



Asthma and rhinitis: what is the relationship?

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Purpose of review

Asthma and rhinitis are commonly associated and they influence their respective control. New observations have contributed to better understand how to assess those conditions and how they influence each other.

Recent findings

Recent studies found that not only the intensity, but also the duration of rhinitis could be correlated with the development of asthma and possibly its remission. The measure of exhaled nitric oxide (FeNO) has been used to show the presence of lower airway inflammation in rhinitic patients, with or without asthma. Furthermore, it has been shown that allergic rhinitis could affect asthma control in children as in adults, and consequently suggested that allergic rhinitis and asthma should be concomitantly approached in regard to their diagnosis and treatment. Additional observations showed improvements in various asthma outcomes with the treatment of rhinitis.

Summary

These new data confirm the strong link between asthma and rhinitis, the importance of their interactions, and the need to identify and treat rhinitis adequately in asthmatic patients.

Keywords

airway inflammation, asthma, corticosteroids, FeNo, rhinitis

INTRODUCTION

Although the link between allergic rhinitis and asthma has been extensively studied, its relationships with other upper airway conditions, such as chronic rhinosinusitis (CRS), nasal polyposis, and nonallergic rhinitis, have recently been further explored. Throughout the past decade, an increased prevalence of rhinitis symptoms, of allergic origin or not, has been observed in a majority of asthmatic patients [1–4]. These two conditions may influence each other and, in regard to the effect of upper on lower airways, various mechanisms of action have been suggested, such as increased oral breathing, allowing the penetration, in lower airways, of increased amounts of allergens or pollutants, and a systemic response, with the release of mediators and cytokines from the nasal mucosa [5,6].

EPIDEMIOLOGY OF ASTHMA AND RHINITIS

The prevalence of asthma and rhinitis has increased in parallel in the last decades, although this may be changing. During the second half of the last century, asthma prevalence increased in western countries and the term ‘asthma epidemic’ was frequently

used. Some considered that it had reached a plateau since the end of the 1990s [7,8], whereas others did not observe such a trend [9,10]. Changes in prevalence of asthma seem to vary according to the geographical area: a reduction of asthma cases being observed in more developed countries, while an increase in prevalence was reported in less developed ones [11]. Nevertheless, there is still a high prevalence of asthma worldwide.

Otherwise, as for asthma, the prevalence of rhinitis seems to still be increasing [7,10], while a plateau has been described by others [12]. In keeping with previous studies [2,3], a recent population-based study by Eriksson *et al.* [13] confirmed the

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KEY POINTS

- New data further confirm the close link between asthma and rhinitis both in adults and children, in terms of prevalence, genetic determinants, and inflammatory mechanisms, as well as their respective influence on each other.
- The duration and severity of rhinitis seem to influence asthma development and possible remission.
- Treatment of rhinitis can positively influence asthma outcomes.
- Rhinitis is often associated with lower airways inflammation and this has been further demonstrated using FeNO measurement.

strong link between asthma and rhinitis: a 64% prevalence of allergic rhinitis was found in asthmatic patients and a 20% prevalence of asthma in rhinitic patients, whereas 24% of patients with CRS had asthma and 8% of asthmatic patients had comorbid CRS.

COMPARATIVE PHYSIOPATHOLOGY

Upper and lower airway diseases may be manifestations of the same inflammatory process as proposed by the 'united airways' hypothesis [5,14]. This concept has emerged mainly from studies [2,15,16] on allergic rhinitis in asthmatic patients. Although usually less marked, inflammatory and remodeling processes, similar to asthma, have been detected in the lower airways of nonasthmatic patients with allergic rhinitis [17–19].

Eosinophilic inflammation is a major characteristic of allergic asthma. Exhaled nitric oxide (FeNO) has been identified as an indirect marker of lower airway inflammation. Although it has been increasingly used to monitor asthmatic patients, its possible use in the assessment and treatment of allergic rhinitis still needs to be determined. In a recent study assessing lower airway inflammation, Ciebiada *et al.* [20[¶]] reported that patients with seasonal rhinitis had significantly higher baseline FeNO levels than controls and that these levels significantly increased during the pollen season. This suggests the presence of subclinical allergic inflammation in the lower airways of seasonal allergic rhinitis patients. More recently, Kalpaklioglu and Kalkan [21[¶]] showed that the increase in FeNO levels was higher in perennial rhinitis compared with seasonal rhinitis and higher in patients with allergic rhinitis compared with nonallergic rhinitis. In another study by Högman *et al.* [22], FeNO levels could not differentiate patients with nonatopic

rhinitis or nonatopic asthma from healthy controls, therefore adding more evidence of different endotypes of asthma in allergic and nonallergic rhinitis. Increased levels of FeNO were observed in both adults and children with rhinitis and airway hyper-responsiveness (AHR) and those with rhinitis and asthma compared with those with rhinitis alone [23,24]. Such 'continuum of gradient' of inflammation suggests that the degree of lower airways inflammation depends on the degree of involvement of both the nose and lungs.

Not only do asthma and rhinitis share common physiopathological characteristics; they can also be triggered by the same environmental agents. Sensitizing agents such as allergens or some occupational agents, in addition to various respiratory 'irritants' such as pollutants, cigarette smoke, diesel exhaust, cold air, and, in intolerant individuals, aspirin, can lead to manifestations and exacerbations of both diseases [25]. More recently, ozone exposure has also been associated with concurrent wheeze and allergic rhinitis [26]. In recent years, increasing attention has been given to urban air pollution as an important causative agent of respiratory diseases. These pollutants appear to induce their adverse effects by affecting the balance between antioxidant pathways and airway inflammation [27]. However, further studies are needed to identify susceptible populations in order to target therapy and to prevent pollution-induced respiratory disease development and exacerbation.

INFLUENCE OF RHINITIS ON THE DEVELOPMENT OF ASTHMA

There is strong evidence that rhinitis often precedes the development of asthma, although in a smaller proportion of patients, asthma can precede rhinitis [28]. Rhinitis is a significant risk factor for incident asthma both in atopic and nonatopic individuals [1], suggesting that atopy is not the only determinant of the strong association between these two diseases. Indeed, nonatopic individuals may even be more at risk of developing asthma than atopic individuals [29,30], although this has not been observed in all studies [31].

Not only can rhinitis be a strong risk factor for asthma development, but also the duration of rhinitis may be considered as an independent risk factor for subsequent asthma. In patients with moderate–severe persistent allergic rhinitis without asthma, trees and house dust mites sensitization, rhinitis duration more than 5 years, and forced expiratory volume in 1 s (FEV₁) less than 86% were significant risk factors of severe AHR [32,33]. Low forced expiratory flow at 25 and 75% of vital

capacity (FEF_{25–75}), an indirect measure of small airway obstruction, may be impaired in allergic rhinitis patients without asthma or AHR [33] and has been reported as a possible marker of early bronchial pathology in these patients [33,34].

In a recent epidemiological study, Eriksson *et al.* [13[■]] showed that the prevalence of asthma increased with increasing number of nasal symptoms, and that the prevalence of rhinitis, chronic rhinitis, and CRS increased with increasing lower respiratory symptoms, all in dose–response manner. They also looked at the risk factors for asthma with various nasal comorbidities. Asthmatic patients with allergic rhinitis were significantly younger, were younger at asthma diagnosis, reported a family history of asthma and allergy more commonly, and had a higher level of education. Asthmatic patients with chronic rhinitis also reported a family history of asthma and allergy, but were less highly educated than patients without chronic rhinitis. In addition, those patients reported a significantly higher number of exposures to irritants. Finally, asthmatic patients with CRS had almost the same characteristics as chronic patients with rhinitis, with even stronger associations with environmental exposures. They also had a higher body mass index than the two other groups. These different risk factor patterns of asthma between allergic rhinitis, chronic rhinitis, and CRS suggest that nasal comorbidities may reflect different disease phenotypes of asthma [13[■]].

INFLUENCE OF RHINITIS ON ASTHMA CONTROL

Both allergic and nonallergic rhinitis may affect asthma control and have a significant negative impact on quality of life (QoL) [35]. Rhinitis has also been associated with increased asthma-related hospitalizations, physician's and emergency department visits, and drug costs [36]. Although several studies have been conducted in adults, the impact of allergic rhinitis on asthma control has been poorly studied in the pediatric population. Recently, De Groot *et al.* [37[■]] performed a cross-sectional study to assess asthma control in children with comorbid allergic rhinitis. They observed that children with allergic rhinitis were significantly more likely to have incomplete asthma control, according to the Asthma Control Questionnaire (≥ 1.0 score), than those without allergic rhinitis.

THERAPEUTIC CONSIDERATIONS

In keeping with the one-airway concept, allergic rhinitis and asthma are now increasingly being approached concomitantly in regard to their

diagnosis and treatment [38]. A combined management approach for patients with allergic rhinitis and concomitant asthma may possibly reduce medical treatment costs for these conditions and improve symptom control and QoL [39], although further studies are required to determine how appropriate treatment of rhinitis could reduce asthma morbidity [35].

In recent years, more studies on the influence of nasal corticosteroid treatment on asthma outcomes have become available. Nasal corticosteroid treatment has been found to decrease upper airway inflammation, as well as improve asthma control and QoL, in asthmatic patients with concomitant allergic rhinitis [40]. In addition, rhinitis therapy with intranasal mometasone has been associated with significantly better upper as well as lower airway outcomes than oral antihistamines [41]. Recently, Kersten *et al.* [42] showed that exercise-induced bronchoconstriction was significantly reduced by intranasal fluticasone furoate in mild-to-moderate asthmatic children with intermittent allergic rhinitis.

Allergic rhinitis and asthma share common IgE-mediated mechanisms and further studies looked at the effects of antihistamines on concomitant asthma. A review of 14 placebo-controlled, double-blind, clinical trials on allergic rhinitis and comorbid asthma, treated with second-generation antihistamines, showed that H₁-antihistamines attenuated the symptoms associated with early and late phase allergic reactions, suggesting that they may have a beneficial effect on asthma [43]. In this regard, Davis *et al.* [44] previously showed a beneficial effect of desloratadine on the allergen-induced late asthmatic response. However, the clinical benefit of antihistamines on asthma, apart from a possible indirect effect through improvement of rhinitis, remains to be determined.

Recent studies have suggested that oral immunotherapy could help both asthma and rhinitis. Yukselen *et al.* [45] suggested that a 1-year immunotherapy treatment was clinically effective on rhinitis and asthma symptoms compared with placebo, although this was done on a limited number of patients. Recently, timothy grass allergy immunotherapy tablet (AIT) was found to improve rhinitis and asthma symptom scores, as well as medication needs [46]. Sublingual immunotherapy showed similar clinical improvement in rhinitis and asthma when compared to subcutaneous immunotherapy [47], in addition to being associated with lower incidence of systemic reactions [48]. However, further studies are needed to confirm the long-term effects of this type of treatment on asthma outcomes.

The effects of novel rhinitis treatment strategies on asthma outcomes have provided mixed results. In asthma, β_2 -agonists have been recognized as effective inhibitors of mediator release from airway mucosal mast cells [49]. Lipworth *et al.* [50] looked at the effects of a 1-week daily treatment with 50 μ g intranasal salmeterol compared with 500 μ g fluticasone propionate alone and as a combination of both on the response to nasal adenosine monophosphate (AMP) challenge in patients with persistent allergic rhinitis. Fluticasone but not salmeterol had anti-inflammatory activity against nasal AMP challenge, without potentiation of fluticasone when given in combination with salmeterol. In another study [51], nasal fluticasone propionate alone or in combination with orally inhaled fluticasone propionate improved allergic rhinitis and asthma control scores as well as FeNO levels over a 6-week period. This further suggests an effect of nasal corticosteroids on comorbid asthma.

EFFECTS OF RHINITIS ON ASTHMA REMISSION

Symptomatic or complete remission of asthma is not well understood and further investigations are needed to assess the mechanisms involved. In the Tasmanian Longitudinal Health Study [52], in 7-year-old schoolchildren who were surveyed twice, 36 years apart, asthma remission was observed in 65.0%. Childhood and later-onset allergic rhinitis, childhood and later-onset eczema, maternal asthma, and childhood 'chronic bronchitis' were negatively associated with remission. The authors suggested that despite inherited factors, the effect of allergic rhinitis or eczema on asthma remission might be altered by early, aggressive treatment.

GENETICS OF ASTHMA AND RHINITIS

Genetic factors play a substantial role in the pathogenesis of asthma, as demonstrated by twin studies and also by family studies. The twin study design, the most powerful to determine the genetic and environmental contribution in complex trait [53], allowed estimation of a heritability of 70% for asthma [54]. Conversely to asthma, the heritability of hay fever and eczema has not been much studied and the data for these allergic diseases were principally based on studies built primarily to assess asthma genetics. According to the populations tested, the liability for eczema and hay fever accounted for 70–72 and 33–82%, respectively [55–59]. Segregation analysis of families with a history of allergic asthma indicate that asthma is under the influence of multiple genes with

moderate effect (i.e. oligogenic trait) and the frequency of allergic rhinitis (hay fever) in asthma families, suggesting that allergic rhinitis is a comorbid condition of allergic asthma. Studies have identified chromosomal regions and putative susceptibility genes for asthma and rhinitis in numerous independent populations with variable results. A recent meta-analysis of almost all genome-wide linkage screens conducted to date in 20 independent populations from different ethnic origins (≥ 3024 families with ≥ 10027 patients), for asthma and asthma-associated phenotypes, identified two regions linked to asthma: 2p21–p14 and 6p21, and four regions linked to atopy-related traits: 2q32–q34, 3p25.3–q24, 5q23–q33, and 17q12–q24 [60]. For allergic rhinitis, genome-wide linkage scans were performed in six different populations (among which only three were ascertained through rhinitis patients, the other populations being recruited through asthma phenotype) and identified 13 chromosomal regions [59] linked to allergic rhinitis with replication for 4q in four independent cohorts

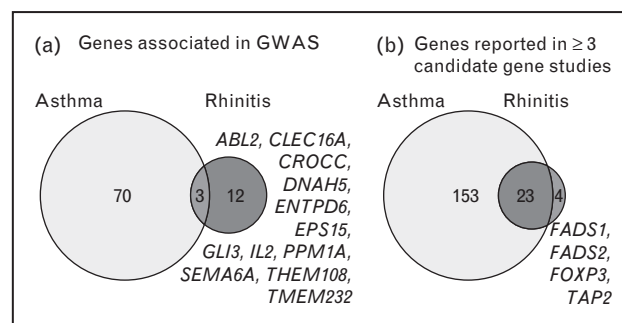


FIGURE 1. Genes associated in asthma and rhinitis through genome-wide association studies or candidate-gene studies. (a) The number of genes associated with asthma (light grey), rhinitis (dark grey), or both (intersect) using genome-wide association studies according to the GWAS Integrator tool of the HuGE Navigator website (version 2, <http://hugenavigator.net/HuGENavigator/gWAHitStartPage.do>). Genes listed in the figure are those that are specific to rhinitis and genes that are common to asthma and rhinitis are *LRRC32*, genes of the *HLA* region, and *TSIP*. (b) The number of genes studied in asthma (light grey), rhinitis (dark grey), or both (intersect) through candidate-gene studies using the Gene Prospector tool of the HuGE Navigator (version 2, <http://hugenavigator.net/HuGENavigator/geneProspectorStartPage.do>). Genes included in (b) are those with three or more publications (positive or negative association studies). Genes listed in the figure are those that are specific to rhinitis and the 23 genes common to asthma and rhinitis are *ACE*, *ADAM33*, *ADRB2*, *CD14*, *CFTR*, *CTLA4*, *CYP2D6*, *FLG*, *GATA3*, *HLA-DQB1*, *HLA-DRB1*, *IL4*, *IL4R*, *IL5*, *IL6*, *IL13*, *IL18*, *SCGB1A1*, *TAP1*, *TGFB1*, *TLR2*, *TLR4*, and *TNF*.

[61–64]. The phenopedia tool of the HuGE Navigator software (<http://hugenavigator.net/HuGENavigator/startPagePhenoPedia.do>) indicates that more than 1000 genes have been studied with asthma in comparison to 175 genes with rhinitis, showing the discrepancy in interest of the scientific community to document the genetics of asthma compared to rhinitis. Figure 1 summarizes the genes associated with asthma and rhinitis by genome-wide association studies and genes associated within three or more independent association studies. This Venn diagram also highlights the disparity in research intensity for asthma genes in comparison to rhinitis ones by showing more genes associated to asthma and rhinitis together ($n=26$ genes) than genes associated only to rhinitis ($n=16$ genes).

CONCLUSION

New data confirm how asthma and rhinitis are closely linked, in terms of both prevalence, genetic determinants, and inflammatory mechanisms as well as their respective influence on each other. These two conditions should be approached concomitantly, as rhinitis treatment has been shown to improve asthma outcomes.

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Conflicts of interest

Marie-Eve Boulay and Andréanne Morin have no conflict of interest to declare.

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- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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