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Functional relationships between allergic rhinitis and asthma

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Summary
Allergic rhinitis and asthma should be considered manifestations of one syndrome in two parts of the respiratory tract. In addition, the notion that these entities affect each other should be strongly entertained. The pathophysiology of allergic rhinitis is very similar to that of allergic asthma and their responses to pharmacological and immunological interventions are very comparable, as well. Epidemiological data attest to the strong link; 85% or more of allergic asthmatics have rhinitis and, in cross-sectional population studies, rhinitis is a major risk factor for asthma. Adults with allergic rhinitis have a threefold higher probability of developing asthma, compared with those without rhinitis. A model has been developed to describe the relationships between allergic rhinitis and asthma. According to the model, the two conditions are linked in a horizontal and a vertical fashion. When both conditions are present, their clinical activity tracks in parallel; however, rhinitis appears as a lone condition in the mildest forms of the syndrome. The vertical relationship reflects the fact that experimentally-induced allergic reactions in the nose can induce changes in the lower airways and the fact that local treatment of rhinitis can have beneficial effects in patients with asthma. Various mechanisms have been proposed to explain the vertical relationship. Investigation into these mechanisms can offer major insights into the physiological and immunological basis of all allergic conditions.

Keywords airways responsiveness, allergic reaction, asthma, nose–lung interaction; rhinitis

One syndrome – two manifestations

The primary principle governing the relationship between allergic rhinitis and asthma is that these two conditions represent manifestations of one nosological entity in two different parts of the respiratory tract. The basis for this principle derives from all known pathophysiological phenomena associated with allergic rhinitis and asthma. For example, inducible acute allergic reactions are characterized by the release of similar inflammatory mediators in both parts of the respiratory tract [1–5]; the pattern of postallergen cellular accumulation in the nasal and the bronchial airways is the same [3,6–9]; allergens can induce late-phase reactions in both the nose [10,11] and the lungs [12] and can similarly increase nasal [13] and bronchial [14] responsiveness. The effects of specific pharmacological interventions, to the extent that they have been examined in both the nose and the bronchi, are also the same. For example, antihistamines reduce the early effects of allergen challenge in both the upper [15] and the lower [16,17] airways and topical glucocorticosteroids block the allergen-induced late-phase reaction [18–20], the allergen-induced increase in airway responsiveness [13,20] and the influx of inflammatory cells (primarily eosinophils) in both parts of the respiratory tract [6,7,21]. Even theophylline, a drug produced with only the lower airways in mind, has been shown to attenuate the acute allergic reaction in the human nose [22].

In the natural presentation of allergic rhinitis and asthma, the evidence that a single condition underlies the clinical picture is also very strong. In a study by Chanez *et al*. for example, eosinophil numbers in the nasal and bronchial mucosa of asthmatics with allergic rhinitis were strongly related [23]. In our hands, eosinophils in nasal lavage fluids were strongly correlated to bronchial responsiveness to methacholine, in adolescents with asthma (unpublished observations). According to the work by other investigators, asthmatics with severe rhinitis are more likely to experience clinical outcomes indicative of severe lower airways disease (e.g. nighttime awakenings or work-loss), compared with asthmatics with mild or no nasal symptoms [24–26].

There are, of course, pathophysiological differences between rhinitis and asthma; however, most of these differences result from the nature of the target organs and not from diverse mechanisms at the origin of the disease. The primary difference, of course, relates to the presence of

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smooth muscle in the lower airways and not in the nose. Therefore, in the lower airways, a major component of obstruction derives from smooth muscle constriction, whereas vascular engorgement is responsible for obstruction in the nasal airways. Another area where the principle that allergic rhinitis and asthma represent the manifestations of one condition in two parts of the respiratory tract is not evident is airways remodelling. It is, for example, unclear whether the *lamina reticularis* of the nasal mucosa is thicker in patients with allergic rhinitis, compared with healthy controls [23,27]. This difference between the nose and the lower airways may be due to the nature of upper airway tissue, which may be able to respond with less 'remodelling' to a chronic inflammatory process. This is perhaps an evolutionary characteristic deriving from the fact that the nasal mucosa develops inflammatory reactions on a more frequent basis, compared with the lower airways. Interestingly, even if it is hard to show morphological differences between the nasal mucosa of healthy and rhinitic individuals, Djukanovic and colleagues, as well as other investigators, have demonstrated that the lower airways of subjects with atopy but no asthma have thicker *lamina reticularis* compared with healthy controls [28–30].

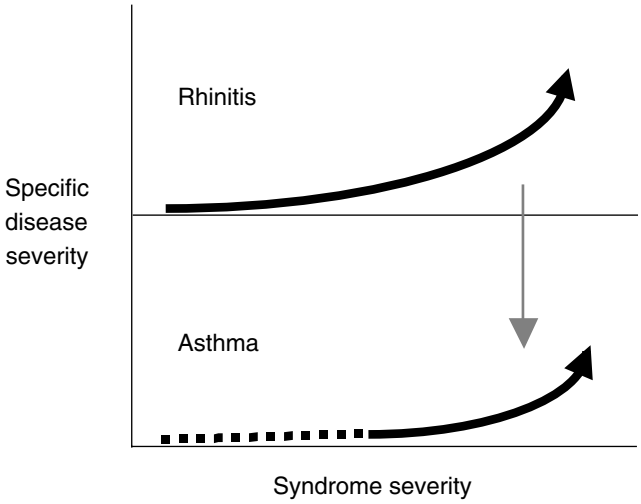

Fig. 1. A model to describe the relationships between allergic rhinitis and asthma viewed as manifestations of one syndrome in two parts of the respiratory tract. The occurrence of each manifestation is not random. In the mildest version of the syndrome, clinical rhinitis occurs alone, although the lower airways show morphological and, in some case, functional abnormalities. At the more severe end, the clinical expression of the syndrome involves both the nasal and the lower airways (asthma). Once both manifestations have been expressed, the severity of the upper and lower airways disease tracks in parallel (horizontal relationship between rhinitis and asthma). In addition, rhinitis has an impact on the lower airways and may worsen asthma (vertical relationship).

Rhinitis and asthma: horizontal and vertical relationships

The relationship between allergic rhinitis and asthma is driven by: (a) the fact that the nasal airways are exposed to aeroallergens and to environmental irritants more frequently and with higher intensity compared with the lower airways; and (b) the fact that the nasal airways play a homeostatic and protective role for the entire respiratory tract. The first fact offers an explanation for the higher prevalence of allergic rhinitis, compared with that of asthma and for the general belief that allergic rhinitis occurs earlier than, or at the same time as, asthma (at least in individuals who develop this syndrome at an age when the diagnosis of chronic rhinitis can be well established) [31–33]. The second fact implies that nasal airway dysfunction or abnormality may pose a burden to the function of the lower airways, especially in patients whose lower airways are also diseased, namely those with asthma.

In an attempt to bring these principles together, a model was developed regarding the relationship between allergic rhinitis and asthma; this model is represented in Fig. 1. This model can be summarized as depicting two types of relationships between allergic rhinitis and asthma: a horizontal and a vertical relationship. According to the horizontal relationship, the severity of the two conditions is in concordance; the vertical relationship indicates that one condition affects the other, namely that rhinitis impacts asthma.

On the basis of this model, if we were to consider allergic rhinitis and asthma as elements of a *chronic allergic inflammatory airway syndrome*, the clinical phenotype of a patient with such syndrome would depend on her/his position in the wide spectrum of severity that this syndrome presents with. At the low end lies a patient with sole nasal airways involvement. In the middle, one could envision the patient with allergic rhinitis and lower airways hyperresponsiveness, and at the high end, the patient with both allergic rhinitis and asthma. From the perspective of airways inflammation, this differentiation is less obvious; as already mentioned, it has been shown that patients with atopy but no asthma demonstrate lower airways inflammation (particularly eosinophilia) and thickening of the *lamina reticularis*, compared with healthy controls [28–30]. In my opinion, the presence of lower airways inflammation in individuals with lone allergic rhinitis, as well as the ability to produce lower airway obstruction in such individuals after allergen inhalation or segmental instillation [5,34], strongly attest to the 'oneness' of this syndrome.

Several postulates deriving from the above model are supported by clinical and epidemiological observations, as well as by experimental evidence. First, rhinitis is almost ubiquitous in patients with asthma [32,33]. At least 85% of patients with asthma report a constellation of upper respiratory symptoms compatible with rhinitis; even those who deny such symptoms have evidence of chronic inflammation in their nasal mucosa [35]. Second, rhinitis (both allergic and nonallergic) constitutes a strong risk factor (or predictor) for the presence or for the development of asthma [33,36,37]. Third, some evidence suggests that the nasal airway disease of patients with lone rhinitis is

milder than that of patients with the fully-developed syndrome, that is, rhinitis and asthma [38,39]. Fourth, as mentioned above, in patients with rhinitis and asthma the severity of nasal disease correlates with that of the lower airways.

The above observations can be considered reflective of the parallel relationship between rhinitis and asthma, as depicted in the model. However, the vertical relationship can be invoked as well, especially in the case of patients with the fully-developed *chronic allergic inflammatory airway syndrome.* In this setting, it can be argued that worsening of the lower airways disease is to some extent secondary to worsening of rhinitis. This possibility is supported by two types of observations. First, evidence has emerged that an allergic reaction that takes place inside the nasal passages may have physiological and inflammatory consequences for the lower airways. Nasal provocation with allergens can produce late reductions in lower-airway function that, in some cases, are quite dramatic [40]. Also, a subgroup of asthmatics with rhinitis develop increased lower airways responsiveness several hours after their nasal airways have been exposed to allergen [41,42]. Even more impressive is the finding that nasal allergen provocation can induce inflammation in the bronchial mucosa [43]. Second, several studies have produced data supporting the concept that treatment of allergic rhinitis with intranasal glucocorticosteroids benefits asthma with improvement in symptoms, medication use, lung function, airways responsiveness and even with reduction in hospitalizations [44–50]. Although most studies addressing this issue have yielded positive results, negative trials have been reported, as well [51,52].

How the nose affects the lower airways

The exact mechanisms underlying the vertical relationship between rhinitis and asthma are not known, but several hypotheses have been proposed [53]. It is quite possible that all proposed mechanisms are operable to a variable extent in each individual. With the nasal mucosa playing a central role in the homeostasis of the lower airways (warming and humidification of inhaled air, trapping of particles and gaseous irritants, strong innate immunity), it is reasonable to hypothesize that bypassing the nasal passages could impose significant stress on the lower airways, especially those of patients with asthma. A classic observation in this respect is that nasal breathing blunts obstructive airways responses to exercise in patients with a history of exercise-induced bronchospasm, whereas oral breathing potentiates these responses [54,55]. Also, chronic bypassing of the upper airways, such as in patients with tracheostomy, produces significant disturbances in the morphology of the lower airways and a chronic bronchitis-like clinical picture [56,57].

Another hypothesis claims that irritation of the sensory nerves of the nasal mucosa through allergic and irritant reactions may generate nasobronchial reflexes with bronchoconstrictive consequences. The existence of the nasobronchial reflex in humans has been questioned in the past [58–61]. Recently, Fontanari and colleagues have provided convincing evidence for such a reflex [62]. These investigators showed that stimulation of the nose with bursts of cold air results in increased lower airways resistance. They also demonstrated that this response of the lower airways could not be generated when cold air was sprayed into the oral cavity. Furthermore, the lower airways response was blocked by pretreatment of the nose with an anaesthetic or pretreatment of the lower airways with atropine. It is notable that strong evidence has accumulated that, in patients with chronically or acutely inflamed nasal mucosa, the sensorineural apparatus is in an up-regulated state, a state of sensorineural hyperresponsiveness [63–66]. Such a state is expected to potentiate nasobronchial reflexes in patients with asthma.

The theory of inflammatory humours generated by the mucosa of the upper airways or by the paranasal sinuses and entering the lower airways to provoke asthma exacerbations has been under debate. Although supported by an animal model [67], this mechanism has not been found operative by the only relevant study that has been performed in humans. In individuals with acute sinusitis, Bardin and colleagues injected radiolabelled material in the maxillary sinus and traced it over time [68]. These investigators failed to detect any radioactivity in the lower airways of their study subjects.

Recently, another hypothesis has been under discussion: allergic inflammation generated at the level of the nasal mucosa may lead to systemic inflammatory events, eventually affecting the lower airways. Evidence for the systemic response derives from the fact that peripheral blood eosinophilia can occur following nasal allergen provocation [69]. Furthermore, we have recently found that spontaneous release of some cytokines from peripheral blood leucocytes becomes substantially up-regulated following nasal allergen provocation [70]. The most important observation in this context has come from Braunstahl and his colleagues. Subjects with allergic rhinitis were locally exposed to allergen in their nasal mucosa [43]. Prior to and 24 h after the allergen challenge, these investigators performed both a nasal and a bronchial biopsy on their subjects. The allergic reaction in the nose produced, as expected, nasal inflammation and peripheral blood eosinophilia. However, it also produced bronchial eosinophilia with up-regulation of various adhesion molecules in the bronchial mucosa. Interestingly, the same investigators have performed the inverse study, in which the allergen was directly delivered to the lower airways through a bronchoscope. In that study, inflammation in the nasal mucosa was detected after 24 h, indicating that this aspect of the relationship between allergic rhinitis and asthma is bi-directional [71,72].

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