

The development of asthma in patients with allergic rhinitis

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Purpose of review

We will review data supporting the link between allergic rhinitis and asthma, examine recent progress made towards understanding the influence of allergic rhinitis on asthma regarding future development or progression of asthma, and discuss possible mechanisms through which this occurs and potential preventive measures.

Recent findings

Several recent reviews have concluded that a close relationship exists between allergic rhinitis and asthma. It has even been proposed that allergic rhinitis and asthma are manifestations of the same disease entity and that they represent a continuum of disease. Allergic rhinitis often precedes the onset of clinical asthma and is a risk factor for the development of asthma. Recognition of this relationship between allergic rhinitis and asthma is highlighted by the recent development of guidelines for the diagnosis and treatment of these disorders by the international Allergic Rhinitis and Its Impact on Asthma workshop. The mechanisms by which allergic rhinitis may be a risk factor for asthma are not entirely understood, although a few recent studies have addressed this question. Some clues in regard to the identification of subjects at risk of developing asthma have been provided by recent studies. Several recent reports support the belief that early introduction of immunotherapy in patients with allergic rhinitis reduces subsequent development of asthma, whereas it remains to be studied whether timely pharmacotherapy for allergic rhinitis may prevent the progression to asthma.

Summary

Because asthma is generally permanent at the time of diagnosis, it would be of great benefit to identify individuals at increased risk of developing asthma in order to provide a window of opportunity in which the progression to asthma could be prevented. As recognition and early treatment of allergic rhinitis could have important consequences in terms of reducing the prevalence and severity of asthma, there is a need to perform further clinical studies that address this issue.

Keywords

allergic rhinitis, development of asthma, risk factor, proposed mechanisms, putative predictors, preventive measures

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Abbreviations

SBP segmental bronchoprovocation
BHR bronchial hyperresponsiveness

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Introduction

Allergic rhinitis and asthma are often comorbid conditions, and the overall characteristics of the diseases and treatment options for the disorders are similar. Several studies demonstrate that allergic rhinitis usually precedes asthma and that allergic rhinitis is a risk factor for the development of asthma. Despite recent studies that attempt to shed more light on the nature of the association, many questions remain to be answered. This article will review data supporting the link between allergic rhinitis and asthma, and will examine recent progress made towards understanding the influence of allergic rhinitis on asthma regarding future development or progression of asthma. Possible mechanisms through which this occurs and potential preventive measures will also be discussed.

Allergic rhinitis

Allergic rhinitis is one of the most common chronic diseases of both children and adults [1]. The prevalence of allergic rhinitis, as with all allergic diseases, has increased dramatically over the past few decades. Approximately 10% of Americans have seasonal allergic rhinitis – a figure which has almost doubled since 1970. The prevalence of perennial allergic rhinitis in the United States ranges from 10 to 20% [2]. Sneezing, rhinorrhea, nasal congestion, and pruritus of the nose, eye or throat, are symptoms of this disease. These symptoms commonly occur for the first time in childhood and adolescence, and 70% of patients experience onset of symptoms before 30 years of age [3].

The symptoms of allergic rhinitis are easily recognized in adults. However, allergic rhinitis is under-diagnosed and under-treated in children, in part because children may not recognize their symptoms and allergic rhinitis symptoms are frequently attributed to recurrent viral upper respiratory tract infections [4•]. This lack of recognition is unfortunate because, although allergic rhinitis does not present with life-threatening exacerbations, it has a significant negative impact on quality of life [5] and can contribute to the development and progression of other disorders, including asthma [6•]. Recently, a panel of 37 physicians from around the world

in association with the World Health Organization wrote new guidelines that focused on allergic rhinitis and its impact on asthma [7]. Included in the discussions regarding this initiative was the recognition that allergic rhinitis is a highly prevalent chronic respiratory disease that impacts negatively on quality of life, work or school performance, productivity, and healthcare costs.

A link between allergic rhinitis and asthma

Allergic rhinitis is an immunologically mediated disease, initiated by a type I antigen–antibody reaction following allergen exposure. It has been clinically recognized as a symptomatic disorder induced by an immunoglobulin E-mediated inflammation affecting primarily the nose [3]. Findings gleaned from recent clinical studies altered this thinking, however, and indicated that allergic rhinitis is not a ‘solitary disease’, but rather a complex syndrome that affects both upper and lower airways [8•]. In support of this hypothesis, several recent reviews [9,10•,11•] concluded that a close relationship exists between allergic rhinitis and asthma. Because the upper and lower airways share common histopathologic features, including contiguous ciliated columnar cell epithelial lining, extensive mucinous glands, vasculature, and innervation, at least some link between upper and lower respiratory tract diseases would be expected.

Allergic rhinitis is an organ-specific manifestation of allergic disease. As such, it coexists with other organ-specific disorders that have a common allergic basis. Epidemiologic data show that allergic rhinitis and asthma frequently co-exist [12]. Asthma has been found in 19–38% of persons with a history of allergic rhinitis but only 3–5% of the general population. As many as 78% of patients with asthma report nasal allergy symptoms, well above the 20% rate in the general population [13].

Current knowledge suggests that the most important link between rhinitis and asthma is the presence of inflammation of the nasal and bronchial mucosae. Inflammation can be present in the lower airways of non-asthmatic rhinitis subjects during natural allergen exposure, even when there are no clinical symptoms or any changes in airway responsiveness [14]. Using allergen segmental bronchoprovocation (SBP), Alvarez *et al.* [15] showed that the allergen-induced increase in sputum eosinophils was similar in non-asthmatic allergic rhinitis to that found in allergic asthma following provocation. Braunstahl *et al.* [16] demonstrated that SBP in allergic rhinitis patients induced eosinophilia in the blood and mucosal inflammation, characterized by increased numbers of eosinophils, and of interleukin-5-positive and eotaxin-positive cells in both upper and lower airways. The allergic inflammatory response in the lower airways of non-asthmatic allergic rhinitis patients after SBP challenge, and concomitant increase in

inflammatory cells in the nasal mucosa, underscore the pathophysiologic link between allergic rhinitis and asthma through common inflammatory processes, possibly through a systemic pathway.

The coexisting presence of inflammation in the airways in a study on asthmatics with or without rhinitis has been shown by Gaga *et al.* [17]. Using biopsies from the nasal mucosa, they showed that eosinophil infiltration occurred in the nasal mucosa of asthmatic patients, irrespective of any signs of rhinitis or not. Using allergen nasal challenges, Braunstahl *et al.* [18] were able to show upregulation of adhesion molecules and a tissue eosinophilia concomitantly in the upper and lower airways, suggesting a more generalized effect of local allergen deposition.

In addition, bronchial hyperresponsiveness (BHR) can be present in patients with allergic rhinitis without clinical evidence of asthma [19]. Little is known about the factors that determine BHR in these individuals, but it may be due to an increased inflammatory activation state within their airways [20]. A recent study found that the non-specific nasal responsiveness has a close relationship with the non-specific bronchial responsiveness in patients with allergic rhinitis and asthma [21•]. Other studies demonstrated that although a nasal allergic response may not cause airflow limitation, it can enhance BHR in patients with asthma and allergic rhinitis [22].

The severity of allergic rhinitis was shown to be directly correlated with asthma severity. Those patients whose allergic rhinitis was severe or poorly controlled had worse asthma control and tended to have more persistent asthma than those with mild or well controlled rhinitis [23]. These data illustrate a direct relationship between allergic rhinitis severity and active asthma and therefore suggest that the effective treatment of one condition may improve the other. Watson *et al.* [24] found that intranasal corticosteroid therapy reduced both rhinitis and asthma symptoms. Because topically applied nasal steroids have not been shown to result in significant deposition to the lungs, the reduction in asthma symptoms may be related to improvements in nasal function as opposed to the direct effects of the medication on the lower airway [25]. There are many other studies showing that treatment of allergic rhinitis through various modalities with the capacity to modulate different aspects of the inflammatory cascade leads to improvement in concomitant asthma [11•]. Thus, therapeutic response studies have provided further evidence buttressing the link between allergic rhinitis and asthma.

Allergic rhinitis is a risk factor for development of asthma

There is increasing evidence that the onset of asthma and rhinitis may be temporally related, and that rhinitis

is a precursor for asthma in some patients. In a study that included adolescents 13–17 years of age with both rhinitis and asthma, 59% either had rhinitis symptoms first or had symptoms appear during the same year [26]. Similar results have been observed in college students with both asthma and allergic rhinitis. In these students, 64% experienced rhinitis symptoms before asthma symptoms, and in 21% the onset of these diseases was concurrent [27].

Several recent epidemiologic studies in the general population have provided evidence to strongly associate the development of asthma with a previous history of allergic rhinitis. The longitudinal study of the Settipane group [28], which had a 23-year follow-up, showed that allergic rhinitis at inclusion resulted in a three-fold risk of developing asthma compared with the group without rhinitis symptoms. In a 12-year follow-up Swedish study by Danielsson and Jessen [29], the number of asthmatics in the group of allergic rhinitis was double that of the group without symptoms at inclusion. A recent analysis of data from the Tucson Epidemiological Study of Obstructive Lung Diseases revealed that rhinitis (atopic and non-atopic) is an independent risk factor for the development of asthma [6••]. Whether the relation is causal or from a natural progression of the disease is unclear.

Recognition of this relationship between allergic rhinitis and asthma is critical and is highlighted by the recent development of guidelines for the diagnosis and treatment of these disorders by the international Allergic Rhinitis and its Impact on Asthma workshop [7].

Proposed mechanisms

Although there is increasing evidence that allergic rhinitis may influence the clinical course of asthma, the underlying mechanisms are not entirely understood. Proposed mechanisms for such a pathologic link include loss of nasal protective function, the progression of inflammation systemically or through contiguous pathways, and the presence of nasal-bronchial reflex.

Nasal blockage resulting from tissue swelling and secretions may cause a shift from the normal pattern of nasal breathing to predominantly mouth breathing. Previous work [30] showed that mouth breathing associated with nasal obstruction resulted in worsening of exercise-induced bronchospasm, whereas exclusive nasal breathing significantly reduced asthma after exercise. Improvements in asthma associated with nasal breathing may be the result of superior humidification and warming of inspired air before it reaches the lower airways [31]. Similarly, it has been speculated that nasal obstruction in allergic rhinitis promotes increased allergen exposure to the lower airways (impaired filtering)

which may then result in lower airway inflammation and bronchial responsiveness in genetically predisposed individuals.

The systemic production of allergen-specific immunoglobulin E that follows local allergic sensitization, and the ability of T cells to migrate from regional lymph nodes and 'home in' on other tissues, could explain how allergic inflammation in the upper airways may 'spread' to the lower airways. In patients with allergic rhinitis with pre-existent asthma, nasal allergen exposure was shown to have an important contributory effect on bronchial inflammation, lung function, and pulmonary symptoms [18,22]. It is thus possible that repetitive allergen stimulation of the nose, inducing a continuous bombardment of the lower airways with systemic inflammatory mediators, may result in the development of asthma eventually.

Another postulated mechanism is that of postnasal drip allowing inflammatory cytokines and mediators from the nasopharynx to be inspired into the lower airways, causing inflammation and bronchoconstriction. Although there is no evidence to support this in human beings, there are animal studies demonstrating such a mechanism [32].

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 [33]. Subsequently, it was shown that application of a local cold stimulus to the nose produced bronchoconstriction [34]. However, no definitive studies have been able to define and identify the exact components of this reflex arc and its physiology. Furthermore, the clinical implications of this theory have not been realized or shown.

Putative predictors

Why some subjects with allergic rhinitis develop asthma and others do not is still not fully understood. However, some clues in regard to the identification of individuals at risk of developing asthma have been provided by recent studies.

Patients with allergic rhinitis and no clinical evidence of asthma frequently have BHR [19]. BHR is considered a hallmark of asthma, and has been shown to precede the development of asthma in children as well as in adults [35]. This has caused some investigators to postulate that BHR may be a marker for the subsequent development of asthma in patients with allergic rhinitis. In a follow-up study of 40 patients with ragweed-sensitive allergic rhinitis, Braman *et al.* [36] showed that three of the 14

subjects with methacholine hypersensitivity developed asthma, whereas no patients developed asthma in the normosensitive group. On the contrary, other studies [37,38] showed that methacholine hypersensitivity is not a reliable marker of the subsequent development of asthma in patients with allergic rhinitis. We also recently showed that airway hypersensitivity could not predict the risk for later asthma, and that subjects with an increased maximal airway response to methacholine were at increased risk of the development of asthma [39•]. The maximal airway response on the dose-response curve to methacholine, another component of BHR, is assumed to reflect the potential degree of airways obstruction in individual patients irrespective of the level of sensitivity [40]. In non-asthmatic patients with allergic rhinitis, maximal airway response, but not airway sensitivity, was found to have a correlation with peak expiratory flow variation [41], and natural allergenic exposure may cause an increase in maximal airway response in a significant number of patients with allergic rhinitis [42]. On the basis of these results, we speculate that subjects with allergic rhinitis and elevated maximal airway response are at increased risk of asthma development if they are exposed to a sufficiently strong allergenic stimulus.

It was demonstrated in an epidemiological study that the presence of an increased inflammatory activation state, as reflected by the presence of both peripheral blood eosinophilia and BHR, increases the risk of developing asthma [43]. In this respect, the observation of Polosa and colleagues [44], that a higher level of bronchial responsiveness to AMP is associated with an increase in the inflammatory activation state in the airways of non-asthmatic subjects with allergic rhinitis, is of particular interest, as it may indicate a predisposition to developing asthma.

Although atopy *per se* carries an increased risk for asthma developing in rhinitic individuals, chronic exposure to perennial allergens, and particularly indoor allergens, seems to be more important than seasonal exposure to such allergens as pollens [45•]. In a study examining the influence of clinical and demographic parameters on the disease evolution, Lombardi *et al.* [46] reported a higher frequency of atopy among first-degree relatives of patients whose rhinitis was subsequently complicated by asthma. These observations suggest that the development of asthma in rhinitic patients is affected by environmental and genetic factors.

Boulay and Boulet [47•] recently evaluated lower airway inflammatory changes following repeated inhalation of very low doses of allergen in non-asthmatic subjects with allergic rhinitis compared with mild allergic asthmatic subjects. By demonstration that some of the former

group showed a reduction in airway inflammation, even when allergen exposure was continued, they concluded that some rhinitic patients have protective or dampening mechanisms against the allergen-induced airway inflammatory process, possibly an immunological tolerance to the inhaled allergen.

Preventive measures

Pharmacotherapy for allergic rhinitis has been shown to result in diminishing asthma symptoms, increasing airway caliber, and decreasing BHR [11•,24]. Treatment of rhinitis has the potential to reduce asthma symptoms to such an extent that treatment with prophylactic anti-asthma drugs may be unnecessary in some patients with a diagnosis of mild asthma. Furthermore, those who were treated for allergic rhinitis were found to have a significantly lower risk of subsequent asthma-related events (emergency department visits or hospitalizations) than those who were not treated [48•]. However, although optimal medical treatment of allergic rhinitis is known to be a prerequisite for a good therapeutic result in asthma, it remains to be studied whether early and timely treatment of allergic rhinitis may prevent the progression to asthma.

Specific immunotherapy is a widely used form of therapy for allergic diseases. Well-controlled clinical trials have demonstrated its efficacy in reducing the severity of symptoms related to allergic rhinitis [49]. It is possible that when given prophylactically to susceptible individuals, immunotherapy may be effective in preventing the development of asthma rather than reversing its course once the disease is established [50]. One investigation showed that none of the patients who initially had only hay fever developed asthma during the total study period of 6 years of immunotherapy [51], and in a study of oral immunotherapy in children with pollinosis, 31% of those in the placebo group, in comparison with none in the active group, developed asthma [52]. Another study suggested that specific immunotherapy, when administered to monosensitized patients with perennial allergic rhinitis, reduces airway responsiveness, and may be an appropriate prophylactic treatment for rhinitic patients with hyperreactive airways [53]. A recent report evaluating immunotherapy to birch and grass pollen sensitive rhinitis patients in relation to subsequent development of asthma further supported the belief that early introduction of immunotherapy in children with allergic rhinitis reduces subsequent development of asthma [54•]. Thus specific immunotherapy has the potential to change the natural course of the allergic disease by prevention.

Conclusion

Allergic rhinitis needs to be considered in the context of systemic allergic disease associated with numerous

comorbid disorders, including asthma. Allergic rhinitis often precedes the onset of clinical asthma and is a risk factor for the development of asthma. It is still unclear why a proportion of individuals with allergic rhinitis eventually develop asthma, or how allergic rhinitis may be a risk factor for asthma. Future research will be needed to get more information in these regards. Because asthma is generally permanent at the time of diagnosis, it would be of great benefit to identify subjects at increased risk of developing the disease in order to provide a window of opportunity in which the progression could be prevented. As recognition and early treatment of allergic rhinitis could have important consequences in terms of reducing the prevalence and severity of asthma, there is a need to perform further clinical studies that address this issue.

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