

Medical progress

Links between allergic rhinitis and asthma

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Allergic diseases of the airway, which include seasonal rhinitis, chronic perennial rhinitis and asthma, are recognized as inflammatory disorders of the airway mucosa,¹⁻³ but differ in the location of the inflammatory reaction and clinical manifestations of the disease. Asthma and allergic rhinitis frequently coexist in the same patient and are thought to share common predisposing genetic factors which interact with the environmental influences. Both diseases have increased in prevalence over recent decades^{4,5} particularly in westernized countries. This increase has been largely attributed to environmental factors such as exposure to aerial pollutants,^{4,6} and early life events, including the degree of exposure to infectious agents which might affect IgE production,^{5,7} since there has been insufficient time for a significant change in the gene pool.

A hallmark of rhinitis and asthma is the presence and activation of inflammatory cells in the airways, notably eosinophils, basophils, mast cells, and T lymphocytes, and stimulation of structural/resident cells, including those of the airway epithelium, fibroblasts and smooth muscle.^{8,9} The inflammatory basis of rhinitis and asthma has been extensively studied by measurement of inflammatory mediators in lavage fluid and respiratory secretions, and by examination of specimens from the target organs for cytology, immunohistochemistry, and indicators of gene expression.^{10,11}

The relationship between asthma and allergic rhinitis is supported by epidemiological studies; by histological, physiological, and immunopathological characteristics; and by the positive effect of various therapies on asthma symptoms in rhinitic patients.

EPIDEMIOLOGICAL EVIDENCE LINKING ALLERGIC RHINITIS TO ASTHMA

Early clinical observations showing an association

between asthma and allergic rhinitis were confirmed in cross-sectional epidemiological studies,¹² as reviewed by Annaesi-Maesano.¹³ For example, among young Italian men assessed in the mid-1990s, allergic rhinitis was present in 77% of those with asthma.¹⁴

Large longitudinal studies revealed that allergic rhinitis usually precedes the onset of asthma.^{15,16} Although such results have been interpreted to define allergic rhinitis as a risk factor for the development of asthma, rhinitis appears to be an early stage of combined allergic airways disease. Disease extension probably occurs both upward and downward through the airways. In a recent survey conducted at Genoa University, 99 patients were followed for up to 10 years after the initial diagnosis of allergic rhinitis, allergic asthma, or both.¹⁷ During the 10-year follow-up, 32% of rhinitic patients developed asthma and 50% of patients with asthma alone developed rhinitis. A family history for atopy was associated with the development of disease, but gender, age, smoking, and skin sensitization were not.

PATHOPHYSIOLOGIC EVIDENCE OF AN UPPER AND LOWER AIRWAY LINK

Although there are important differences between upper airway disorders and asthma, strong pathophysiologic parallels occur between these diseases, principally in their histopathologic features. Proposed mechanisms for such a histopathophysiologic link include the different structures of the upper and lower airways, loss of nasal protective

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function, the potentiation of allergens by the nasal mucosa, and the presence of nasal- bronchial reflex.

Structural and histologic considerations

The structural differences of the upper and lower airways result in different responses to allergic stimuli: rhinorrhoea/blockage in the rigid nose and sinuses, but mucus secretion/bronchoconstriction in elastic tissues of the lung. The lower airway response to nasal challenge is demonstrated by morphological changes and by bronchoconstriction. Thickening of the reticular basement membrane is characteristic of airway remodeling in asthma, but similar degrees of thickening are seen in patients with perennial rhinitis and those with perennial allergic asthma.¹⁸ Histological similarities and physiological relationships suggest that the respiratory tract is a single morphofunctional entity. The respiratory epithelium (ciliate epithelium and mucinous glands) extends from the smaller bronchi to the upper tract; bronchial/mucosal-associated lymphoid tissues (BALT or MALT) are present in both the upper and lower airway.¹⁹ The upper respiratory tract functions as a physical filter, resonator, heat exchanger, and humidifier for inhaled air, the failure of which may compromise the homeostasis of the lower airways.²⁰

Bronchial hyperresponsiveness (BHR) in allergic rhinitis

One of the main clinical features of asthma is an increase in BHR. However, non-asthmatic subjects with allergic rhinitis can present BHR when exposed to an allergen to which they are sensitized. Prieto et al²¹ studied allergic rhinitic subjects during and out of the pollen season. Airway responsiveness to either methacholine or AMP was significantly decreased out of the pollen season compared with during the season. Furthermore, during the season, BHR in the asthmatic range was observed in these subjects. Other studies have shown that nasal challenge can induce an increase in BHR. A double-blind, placebo-controlled, crossover study explored the relationship between allergic rhinitis and lower airway dysfunction using randomized nasal challenges with either allergen or placebo in 11 subjects with a history of asthma exacerbations associated with seasonal symptoms of allergic rhinitis. The technique used a nasal provocation that limited allergen (timothy grass extract) delivery only

to the nose. After the induction of a marked nasal allergic response, no changes were observed in forced expiratory volume in 1 second (FEV₁), specific conductance, lung volumes, or peak expiratory flow rates (PEFRs). Yet when compared with placebo, allergen nasal provocation resulted in a significant increase in BHR to methacholine at 30 minutes and 4.5 hours after the challenge.²² These results demonstrate that although a nasal allergic response may not cause airflow limitation, it can enhance BHR in patients with asthma and allergic rhinitis.

Nasal protection as a factor influencing lower airway responses

Several potential mechanisms have been proposed to explain the connection between the upper and lower airways in asthma and allergic rhinitis. However, a plausible explanation is that of the loss of nasal protection with a shift from nasal to mouth breathing as a result of nasal congestion. The resulting loss of nasal warming, humidifying and filtering functions may result in an increased exposure of the lower airways to allergens and irritants, leading to inflammation.^{23,24}

More recent studies, however, dispute these conclusions. In one study, the nasal conditioning capacity (NCC), or the ability of the nasal passage to warm and humidify the air, was measured and compared in 20 patients with seasonal allergic rhinitis outside their allergy season before and 24 hours after nasal allergen challenge. For these patients, there was a significant increase in NCC 24 hours after allergen challenge compared with their prechallenge baseline. Even with increased nasal epithelial inflammation induced by either seasonal exposure to allergens or antigen challenge, the ability of the nose to condition inspired air remained intact and even increased. According to the authors, increased local inflammation of the nose produces increased amounts of secretions, and thus more water to humidify inspired air and increased heat. Another resultant effect was the increased surface area of contact between inspired air and the nasal mucosa. The resultant effects of allergic rhinitis on the lower airways are probably mediated primarily through other mechanisms other than disruption of airway mechanics.²⁵

Allergen potentiation of airways inflammation

The type and intensity of allergen exposure can play an important role in the clinical manifestations of atopy. Indoor allergens seem to be more frequently associated with BHR and asthma, while outdoor ones are more closely related to allergic rhinitis. In a recent study, Boulay et al²⁶ observed that sensitized allergic rhinitic subjects exposed to an animal at home had increased BHR (although it remained in the asthmatic range) and higher sputum eosinophilia compared with unexposed allergic rhinitic subjects, both in and out of the pollen season.

It has been proposed that the nasal mucosa may process allergens into a form more capable of inducing nasal and bronchial reactions. In one study, Phl p 5, a major allergen in timothy grass that can cause rhinitis and bronchial asthma symptoms, was converted to smaller molecular forms by proteolytic enzymes found in nasal secretions. In allergic patients, skin prick testing with the fragmented protein ranging in sizes between 10 and 20 kD induced a significantly greater allergic response, as measured by wheal area and histamine release assays, than the parent protein. In contrast, pancreatic secretions completely eliminated its allergenicity. Thus, proteolytic degradation of Phl p 5 in the nasal mucosa may result in peptide fragments of a size more allergenic than the parent compound.²⁷

Nasal-bronchial reflex

More than 30 years ago, the existence of a nasal-bronchial reflex was proposed as a possible basis for a physiologic connection between upper and lower respiratory tract disorders. In this paradigm, nasal stimulation promotes bronchoconstriction through a reflex arc with the afferent arm located in the pharyngolaryngeal area, a central locus possibly in the hypothalamic area and vagal efferents. The study that highlighted this theory included six patients without lung disease who underwent unilateral trigeminal nerve resection for trigeminal neuralgia. Upon insufflation of silica particles in the nares on the side where the trigeminal nerve was intact, a decrease in lung function and bronchoconstriction was effected whereas no bronchoconstriction was effected upon insufflation in the nares on the resected side. Bronchoconstriction in response to nasal silica was

inhibited by previous topical atropine administration, suggesting that the bronchoconstriction could have resulted from activation of a cholinergic reflex arc.²⁸ Since that early study, however, no definitive studies have been able to define and identify the exact components of this reflex arc and its physiology.

IMMUNOLOGICAL EVIDENCE IN THE LINKAGES OF UPPER AND LOWER AIRWAY ALLERGIC INFLAMMATION

It seems that asthma and allergic rhinitis result from similar inflammatory processes induced by allergens in the upper as well as in the lower airways of sensitized subjects.²⁹ The nose and lung should thus be seen as a continuum, with "information" traveling in both directions, rather than as two distinct compartments. In this regard, the concept of "united airways" has been proposed,³⁰ and increasing numbers of studies have agreed with this model. Allergic rhinitis and asthma are connected via an immunological response to airborne allergens that is evident throughout the entire body and through bronchial reaction to intranasal challenge.

In keeping with the "united airways" concept, it has been shown that challenging the nose with relevant allergens may induce bronchial inflammation. Indeed, Braunstahl et al³¹ performed nasal allergen provocations in allergic rhinitic subjects without asthma and in normal control subjects. They observed an increase of eosinophils as well as increased expression of intercellular adhesion molecule-1 in nasal and bronchial biopsies of allergic rhinitis patients compared with controls. By the same token, bronchial provocations could induce nasal as well as bronchial inflammation. In another study, Braunstahl and collaborators³² showed a decrease in the number of mast cells in the nose, interpreted as a result of degranulation, 24 hours after segmental broncho-provocation in non-asthmatic subjects with allergic rhinitis. Mast cells are considered key factors in the initiation of allergic inflammation, and this study further suggests that "crosstalk" between the upper and lower airways takes place at initiation of the inflammatory process, possibly through a systemic pathway, or via cytokine release of mast cells, which are abundantly present throughout the respiratory mucosa.³³

The body-wide immunological response to airborne allergens is evident by the presence of antigen-specific responses of peripheral blood mononuclear cells (PBMCs), resulting in increased IL-4 production and reduced IFN- γ production,³⁴ and by the presence of eosinophilia systemically as well as in secretions from the nose and sputum.²⁹ Studies performed on respiratory secretions and biopsies of the airways in patients with allergic rhinitis and asthma suggest that eosinophils play a central role in the pathogenesis and clinical expression of the disease.⁹ The recruitment and activation of these cells appear to be controlled by the release of cytokines such as IL-5, specifically involved in eosinophil growth and maturation,³⁵ and chemotactic agents such as eotaxin, a CC chemokine derived from antigen-stimulated T lymphocytes and airway epithelium, which stimulates the migration of eosinophils from bone marrow into the tissue.³⁶ Eosinophils and their progenitors are released from the bone marrow under the influence of both IL-5 and eotaxin, resulting in an increase of circulating and tissue eosinophils.^{37,38}

Denburg and his colleagues³⁹⁻⁴² have previously provided evidences that an important aspect of allergic inflammatory responses is the induction of inflammatory cell progenitor lineage and commitment and maturation, which contribute to allergic rhinitis and asthma through the continued production of inflammatory effector cells. In their recent established pure upper and/or lower airways eosinophilic inflammatory murine models,⁴³ they found that systemic IL-5 and eosinophils as well as bone marrow eosinophilic and basophilic (Eo/B) progenitor cells were up-regulated regardless of development of pure upper, or lower, or both upper and lower airway inflammation, and multiple-site antigen challenges cause earlier increases of local and systemic IL-5 and eotaxin, accompanied by earlier up-regulation of marrow responses.

However, Boulay et al³⁰ recently established that non-asthmatic subjects with allergic rhinitis showed a different lower-airway inflammatory pattern in response to low doses of allergen compared with mild allergic asthmatic subjects. Although there was no change in FEV1 or provocative concentration of methacholine giving a 20% fall in FEV₁ (PC₂₀), sputum eosinophils increased significantly following

two days of challenge and decreased subsequently at day four despite continuous allergen exposure. In contrast, they increased gradually over the four challenge days in asthmatic subjects. The important difference between asthma and rhinitis is that a greater dose of allergen is necessary to cause bronchoconstriction in rhinitic patients.⁴⁴ These evidences suggest an adaptation process in allergic rhinitic subjects that may protect against developing asthma. However, these mechanisms need to be further evaluated.

THERAPEUTIC EVIDENCE OF AN UPPER AND LOWER AIRWAY LINK

Therapeutic response studies have provided further evidence buttressing the link between upper respiratory disorders and asthma. Generally, when one of these disorders responds to treatment, the other shows improvement as well, thus pointing to a common pathologic mechanism.

β_2 -adrenergic agonists dilate the elastic lower airways, but are ineffective in the rigid upper airways. In contrast, the structural differences between the upper and lower airways are not a barrier to system-wide effects of other treatments options, such as intranasal corticosteroids and systemic antihistamines. For example, the use of intranasal corticosteroids (e.g., beclomethasone and fluticasone propionate) for rhinitis symptoms significantly reduces bronchial hyperresponsiveness to methacholine and has been shown to improve asthma symptoms.⁴⁵⁻⁴⁷ In a double-blind, double-dummy, placebo-controlled study of rhinitic patients with documented carbachol-induced bronchial hyperresponsiveness, beclomethasone 100 μ g given intranasally four times daily—but not by inhalation—reduced bronchial hyperresponsiveness.⁴⁸ Several studies have documented the efficacy of antihistamine therapy in reducing symptoms of asthma in people with seasonal allergic rhinitis when given alone,⁴⁹ or in combination with decongestant⁵⁰ or an antileukotriene.^{51,52} Furthermore, the Early Treatment of Atopic Child (ETAC) study showed that the onset of asthma was prevented by continuous antihistamine treatment in a defined subset of patients.⁵³

Asthma and allergic rhinitis are associated with a

profound immunological deregulation characterized by an over production of Th2 cells. Bacille Calmette-guerin (BCG) vaccination may inhibit allergen-induced pathologic changes in both asthma and allergic rhinitis through stimulating the production of Th1 cytokines and decreased the Th2 cytokine secretion.⁵⁴ Our data also showed that BCG polysaccharide nucleotide had a symptomatic effect on allergic rhinitis and it could also reduce the dosage of H1 blocker as well as inhaled beclomethosone in the treatment of mild to moderate asthma and allergic rhinitis.⁵⁵

Specific allergen immunotherapy (SIT) for the management of asthma and allergic rhinitis continues to be a matter for discussion. The clinical effects obtained with SIT may be explained by several mechanisms:⁵⁶ (1) reduction in specific IgE antibodies; (2) induction of blocking IgG antibodies; (3) alteration of T-cell cytokine production (increase in T helper 1 (Th1) cytokines); (4) induction of specific T-cell specific T-cell tolerance (T-cell anergy, regulatory T cells). A Cochrane analysis from 2003 of all studies on SIT published in the last 35 years demonstrated that SIT is beneficial for the treatment of adult asthma.⁵⁷ Compared with placebo, patients treated with SIT experienced significant improvements in symptom scores, asthma medication use and allergen-induced airway responses, but had no signs of overall enhanced lung function. This analysis was supported by our recent double-blind placebo controlled studies on SIT for patients with mite-mediated asthma. SIT patients showed increased asthma symptom and treatment scores, enhanced peak flow rates after one year of treatment, and reduced asthma medication use compared with placebo-treated patients.⁵⁸

SIT is considered as the only curative treatment for allergic rhinitis as long as its prerequisites are fulfilled: a small number of sensitizations, and administration of adequate doses of standardized allergens.^{59,60} The effectiveness of SIT for the treatment of seasonal allergic rhinitis has been confirmed in several studies with grass, ragweed and birch pollen sensitized patients. Moreover, SIT was successful even in patients with severe summer hay fever, where conventional drug therapy had failed.⁶¹

One of the main differences between SIT and

symptomatic therapy is that the beneficial of SIT can be observed even years after discontinuation of treatment.^{62,63} In addition, SIT may prevent the occurrence of new sensitization.^{64,65} Furthermore, it was established that SIT is able to prevent the extension of upper airway disease to the lower airways.⁶⁵

Application of anti-IgE antibodies effectively reduces IgE serum levels regardless of allergen specificity. This treatment has been successfully tested in patients with allergic rhinitis, asthma and food allergy, showing significant efficacy in reducing symptom scores and rescue medication use. Anti-IgE therapy is limited by high costs and the necessity for permanent or every-season treatment. Anti-IgE is not a curative approach since it does not aim to inhibit the induction phase of an allergic immune reaction or to induce allergen-specific (immune) tolerance. Therefore, treatment with anti-IgE has to be repeated or prior to consumptions of food allergens. Moreover, anti-IgE targets just one of many mediators released during an allergen-mediated immune cascade, therefore missing many pathways that are independent of IgE.

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