced bronchospasm. Another theory suggests that inflammatory products from the upper airway may be aspirated into the lower airway, however, this remains unproven. The theory that is backed by most evidence relates to local inflammation in one organ system affecting a distant organ.

LOCAL AIRWAY CHALLENGES AND SYSTEMIC INFLAMMATION

The best evidence for “cross-talk” between the nasal and bronchial mucosa was published in a series of experiments by Braunstahl *et al.*^{17,18} They studied non-asthmatic subjects with seasonal allergic rhinitis and healthy control subjects. One set of experiments evaluated nasal allergen provocation and resulting changes in bronchial mucosa. After nasal allergen challenge, they found typical findings in the nasal epithelium of increased eosinophils that was also seen in bronchial epithelium and lamina propria. Several adhesion molecules were found to be overly expressed in both the nasal and the bronchial tissue. In the bronchial subepithelium, the number of eosinophils correlated with expression of adhesion molecules on the blood vessels. The conclusion of the study was that nasal provocation and allergic rhinitis resulted in generalized airway inflammation *via* up-regulation of adhesion molecules.

The second series of experiments involved the reverse procedure, that of bronchial provocation and evaluation of both bronchial and nasal mucosa. Segmental bronchial provocation was performed in the right middle lobe and the right upper lobe was saline challenged. The number of eosinophils increased in not only the challenged right middle lobe mucosa, but also in the unchallenged right upper lobe and left lung bronchial mucosa, and peripheral blood. In addition, eotaxin-positive cells (eosinophils) were detected in the nasal lamina propria and there was increased expression of interleukin-5 in the nasal epithelium. This study showed that segmental bronchoprovocation in non-asthmatic allergic rhinitis patients resulted in a peripheral blood eosinophilia as well as allergic inflammation in the nose.

The results of these two studies is suggestive of a general systemic activation of eosinophils, which leads

to migration of these cells into both the upper and the lower respiratory mucosa. The authors speculate that absorption of inflammatory mediators at the site of allergen challenge results in release of eosinophils from the bone marrow and the blood and, subsequently, in the recruitment into nasal and bronchial mucosa through the up-regulation of adhesion molecules. Recent studies of asthma have shown that exosomes, nanosized membrane vesicles may have a role in orchestrating airway inflammation.¹⁹ Whether exosomes are involved with the unified airway theory has not been studied. Whatever the mechanism, these studies clearly support the united airway theory.

ASTHMA AND SINUSITIS

The united airway theory is typically thought to represent the link between allergic rhinitis and asthma; however, the sinuses are also part of the upper airways and there is certainly evidence for a link between sinusitis and asthma. The coexistence of asthma and sinusitis has been noted for centuries. The immunopathology of asthma and chronic rhinosinusitis is also similar with Th2 inflammation and tissue eosinophilia in most patients, while some patients have tissue neutrophilia, which potentially could be related to Th17 inflammation.²⁰ A study of 89 patients with severe asthma found that 84% of these patients had abnormalities on computed tomography sinus radiography with extensive disease found in 24% of patients.²¹ In this study, disease severity found on computed tomography scans correlated with both sputum eosinophilia as well as exhaled nitric oxide, indicating a correlation between markers of inflammation in the lower airway and radiological evidence of inflammation in the upper airway.

Another example of the link between sinusitis and asthma is in patients with aspirin-exacerbated respiratory disease (AERD). Patients with AERD have eosinophilic tissue inflammation in their lower airways and nasal polyps. AERD patients have both upper airway responses (rhinoconjunctivitis) and lower airway responses (bronchospasm) to the same stimulus, aspirin and nonsteroidal anti-inflammatory drugs. Aspirin desensitization followed by aspirin therapy can improve outcomes for both the upper and the lower airway in these patients.²²

PARALLEL RESPONSES TO THERAPY

Finally, another line of evidence supporting the link between allergic rhinitis and asthma relates to the pharmacotherapy of rhinitis and its impact on asthma. Early studies with first-generation antihistamines showed minimal benefit on asthma; however, it was unclear whether this benefit may have been attributed to anticholinergic properties. Studies with second-generation

antihistamines (lacking anticholinergic activity), however, have shown some limited benefit in patients with asthma including improvement in asthma symptoms and in some studies improvement in measures of lung function.²³ One of the more robust studies evaluated loratadine and pseudoephedrine in 193 subjects during the fall allergy season in a randomized double-blind placebo-controlled trial.²⁴ The antihistamine–decongestant combination significantly improved nasal and asthma symptoms, pulmonary function, and quality of life in these patients with seasonal allergic rhinitis and concomitant mild asthma.

Intranasal corticosteroids, which are more effective than antihistamines in allergic rhinitis, have also been evaluated in subjects with asthma. Multiple studies have shown benefits in asthma outcomes after treatment with intranasal corticosteroids manifesting as improvement in asthma symptoms, lung function, and reduced BHR.²⁵ In a retrospective review of asthma patients from a health care plan in Massachusetts, patients prescribed intranasal corticosteroids had a reduced relative risk for an emergency department visit.²⁶ The results of this study have been challenged based on a potential improper time-dependent analysis. A similar study evaluating the effect of intranasal corticosteroids on hospitalizations showed an initial protective effect but when analyzed in a time-dependent manner, no protective effect was seen.²⁷ A Cochrane meta-analysis from 2003 concluded that intranasal corticosteroids were well tolerated and tended to improve asthma symptoms and FEV₁ but the results did not reach statistical significance.²⁸ Given the small number of studies analyzed and the trends that were observed, it is certainly possible that with further research and larger studies, a more significant effect could be seen. At this juncture, relying on intranasal corticosteroids as monotherapy to manage asthma is certainly not recommended.

Although most studies have focused on the impact of rhinitis pharmacotherapy on asthma, there are data looking in the other direction—the impact of asthma pharmacotherapy on rhinitis. Greiff and colleagues studied 35 patients with birch allergic rhinitis without asthma in a double-blind placebo-controlled trial using budesonide 600 µg twice daily inhaled through the mouth.²⁹ Inhaled budesonide attenuated seasonal nasal symptoms and reduced nasal brush eosinophils, nasal lavage fluid levels of eosinophil cationic protein, and peripheral blood eosinophilia. In contrast, a larger study of 262 pollen-allergic subjects evaluated the effect of intranasal fluticasone, inhaled fluticasone (250 µg twice daily), or a combination of the two versus placebo on pollen-induced rhinitis and asthma.³⁰ In this study, the inhaled steroid group had no effect on the absence of nasal symptoms (a more rigorous end point) and the intranasal steroid group had no signif-

icant impact on asthma symptom-free days or nights, FEV₁, or attenuation of increased methacholine responsiveness during the pollen season.

From a scientific standpoint, it is certainly interesting to analyze the effect of medications aimed at a single target organ and analyzing the outcome on a distant target organ; however, systemic therapies are certainly more likely to be beneficial in both asthma and rhinitis. Leukotriene-modifying drugs have been shown to be effective for both rhinitis and asthma. Furthermore, allergen avoidance, allergen immunotherapy, and immunomodulatory interventions have also been effective in rhinitis and asthma.³¹ Finally, allergen-specific immunotherapy has been shown, in a 10-year follow-up study, to prevent the development of asthma in children with allergic rhinitis, up to 7 years after a 3-year course of immunotherapy.³²

CONCLUSIONS

The united airway disease theory is supported by epidemiological, pathophysiological, and clinical studies. An integrated approach is therefore optimal for patients with concomitant upper and lower airway diseases. Although therapeutically targeting a single organ (nose or lung) can result in clinical improvement in the nontargeted organ, the benefits of such organ-specific therapy is usually modest. Systemic approaches (e.g., immunotherapy) tend to yield better outcomes for both controlling upper and controlling lower airway allergic disease. The role of sinus disease in asthma is less well defined and requires further study. Additional studies designed to understand the mechanistic links as well as impact of various therapies on the united airway disease are still needed.

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