

The nose–lung interaction in allergic rhinitis and asthma: united airways disease

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The link between upper and lower respiratory tracts has been repeatedly observed in the past 50 years but only carefully investigated during the past decade. Several clinical and experimental observations suggested the hypothesis of the unity of upper and lower airways (allergic rhinobronchitis or united airways disease). The relationships between rhinitis (and sinusitis) and asthma also include non-epidemiological aspects such as viral infections and bronchial hyperreactivity. The hypotheses have been confirmed by means of epidemiological observations, functional and immunological evidence and, indirectly, by observing the effects of drugs used mainly for rhinitis on asthma symptoms. In this article, therefore, we collected and reviewed the most relevant experimental results available to support the hypothesis for united airways disease and the studies conducted on the possible mechanisms of nose–lung interaction. *Curr Opin Allergy Clin Immunol* 1:7–13. © 2001

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Abbreviation

UAD united airways disease

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Introduction

The overall pathogenic view of respiratory allergy has profoundly changed and evolved over the past 10 years. Particular attention has been paid to the relationship between rhinitis and asthma, i.e. between the upper and lower respiratory airways. Evidence for this strict link has mainly been found through clinical observations and epidemiological studies, but also from immunological observations and outcomes of therapy. Furthermore, an increasing amount of proof has been provided for (a) the frequent coexistence of rhinitis and asthma; (b) the possible role of upper respiratory infections in exacerbating asthma; (c) the presence of rhinitis as a risk factor for developing asthma and (d) the importance of paranasal sinus infections (sinusitis). It is noteworthy that all these aspects are particularly evident in children. These observations taken together lead to the operative definition of allergic rhinobronchitis [1] or, as we recently proposed, of united airways disease (UAD) [2]. The increasingly detailed knowledge of the fine mechanisms sustaining allergic inflammation in the respiratory tract (i.e. antigen presentation, cytokines, chemokines and adhesion molecules) have partly clarified the functional relationships between nose and bronchi. In this regard it is logical to expect that allergy is not a disease confined to a specific target organ, but rather a disorder of the whole respiratory tract with a broad spectrum of clinical manifestations. The concept of UAD also has relevant diagnostic and therapeutic implications.

The epidemiological evidence

Almost all data concerning the association of the upper and lower airways come from epidemiological studies. It has to be remembered that most of these studies were carried out using specific questionnaires aimed at assessing a clinical diagnosis. The problem is further complicated by the lack of precise criteria for diagnosing diseases such as rhinitis and sinusitis. Moreover, some studies addressed the issue of atopy and used biological criteria (skin test, IgE) whereas in other studies a distinction between allergic or nonallergic rhinitis and asthma was not made. Despite these limits, the data coming from the literature are consistent as summarized below.

Very early clinical observations performed during the 1960s to assess the effectiveness of specific immunotherapy [3] showed that there was an association between

allergic rhinitis and asthma: approximately 50% of the control cohort (no immunotherapy) of children with allergic rhinitis developed asthma within a few years. This study [3] had methodological limits but the observation was confirmed in more recent years in better designed trials [4–8], as previously reviewed by Annaesi-Maesano [9•]. In cross-sectional studies it is easy to assess the coexistence of rhinitis and asthma, but it is even more interesting to follow up patients in longitudinal studies in order to elucidate the natural history. When patients were followed-up for a long enough period it became apparent that allergic rhinitis usually precedes the onset of asthma. In fact in a 23-year survey [6] approximately two-thirds of individuals with allergic rhinitis appeared to be more likely to develop asthma than controls. The same was seen in other large longitudinal studies [10,11] where the odds ratio for association between current rhinitis and asthma onset after 7 years was 7.1 [10] and 3.9 [11], respectively. In a recent survey [12], we followed up 99 patients for up to 10 years after the initial diagnosis of allergic rhinitis, allergic asthma or both. We observed that 32% of rhinitic patients developed asthma during the 10-year follow-up and that 50% of patients with asthma alone developed rhinitis. Moreover, in a study performed on conscripts we showed that the association with allergic rhinitis is present in more than 70% of asthmatics [13].

Allergic rhinitis has been defined as risk factor for developing asthma [6,8], but this is not completely correct: allergic rhinitis probably represents a particular (early) stage of UAD and the subsequent onset of asthma may be its evolution. In fact, a relevant percentage of patients suffering from rhinitis alone have an objective nonspecific bronchial hyperresponsiveness: a characteristic feature of asthma [14]. Moreover, support for the hypothesis that rhinitis and asthma are two aspects of a unique disease comes from a study by Kapsali *et al.* [15]. When rigorous diagnostic criteria are used, the presence of concomitant rhinitis can be demonstrated in approximately 90% of allergic asthmatic patients. By contrast, the analysis of a subpopulation of nonatopic subjects from the European Community Respiratory Health Survey (ECRHS) showed that perennial rhinitis is an independent risk factor for asthma even in the absence of any marker of atopic status [16•]. In this latter case, functional and neuronal mechanisms rather than immunological mechanisms are considered to be responsible.

Finally, the coexistence of sinusitis and asthma, particularly in children, has been recognised for at least 20 years [17]. The frequent involvement of paranasal sinuses (rhinosinusitis) is currently considered very relevant to the development of disease of the lower respiratory airways in allergic patients [18], as extensively reviewed

by De Benedictis and Miraglia del Giudice [19]. In a very recent study using endoscopic assessment in children, we observed that sinusitis or adenoiditis occurs in more than 50% of asthmatic individuals [20].

Functional considerations

The respiratory tract can be considered as a single morpho-functional entity. It is entirely covered until the smaller bronchi by ciliate epithelium and mucinous glands and an extensive vasculature and innervation serve it. The type of innervation is quite similar in the upper and lower compartment [21], and this fact leads to the hypothesis of the naso-bronchial reflex as a possible pathogenic mechanism. The naso(sinus)bronchial muscarinic reflex was first hypothesised at the beginning of the twentieth century [22] and has been well studied in animals, but its role in humans remains controversial. Nevertheless, it has been demonstrated that nasal challenge can elicit a contractile response of bronchi or an increase in bronchial responsiveness [23–25].

The respiratory mucosa is rich in mast cells with different functional aspects and these cells are thought to significantly contribute to nose–bronchi connections via cytokine release [26]. Moreover, the lymphoid tissue constitutes the bronchial- (mucosal-) associated lymphoid tissue (BAL/T or MAL/T), which is largely represented in both the nose and bronchi. The significant difference between the two compartments is that the nose and paranasal sinuses are rigid boxes in which erectile sinusoid vessels predominate, whereas the lower airways are included in an elastic parenchyma and they are rich in peribronchial smooth muscles [27•,28]. This anatomical diversity accounts for the different response to offending stimuli: rhinorrhea/blockage in the nose and mucus secretion/bronchoconstriction in the lung.

The upper respiratory tract has the functions of physical filter, resonator, heat exchanger and humidifier for inhaled air. The inhaled air arrives into the bronchi with a temperature of approximately 37°C and is almost completely saturated in humidity. Moreover, particles larger than 5–6 mm are efficiently retained in the nose [29]. It is easy to understand that a failure of any one of these functions may result in an alteration of the homeostasis of the lower respiratory airways [30]. Evidence exists that oral hyperventilation with cold air in asthmatics decreases the forced expiratory volume, but also increases the nasal resistance [31•].

Another possible functional link between the nose and bronchi has been identified recently – the systemic connection via soluble mediators to the bone marrow [32]. In fact, it has been demonstrated that bone marrow can promptly and specifically respond to nasal challenge

by increasing the maturation and production of eosinophilic precursors bearing the high affinity IL-5 receptors [33,34].

From a functional point of view, it is interesting to highlight the frequent association of the non-specific bronchial hyperresponsiveness with rhinitis. This has been observed in several well documented studies [14,35,36]. Conversely, no significant relationship seems to exist between nasal and bronchial non-specific hyperreactivity [37]. A possible and recently highlighted mechanism of the nonspecific reactivity is the so-called neurogenic inflammation, in which neuropeptides (substance P, neurokinin A) are involved. In fact, the regulation of capacitance vessels (and, therefore, the plasma extravasation and oedema) is mainly due to sensory-neural apparatus [38,39].

Clinical and epidemiological observations would suggest that the natural progression of disease usually occurs from the upper respiratory airways towards the lower airways [40]. Nevertheless, it has recently been demonstrated that segmental bronchial challenge is able to induce nasal symptoms as well as nasal inflammation in patients with allergic rhinitis [41]. This latter aspect is difficult to interpret from a practical viewpoint because there is no clinical situation in humans in which a primary bronchial disease can result in a nasal disorder, but such an observation has to be taken in account in the overall view of the united respiratory airways.

Immunological aspects

When an allergic reaction takes place (i.e. allergen-IgE-mast cell), the so-called early phase occurs within minutes [42]. This first step involves release of histamine, vasodilatation, increased permeability and bronchoconstriction. This early phase is followed by a complex network of inflammatory phenomena in which T lymphocytes, cytokines and adhesion molecules are involved. The adhesion machinery in particular seems to be crucial for the recruitment of inflammatory cells at the target organ. During the early phase, specific adhesion molecules are newly expressed or upregulated on the surface of endothelium (selectins) and epithelium (integrins). The adhesion molecules favour the rolling over, extravasation and migration of inflammatory cells towards the epithelium [43], and the ICAM-1 (CD54) molecule seems to be a good hallmark of ongoing allergic inflammation. The kinetics of allergic inflammation involve a migration of inflammatory cells to the mucosa, which begins to become apparent approximately 30 minutes after specific challenge, continues to increase during the following 24 hours and then slowly subsides. This can be easily observed and measured at nasal and conjunctival levels [44], but experimental evidence suggests that the same occurs also in the bronchi of

asthmatics [45–47]. Interestingly, a weak inflammatory infiltration is present in the mucosae even in the absence of symptoms, when a sub-threshold exposure to the allergen persists (Fig. 1). This is called minimal persistent inflammation and it has been demonstrated in both mite- [48] and pollen-induced [49] rhinitis. Minimal persistent inflammation also involves a weak and persistent expression of the ICAM-1 molecule which is the major receptor for human rhinoviruses [50]. Minimal persistent inflammation and ICAM-1 expression in symptom free allergic individuals is important because exacerbation of asthma in children is frequently related to upper respiratory viral infections [51,52], mainly caused by rhinoviruses. This latter aspect has been confirmed *in vivo* by means of an experimentally induced infection with human rhinoviruses [53,54].

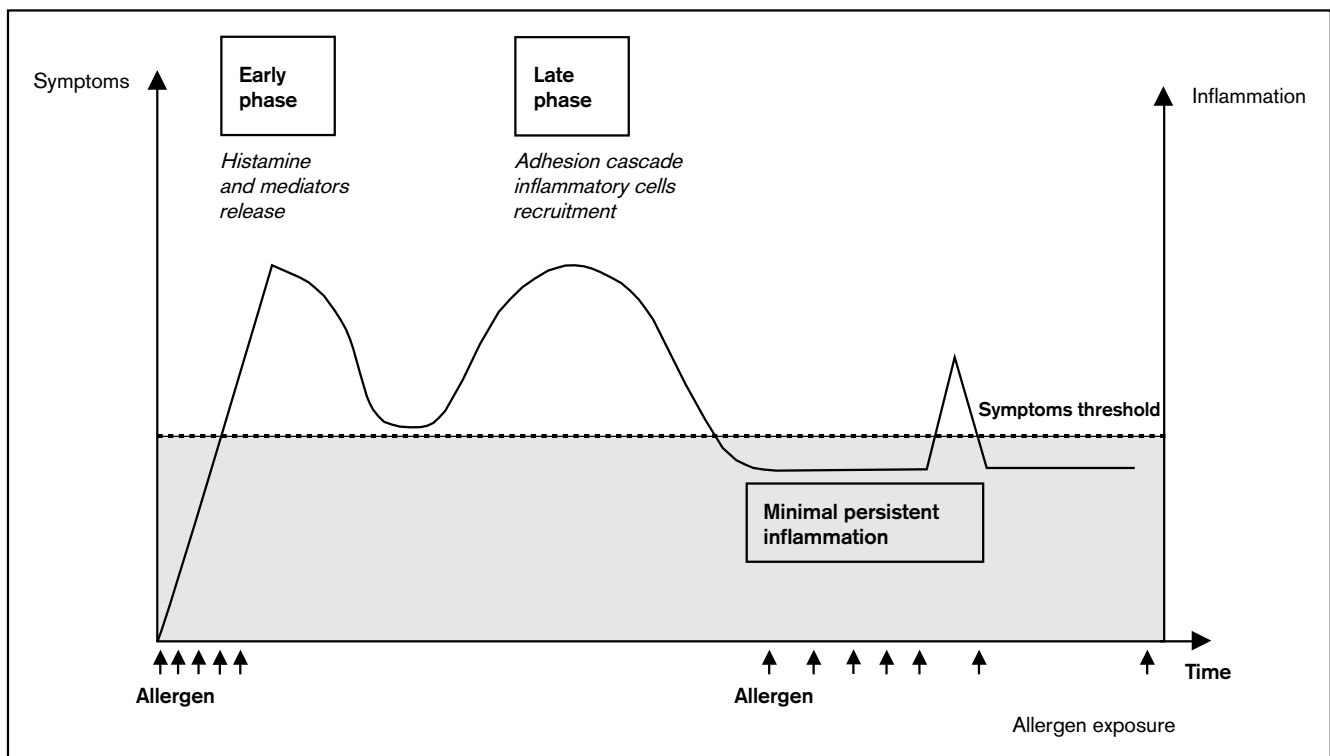
The effects of the treatment of upper airways on asthma: an indirect evidence

The strict link between the upper and lower respiratory tracts can also be viewed from the perspective of therapeutic outcomes. It is well known that β_2 agonists are highly effective in asthma but they have virtually no effect on rhinitis; conversely, antihistamines treat rhinitis symptoms but are ineffective in asthma. These discrepancies can be easily explained by the different anatomical structures of the two compartments (see section Functional considerations). Nevertheless, when appropriate methods are used, the influence exerted on bronchial disease by treating rhinitis or sinusitis can be demonstrated [55].

It has been observed that 326 $\mu\text{g/day}$ intranasal beclomethasone [56] and 200 $\mu\text{g/day}$ fluticasone propionate [57] were able to significantly reduce bronchial hyperresponsiveness to methacholine in asthmatic patients. Moreover, in another study [58] it was observed that intranasal beclomethasone (200 μg twice daily) improved symptoms of asthma and significantly reduced methacholine hyperresponsiveness. In a double-blind, double-dummy placebo controlled study [59] with either intranasal or inhaled beclomethasone (100 μg four times daily) it was seen that intranasal administration, not inhaled administration, could reduce carbachol-induced PD35% bronchial hyperresponsiveness. Another study [60], however, failed to demonstrate the effects of intranasal corticosteroids on bronchial function. Nevertheless in this second study there was no evidence of a preexisting bronchial hyperresponsiveness.

In a placebo-controlled study of 186 patients, 10 mg cetirizine significantly reduced symptoms of asthma during the pollen season, although no significant difference could be seen in pulmonary function parameters [61]. On the other hand, the administration of 5 mg loratadine and 120 mg pseudoephedrine twice

Figure 1. The paradigm of minimal persistent inflammation



When subliminal exposure to an allergen occurs the patient is symptom free but subclinical inflammation is present.

daily significantly improved symptoms of asthma and peak expiratory flow and reduced albuterol intake in patients with seasonal allergic rhinitis and mild asthma [62]. Such a synergistic effect between different drugs has been also demonstrated, for example, with antihistamines in association with antileukotrienes [63,64].

The link existing between upper respiratory disease and asthma was further demonstrated in children [65,66], in whom the occurrence of upper respiratory infections and exacerbation of asthma can be controlled by continuous antihistamine treatment. These observations from small experimental groups were recently confirmed by the large Early Treatment of Atopic Child (ETAC) study [67], which demonstrated that continuous antihistamine treatment was capable of reducing the subsequent onset of asthma. It is interesting to notice that detailed education of patients on how to correctly treat their rhinitis with continuous, long-term nasal corticosteroids leads to a significant improvement of concomitant asthma symptoms [68]. Finally, when sinusitis coexists with asthma, proper treatment (either pharmacological or surgical) of diseased paranasal sinuses can significantly improve asthma symptoms, as demonstrated in several studies [69–71].

The overall view of respiratory allergy as a systemic disease and the evidence coming from pharmacological studies would suggest a promising integrated therapeutic approach (Fig. 2) based on pathophysiological knowledge of the unity of the airways.

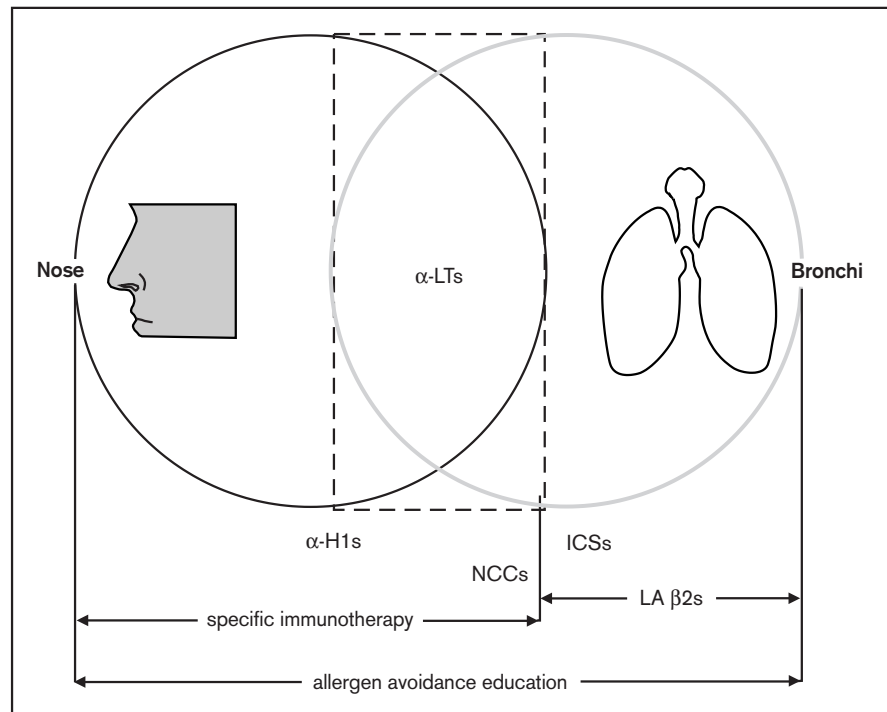
Conclusion

The Galileian procedure should be applied to every medical theory: first, clinical observation, second, formulation of a hypothesis and third, validation of the hypothesis through controlled and reproducible experiments.

UAD was born as a hypothesis aimed at explaining the complex relationship between the upper and lower airways and the variable clinical aspects of diseases. At present, we have many epidemiological and clinical observations available to strongly support this hypothesis [72•]. The epidemiological evidence and the data available from basic immunology suggest that allergy is not a disease confined to a specific target organ, but rather a systemic disorder of the respiratory tract. This disorder may have a broad spectrum of clinical manifestations, from rhinitis (and rhinosinusitis) to asthma.

Figure 2. An integrated approach to treatment of united airways disease

α -H1, antihistamines; α -LT, antileukotriene;
LA β 2, long acting beta2 agonists; ICS, inhaled
corticosteroid; NCC, nasal corticosteroid.



The strength of the considerations mentioned in this review prompted the WHO to publish an extensive position paper fully devoted to the relationship between rhinitis and asthma and its therapeutic implications. This position paper has been entitled ARIA: allergic rhinitis and its impact on asthma [73••].

Some questions remain unanswered but UAD is beginning to be considered an evidence-based entity and, therefore, a possible new therapeutic rationale in the management of respiratory allergy is to be expected.

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