

Review article

Relationships between rhinitis and asthma

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Is the nose the part of the lungs which is accessible to the fingers? Dysfunction of the upper and lower airways frequently coexists. Epidemiologic, pathophysiologic, and clinical studies have strongly suggested a relationship between rhinitis and asthma. These data have led to the concept that the upper and lower airways may be considered a unique entity influenced by a common and probably evolving inflammatory process, which may be sustained and amplified by intertwined mechanisms. Allergic rhinitis is correlated with, and probably constitutes a risk factor for, the occurrence of asthma, and it has been proposed that the prevention or early treatment of allergic rhinitis may help to prevent the occurrence of asthma or the severity of bronchial symptoms. However, although the nasal and bronchial mucosa present similarities, there are also differences which might suggest that rhinitis and asthma are two different airway diseases.

Epidemiology

Epidemiologic studies have consistently shown that asthma and rhinitis often coexist in the same patients (1, 2). The prevalence of asthma is greater in patients with rhinitis than in those without nasal symptoms (1). Approximately 30% of patients with perennial allergic rhinitis have signs of asthma. Most patients with asthma present hay-fever symptoms (2). Rhinitis occurs in about 75% of patients with allergic asthma and 40% of patients with nonallergic asthma (1, 3). However, in many

instances, symptoms predominate in one of the disorders and may be hidden in the other.

Sinusitis is common in asthma and may contribute to the severity of the bronchial symptoms (4). Patients with severe asthma tend to have sinusitis more commonly than those with a milder form of the disease.

The same triggers can cause rhinitis and asthma

Among the causative agents inducing asthma and rhinitis, some (e.g., allergens and aspirin [5]) are well known to affect both the nose and the bronchi. Most inhaled allergens are associated with nasal (1) and bronchial symptoms, but differences have been observed in epidemiologic studies. The prevalence of IgE sensitization to indoor allergens (house-dust mite and cat) is positively correlated with both the frequency of asthma and its severity (6, 7). *Alternaria* (8, 9) and insect dusts (10) have also been found to be linked with asthma, but pollen sensitivity has not been found to be associated with asthma in epidemiologic studies (9, 11). On the other hand, pollen sensitivity is always associated with rhinitis (1). There may also be differences depending on the time of acquisition of the atopy. In Australian children sensitized before the age of 6 years, early onset atopy is highly associated with respiratory symptoms, whereas, in those sensitized later, late-onset atopy is associated with rhinitis and to a lesser extent with asthma (12). Data from studies in the former East Germany also support

this concept of organ specificity depending on the age of sensitization.

An intriguing model to study the relationships between rhinitis and asthma has been offered by occupational asthma. Subjects with occupational asthma may also report symptoms of rhinoconjunctivitis. Rhinitis is less pronounced in the case of low-molecular-weight agents, but more often appears before occupational asthma in the case of high-molecular-weight agents, as in small mammals (13). In addition, rhinitis caused by some low-molecular-weight compounds such as ninhydrin or 1,2-benzisothiazolin-3-one develops into occupational asthma (14, 15), highlighting the importance of the cessation of allergen exposure in occupational allergic rhinitis, in order to prevent asthma.

Thus, there is strong epidemiologic evidence of a close link between rhinitis and asthma, suggesting a common genetic background for both these diseases. However, it has been observed that some genes may be restricted to nasal symptoms. Some HLA-DR haplotypes distinguish subjects with asthma from those with rhinitis only in ragweed pollen allergy (16).

Natural history of the diseases

Studies also have identified a temporal relation between the onset of rhinitis and asthma, rhinitis frequently preceding the development of asthma. Allergic rhinitis developing in the first years of life is an early manifestation of an atopic predisposition, which may be triggered by early environmental exposures (17). Allergic rhinitis and positive allergy skin tests are significant risk factors for developing new asthma. A 10-year prognosis for childhood allergic rhinitis was carried out, and it was found that asthma or wheezing had developed in 19% of cases and was more common among those with perennial allergic rhinitis than among those with seasonal allergic rhinitis (18). Patients with either of these diagnoses are about three times more likely to develop asthma than negative controls (19). However, upper and lower airway symptoms can also develop simultaneously in about 25% of patients.

The mucosa of the airways

In normal subjects, the structure of the airways mucosa in the nose and the bronchi is similar. Both nasal and bronchial mucosa are characterized by a pseudostratified epithelium with columnar, ciliated cells resting on a basement membrane. Underneath the epithelium, in the submucosa, vessels and mucous glands are present with structural cells (fibroblasts), some inflammatory cells (essentially

monocytic cells, lymphocytes, and mast cells) (20), and nerves.

There are also differences between the nose and the bronchi. In the nose, there is a large supply of subepithelial capillary and arterial system and venous cavernous sinusoids. The high degree of vascularization is a key feature of the nasal mucosa, and changes in the vasculature may lead to severe nasal obstruction (21). On the other hand, smooth muscle is present from the trachea to the bronchioles, explaining bronchoconstriction in asthma.

The nerves present in the nasal mucosa include adrenergic and cholinergic nerves, and nerves of the NANC (nonadrenergic noncholinergic system) (22–24). Neurotransmitters and neuropeptides released within the autonomic nervous system exert homeostatic control of nasal secretion by plasma extravasation as well as mucous and serous cell secretion. Sensory neuropeptides are present in human bronchial nerves, beneath and within the epithelium, around blood vessels and submucosal glands, and within the bronchial smooth-muscle layer (25, 26). Cholinergic nerves are the predominant bronchoconstrictor pathway. On the other hand, there is no direct functional adrenergic supply to the human airways. The role of the NANC system is still poorly understood in asthma (27), although the imbalance between sensory neuropeptides has been supposed to play an important role in the mechanisms of asthma (28, 29). Moreover, the adrenergic control of the nose and bronchi differ, since α -adrenergic agonists are effective nasal vasoconstrictors in rhinitis whereas β_2 -adrenergic agonists are effective bronchodilators in asthma.

Nitric oxide (NO) is an intercellular transmitter, both in the central and in the peripheral nervous system. In addition to nerve cells, NO is also produced in epithelial cells of various tissues and in the endothelium. NO is produced in large amounts in the noses of normal subjects. NO is an important mediator of the effector arm of the nasonasal reflex that increases vascular permeability but is not involved in the sensory nerve afferent pathway (30). NO plays a key role as a vasodilator, neurotransmitter, and inflammatory mediator in the bronchi and is produced in increased amounts in asthma (31). In healthy subjects, exhaled NO originates mainly from the upper airways with only a minor contribution from the lower airways and the lungs (32).

Relationships and differences between rhinitis and asthma

The recent progress achieved in the cellular and molecular biology of airways diseases has clearly

documented that inflammation plays a critical role in the pathogenesis of asthma and rhinitis. A growing number of studies show that the inflammation of nasal and bronchial mucosa is sustained by a similar inflammatory infiltrate, which is represented by eosinophils, mast cells, T cells, and cells of the monocytic lineage (24, 33, 34). The same pro-inflammatory mediators (histamine, sulfidopeptide leukotrienes), Th2 cytokines (IL-4, IL-5, IL-13, and GM-CSF) (33, 35–38), chemokines (RANTES and eotaxin (39–41), and adhesion molecules (42–45) appear to be involved in the nasal and bronchial inflammation of patients with rhinitis and asthma.

Atopic patients without asthma present some degree of bronchial inflammation; in particular, a few activated eosinophils (46). An irregularly distributed subepithelial fibrosis of the bronchi is observed in subjects with allergic rhinitis (47). It results from the deposition of type I and III collagens and fibronectin and suggests the presence of an active structural remodeling in the lower airways of allergic rhinitic subjects that is similar in nature to that seen in asthma, although less marked. After bronchial segmental allergen challenge in nonasthmatic rhinitics, an early- and a late-phase reaction can be observed (48), suggesting that the bronchial mucosa of rhinitics can be triggered by allergens. An increase in airways inflammation was found after segmental challenge in the same patients (48). Inflammatory cells assessed by sputum induction are present not only in the airways of patients with asthma but also in the airways of patients with seasonal allergic rhinitis, even outside natural exposure (49).

It is well established that bronchial mucosal inflammation causes epithelium shedding, increased thickness of the reticular layer of the basement membrane, and hypertrophy of smooth-muscle cells (50). On the other hand, in perennial rhinitis, the epithelium is usually not shed and the basement membrane is at least moderately thickened (51, 52). Therefore, the nasal and bronchial abnormalities observed in asthmatics appear to present distinct entities, but interrelated conditions are not yet excluded. It is still not clear whether in patients suffering from asthma and rhinitis the inflammatory features of the bronchial mucosa resemble those of the nasal mucosa. Comparative studies on whether the release of inflammatory cytokines in the nose and the bronchi causes similar or different structural alterations of the mucosa still remain to be fully evaluated. Moreover, it is not completely elucidated whether mucosal alterations occur in the nose of asthmatic patients.

In rhinitis and asthma, similarities (submucosal inflammatory infiltrate) and differences (epithelial shedding, thickness of the basement membrane)

can therefore be demonstrated even though the mechanisms underlying these differences are not understood.

Physiologic relationships between rhinitis and asthma

The inflammatory reaction of the nose can participate in the worsening of asthma by several different mechanisms. Although a nasal-allergic response does not induce airflow limitation of the lower airways, it may alter bronchial responsiveness (53). Bronchial hyperreactivity is increased in patients with allergic rhinitis (54–60).

Several mechanisms have been proposed to link uncontrolled allergic rhinitis and the occurrence or worsening of asthma (61). Nasal challenge induces the release of mediators which can in turn cause bronchoconstriction. The postnasal mucous drip may induce a contraction of the bronchial smooth muscle or an inflammation of the lower airways. Mouth breathing secondary to nasal obstruction is a common feature in asthmatics and may play a role in the severity of asthma. A putative reflex between the nose and the lungs has been proposed (62) but has to be fully demonstrated.

There are also close links between nasal infection by viruses and asthma exacerbations (63). Rhinoviruses have been widely identified in nasal secretions during asthma exacerbations in both children and adults (64). Nasal virus infections increase bronchial hyperreactivity in asthmatics. Experimental nasal rhinovirus infection induces an increase in bronchial hyperreactivity (65, 66) and an increase in bronchial inflammation including eosinophilia (67, 68).

Treatments of rhinitis and asthma

Specific immunotherapy

The indications of immunotherapy in allergic asthma and rhinitis have been separated in some guidelines (69, 70). This artificial separation has led to unresolved issues (71, 72), possibly because the allergen-induced IgE-mediated reaction has not been considered to be a multiorgan disease. Therefore, it is important to consider immunotherapy based on the allergen sensitization rather than on the disease itself, since most patients with allergic asthma also present rhinitis or rhinoconjunctivitis.

In allergic rhinitis (73), immunotherapy is indicated for subjects:

- 1) in whom antihistamines and topical medications insufficiently control symptoms
- 2) who do not wish to be on pharmacotherapy

- 3) in whom pharmacotherapy produces undesirable side-effects
- 4) who do not desire to receive long-term pharmacologic treatment.

In allergic asthma (73), immunotherapy is indicated for subjects:

- 1) who do not present a severe form of the disease; FEV₁ levels should be over 70% from predicted values after adequate pharmacologic treatment
- 2) in whom symptoms are not adequately controlled by allergen avoidance and pharmacologic treatment
- 3) who have both nasal and bronchial symptoms
- 4) who do not wish to be on long-term pharmacotherapy
- 5) in whom pharmacotherapy produces undesirable side-effects.

Oral in comparison with inhaled drugs

Medications for asthma and rhinitis can be administered via local (nasal, conjunctival, or bronchial), oral, and parenteral routes. The major advantage of delivering drugs directly into the airways or the nose is that high concentrations can be delivered more effectively into the target organ and systemic side-effects are avoided or minimized (69, 70). Moreover, some drugs, such as cromoglycate or nedocromil, are not absorbed when given orally and are only effective when administered locally. In patients suffering from asthma and rhinitis, local administration of drugs requires that they be given both nasally and bronchially, and this may decrease compliance with treatment, which is low in asthma and rhinitis. On the other hand, drugs administered by the oral route may have an effect on both nasal and bronchial symptoms.

The observation that management of allergic rhinitis also relieves symptoms of asthma has heightened interest in the link between these diseases.

The topical treatment of rhinitis with corticosteroids was found to improve asthma, at best moderately, in some but not all studies (74). Symptoms (75, 76) and pulmonary function tests (75) were improved, and exercise-induced asthma (77) or bronchial hyperresponsiveness (58, 76, 78) was reduced. This treatment modality may have advantages over the ordinarily used nasal and bronchial topical treatment in patients with both asthma and rhinitis, especially when conventional inhaled therapy is associated with side-effects. These data suggest that treating nasal inflammation may help to control asthma. However, a number of aspects, such as the extent to which the pathophysiology of the two diseases overlaps and whether treating one will affect the other, still remain to be clarified.

H₁-blockers represent the first-line treatment of allergic rhinitis, but although some studies have found a modest effect on asthma symptoms (79), they are not recommended for the control of asthma (70, 80, 81). However, a recent study has shown that loratadine plus pseudoephedrine improved nasal and asthma symptoms, pulmonary function, and quality of life in patients with seasonal allergic rhinitis and concomitant mild asthma, whereas both drugs are usually ineffective (82). Leukotriene modifiers were shown to be effective in controlling symptoms of mild to moderate asthma, and some limited studies have suggested that they may be effective in the treatment of rhinitis. A recent study showed that an antileukotriene antagonist (montelukast) potentiated the effectiveness of an H₁-blocker (loratadine) on symptoms of allergic rhinitis. Therefore, antileukotrienes have the potential to treat asthma and possibly rhinitis, but more data are needed to evaluate their real effect fully. Theophylline was found to reduce nasal inflammation (83). It has also been observed that theophylline can reduce bronchial hyperresponsiveness in patients with allergic rhinitis (57), but there are no controlled data on the therapeutic effect of this drug on nasal symptoms (69). Oral corticosteroids are highly effective in the treatment of rhinitis and asthma, but side-effects after long-term use are common.

Conclusion

Upper and lower airways may be considered a unique entity, supporting the concept of "united airways", but there are also differences which should be highlighted. Allergic rhinitis is correlated with, and constitutes a risk factor for, the occurrence or severity of asthma. The treatment of asthma and rhinitis is similar, since the same drugs are effective in both diseases (e.g., corticosteroids), and different, since different drugs are effective in both diseases (e.g., α - and β -adrenergic agonists). Moreover, some drugs are more effective in rhinitis than in asthma (e.g., H₁-blockers). Finally, optimal management of rhinitis may partly improve the coexisting asthma.

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