Relationship between Asthma and Rhinitis: Epidemiologic, Pathophysiologic, and Therapeutic Aspects

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Abstract
Over the last few years, the evidence of links between rhinitis and asthma has been strengthened. This has led to the introduction of the concept of united airway disease. Rhinitis and asthma appear to be interrelated at the epidemiologic level and at the pathophysiologic level. This article reviews current epidemiologic and pathophysiologic evidence of the relationship between rhinitis and asthma and discusses the effect of treatment of one site on the other site.

Epidemiologic Links: Atopy
Asthma and rhinitis are frequently associated with atopy with preferential sensitization to airborne allergens. Atopic diseases can manifest themselves at different sites on the body and can present as urticaria, allergic rhinitis, atopic dermatitis, conjunctivitis, food allergy, and asthma.

Allergic Rhinitis and Asthma Prevalence
Allergic rhinitis is an important health problem and affects up to 40% of the worldwide population.1,2 Its prevalence in the Canadian population is between 10 and 25%1. Forty percent of allergic rhinitis patients have asthma, and as much as 94% of allergic asthma patients have allergic rhinitis.3-6 In Canada, the current prevalence of asthma is 8.4%7 whereas worldwide prevalence varies from 1.6 to 37%.1

Allergic Rhinitis as a Risk Factor for Asthma
Settipane and colleagues conducted a prospective study on a cohort consisting of young university students to determine the long-term risk factors for developing asthma and allergic rhinitis.8 The follow-up study 23 years later revealed that the incidence of asthma and allergic rhinitis increases with age. Furthermore, the presence of allergic rhinitis and positive results of allergen skin tests were shown to be important risk factors of asthma development. Patients with allergic rhinitis have a threefold greater chance of developing asthma.9 Interestingly, the relief of rhinitis symptoms over time correlates with the improvement of asthma symptoms. Patients with more severe and persistent rhinitis are at a higher risk of developing asthma.9 A strong association between perennial rhinitis and asthma in nonatopic subjects was also demonstrated in the European Community Respiratory Health Survey.10

To better understand the possible links between asthma and allergic rhinitis, the World Health Organization, through the Allergic Rhinitis and its Impact on Asthma (ARIA) program, examined the impact of allergic rhinitis on asthma.2 The ARIA study concluded that allergic rhinitis is a
major chronic respiratory disease owing to its prevalence, impact on quality of life, impact on school and work performance and productivity, economic burden, and links to asthma. According to the ARIA study and previous observations, allergic and nonallergic rhinitis should be considered risk factors for asthma, along with other known risk factors.

**Physiopathologic Links**

The mucous membranes of both the upper and the lower airways are covered by a pseudostratified columnar ciliated epithelium with a continuous basement membrane. For this reason, these airways share a mucosal susceptibility to inhaled allergens. The obvious anatomic difference is the presence of smooth muscle in the lower airway as opposed to large venous sinusoids and prominent glands within the submucosa in the upper airway. The following section describes similarities and dissimilarities between rhinitis and asthma pathologies.

**Allergy**

Exposure to an allergen triggers an immediate reaction coordinated by mast cells and their mediators such as histamines, leukotrienes, and prostaglandins. In allergic rhinitis, this immediate reaction leads to nasal congestion and runny nose from an increase in vascular permeability. In asthma, the immediate reaction results in bronchospasm. Late-phase reaction occurs in both asthma and rhinitis following allergen exposure and is mainly triggered by CD4+ T cells. Allergic rhinitis and asthma share many pathologic features. In fact, the same profile of inflammation, mediators, and adhesion molecules can be observed in upper- and lower-airway allergic diseases. There is a common cellular inflammation pattern characterized by eosinophil, mast-cell, and CD4+ T-cell infiltration. Mediators (including histamine; cysteinyl leukotrienes; interleukin [IL]-4, IL-5, IL-13; regulated on activation, normal T-cell expressed and secreted [RANTES] chemokine; and eotaxin) are expressed in both upper and lower airways. Although the initial inflammation induced by allergens is similar in upper and lower airways, the long-term structural consequences differ. The respiratory epithelium is disrupted in bronchial asthma whereas only minimal epithelial shedding is observed in allergic rhinitis. The subepithelial basement membrane is thickened with an increased amount of collagen deposition in asthma. Although this thickening can also occur in the upper airway in rhinitis, the extent of this process is less than that seen in the lower airway in asthma.

**Allergic Rhinitis, Airway Hyperresponsiveness, and Asthma**

It is well established that 40% of nonasthmatic patients with allergic rhinitis have increased airway hyperresponsiveness. Allergen nasal challenge or seasonal allergen exposure leads to increased airway hyperresponsiveness in rhinitis patients. The number of eosinophils in the sputum correlates with nonspecific airway hyperresponsiveness not only in asthma but also in allergic seasonal rhinitis. Nasal eosinophilia correlates with bronchial reactivity in allergic children who have both asthma and rhinitis. Gaga and colleagues found eosinophilic infiltration in the nasal mucosa of asthmatic patients even in the absence of rhinitis. The relationship between nasal allergy and asymptomatic airway hyperresponsiveness supports the concept of one airway, one disease.

**Nonallergic Rhinitis and Nonallergic Asthma**

An inflammatory pattern has been characterized in asthmatic children suffering from allergic rhinitis and in those with nonallergic rhinitis. Surprisingly, both groups have a typical T-helper 2 (Th2) cytokine inflammatory pattern as measured in rhino-sinusal lavage. Nonatopic or intrinsic asthmatic patients have an inflammatory pattern similar to that of atopic asthma patients although this nonatopic group has been less extensively studied. Increased levels of IL-3, IL-4, IL-5,
granulocyte-macrophage colony-stimulating factor (GM-CSF), and eosinophils were found in endobronchial biopsy specimens from nonatopic asthma patients.24-27 Even in the absence of an allergic process, rhinitis and asthma share similar inflammatory profiles, linking both diseases. Epidemiologic studies are consistent with these findings, as nonatopic rhinitis has also been reported to be an independent risk factor for developing asthma.2

Allergic Challenge

To better understand the allergen relationship between upper and lower airways, many studies have examined this paradigm, using nasal or bronchial allergen challenge and observing its effect on the opposite site of the airway.

Effect of Nasal Allergen Exposure on Lower Airways

Nasal allergen challenge increases eosinophils and adhesion molecules in both nasal and bronchial biopsy specimens from nonasthmatic patients with rhinitis.28 Chakir and colleagues also showed that natural pollen exposure is associated with an increase in lymphocyte numbers, eosinophil recruitment, and IL-5 expression in the bronchial mucosa of nonasthmatic persons with allergic rhinitis.29 In another study, Chakir and colleagues showed that allergic nonasthmatic patients with seasonal pollen-induced rhinitis had airway pathologic changes (as seen in bronchial biopsy specimens) similar to those observed in asthmatic patients.30 These changes consisted of cellular infiltration, mucosal edema, increased epithelial desquamation, and focal basement-membrane thickening.

Effect of Lower-Airway Allergen Exposure on Nasal Mucosa

Segmental bronchial allergen challenge in nonasthmatic allergic rhinitis patients leads to a decrease in nasal peak inspiratory flow and a concomitant increase in nasal symptomatology.31 It also increases eosinophils, eotaxin-positive cells, and IL-5 expression in nasal mucosa biopsy specimens31 and decreases mast cells.32 The decrease in the number of mast cells is attributed to a higher rate of degranulation.

Mechanisms That Might Explain the Link between Upper and Lower Airways

A number of mechanisms have been suggested to explain the link between upper and lower airways and the concept of united airway disease. They include genetic factors, an anatomic link between upper and lower airways, neural interaction between the nose and the lower airway, and mediator- or inflammatory-cell circulation. Inflammatory mediators can reach the lower airway from the upper airway through the airway passages. They might also be able to reach the lower airway through the blood. A number of these mediators, such as histamine, cysteinyl leukotrienes, and some cytokines, have the ability to spill over into the systemic circulation. However, very few data support this concept, and most of the cytokines have a very short half-life and do not act in an endocrine fashion. Inman33 and Denburg34 suggested that inflammatory mediators such as IL-5 and GM-CSF can travel from the lung to the bone marrow, where they could stimulate the progenitors’ release to the circulation and to the target organs. We have shown that after antigen challenge, there is an increase in IL-5-producing T cells in the bone marrow and an increase in high-affinity IL-5 receptor, which is associated with an elevated number of eosinophil progenitors.35,36 Recently, we showed that this process is most likely due to retrograde migration of antigen-specific T cells from the airways to the bone marrow, where antigen-specific T cells can produce a number of cytokines and help to release and differentiate the progenitor cells.37 Progenitor cells can be found along the entire airway in atopic individuals38 and can differentiate into mature eosinophils in response to local antigen challenge39 (Figure 1).
Treatment of Asthma and Allergic Rhinitis

As mentioned earlier, the pathophysiology of allergic rhinitis is very similar to that of allergic asthma, and the responses of the two conditions to pharmacologic and immunologic interventions are comparable. The most commonly used drugs for both conditions are corticosteroids. However, other anti-inflammatory drugs with systemic effects have been recently introduced for the management of both diseases.

Effect of Rhinitis Treatment on Asthma

A recent meta-analysis of asthma outcomes and the treatment of rhinitis with intranasal corticosteroids failed to show any significant improvement in asthma symptoms or in lung function although a trend in favor of intranasal corticosteroids was reported. In nonasthmatic children with allergic rhinitis, intranasal corticosteroids significantly improved airway hyperresponsiveness to methacholine but had no effect on asthma symptoms. Corren and colleagues reported that intranasal corticosteroids prevent the increase of bronchial responsiveness associated with seasonal pollen exposure in allergic rhinitis patients with asthma. Other anti-inflammatory drugs (montelukast and cetirizine), when used for rhinitis patients, have also been reported to improve asthma symptoms and to decrease the use of β₂ agonists. Recent studies have reported a decrease in asthma exacerbation in patients with concomitant allergic rhinitis when these patients received any kind of rhinitis treatment. Cetirizine, an antihistamine, has shown effectiveness in relieving upper- and lower-airway symptoms in patients suffering from concomitant allergic rhinitis and asthma. Cetirizine was found to be protective against late bronchial hyperresponsiveness that follows nasal allergen challenge in patients with allergic rhinitis. Combined therapy with montelukast and cetirizine for asthmatic patients with seasonal allergic rhinitis lessens the need for a rescue inhaler and improves lung function and asthma symptom score to the same extent as does inhaled budesonide combined with intranasal budesonide.

Effect of Asthma Treatment on Rhinitis

Greiff and colleagues treated nonasthmatic allergic rhinitis patients with inhaled corticosteroids during pollen season. They found an inhibition of the increase of eosinophils in blood and nasal tissues that is usually observed in pollen season. The patients who received inhaled budesonide had significantly milder nasal symptoms. In a recent clinical study, asthmatic individuals with nasal...
polyposis treated with montelukast had a 70% improvement of nasal symptoms and a 60% to 90% improvement in asthma clinical score.\(^5^9\) In a study comparing treatment with montelukast alone to treatment with inhaled and intranasal corticosteroids in patients with allergic rhinitis and in patients with asthma, only the group treated with corticosteroids showed a significant reduction in nasal nitric oxide and in nasal peak flow, whereas both treatments were efficient in decreasing rhinitis symptoms.\(^5^0\)

**Immunotherapy**

Immunotherapy is reserved for patients with moderately severe allergic rhinitis. Immunotherapy reduces inflammatory-cell recruitment and activation as well as the secretion of mediators.\(^2\) In a group of allergic rhinitis patients with asthma, immunotherapy improved methacholine hyperreactivity and quality of life and reduced seasonal asthma symptoms.\(^5^1\) Reducing the allergen sensitivity not only leads to relief of rhinitis but also helps control asthma (although less effectively).

**Conclusion**

It is important to carefully assess the upper airways in asthmatic patients and the lower airways in patients with allergic rhinitis. Allergic rhinitis is an important risk factor for developing asthma and is also an important cause of nonoptimal control of asthma. Links between upper- and lower-airway diseases exist through inflammatory mediators, but other mechanisms, such as mouth breathing and postnasal drip, can contribute. Many therapeutic options are currently available although corticosteroids remain the most effective anti-inflammatory drugs. Antileukotrienes have beneficial effects on rhinitis and asthma because they work through a systemic effect. Our common approach to the treatment of asthma and rhinitis needs to be revised to prevent the expression of the asthma phenotype in individuals who have rhinitis and to achieve better control of asthma in patients who already have both rhinitis and asthma.

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