

EDITORIAL

Rhinitis and asthma: a continuum of disease?

The nasal and bronchial mucosa present similarities and most patients with asthma also have rhinitis [1–3], suggesting the concept of ‘one airway one disease’. Links between asthma and rhinitis are supported by epidemiological evidence, nasal inflammation in asthma and bronchial inflammation in rhinitis. However, there are some differences between rhinitis and asthma which need to be further studied. Moreover, there have been no animal studies which showed a link between nasal and bronchial inflammation.

Epidemiological evidence

Epidemiological studies have consistently shown that asthma and rhinitis often coexist in the same patients. In epidemiological studies, between 60% and 80% of asthmatics have had concomitant rhinitis [4–6]. These trends were confirmed in large clinical studies in which up to 95% of asthmatics had rhinitis [7]. However, only 30–40% of rhinitis patients have clinically demonstrable asthma. Allergic and non-allergic rhinitis are associated with asthma [5]. The Midspan family study [8] estimated trends during 1972–1976 and 1996 in the prevalence of asthma and hay fever in adults by surveying offspring of parents. The prevalence of asthma in adults has increased more than twofold in 20 years, largely in association with hay fever. No evidence was found for an increase in diagnostic awareness being responsible for trends in atopy, as measured indirectly by the prevalence of trends in atopic asthma.

Subjects with occupational asthma very often report symptoms of rhinoconjunctivitis [9,10]. Many patients with allergic rhinitis have increased bronchial sensitivity to methacholine or histamine [11,12].

Nasal inflammation in asthma

The recent advances made in the cellular and molecular biology of airways diseases have clearly documented that inflammation plays a critical role in the pathogenesis of asthma and rhinitis. The same inflammatory cells and mechanisms appear to be present in the nasal [13] and bronchial mucosa [14]. Moreover, eosinophilic inflammation of the nose exists in asthmatics with or without nasal symptoms [15].

However, there are differences between both sites. Although the nasal and bronchial mucosa are exposed to the same noxious environment (and even more so in the

nose), epithelial shedding is more pronounced in the bronchi than in the nose of the same patients suffering from asthma and rhinitis, and features of airways remodelling appear to be less extensive in the nasal mucosa than in the bronchial mucosa [16].

For more than 70 years the coexistence of asthma and rhino-sinusitis has been noted in the medical literature [17]. In the light of current knowledge, it seems that rhino-sinusitis and asthma are linked by a common process that is mainly inflammatory, and central to the pathogenesis is the role of eosinophils and airway epithelium [18]. In severe asthma, all patients have an abnormal sinus CT-scan [19].

On the other hand, patients with COPD have few nasal and sinus signs and symptoms, showing that the nasal involvement of asthma is not due to a non-specific bronchial disease.

Bronchial inflammation in rhinitis

Some studies have examined the bronchial mucosa in atopic non-asthmatic patients or in patients with allergic rhinitis. They all combined to indicate that there was a slight increase of the basement membrane size [20] and a moderate eosinophilic inflammation [21].

Natural exposure to pollen during the season provokes an increase in airway responsiveness in non-asthmatic subjects with seasonal allergic rhinitis and also induces inflammatory cell recruitment and IL-5 expression, leading to bronchial inflammation [22].

Endobronchial allergen challenge was carried out in patients with seasonal rhinitis who had never presented with asthma before. These patients developed a bronchoconstriction and lavage carried out serially after challenge demonstrated the occurrence of pro-inflammatory mediators and cytokines as well as the recruitment of inflammatory cells [23–25].

These studies combine to indicate that patients with nasal symptoms can only react if the allergen is properly administered into the airways. It may be argued that the doses of allergen inducing these bronchial reactions are far greater than those naturally occurring during allergen exposure. This situation seems to exist in thunderstorm-induced asthma [26] which is associated with grass pollen allergy [27]. The aerodynamic size of pollen grains ranges from 10 to 100 μm and only a fraction of them can be deposited into the bronchi, thus most patients only present

rhinitis without asthma. However, when exposed to water, pollen allergens are released in submicronic particules, the starch granules, which can reach the lower airways and induce asthma [28].

Bronchial challenge of rhinitis patients leads to nasal inflammation

In a recent study, endobronchial allergen challenge induced nasal and bronchial symptoms as well as reductions in pulmonary and nasal function [29]. In this study the number of eosinophils increased in the challenged bronchial mucosa, in the blood and in the nasal mucosa 24 h after bronchial challenge. Moreover, eotaxin-positive cells in the nasal lamina propria and enhanced expression of IL-5 in the nasal epithelium were found 24 h after bronchial challenge. Braunstahl *et al.* (unpublished data) found that nasal challenge increased eosinophils in the bronchial mucosa.

The animal study: the missing link

Human studies combine to indicate that there is a strong link between rhinitis and asthma but there are some differences which need to be further studied. Moreover, there have been no animal studies which showed a link between nasal and bronchial inflammation.

In the present issue of *Clinical and Experimental Allergy* Hellings *et al.* [30] set up an experimental model to investigate the development of nasal inflammation in mice during the development of an asthma-like reaction and after an acute allergen provocation. BALB-c mice sensitized intraperitoneally to ovalbumin were exposed on 8 consecutive days to a nebulized allergen solution. Such a 'chronic' allergen exposure led to the development of a simultaneous and progressive allergic inflammation of the upper and lower airways, characterized by an eosinophilic inflammation, IL-5 production and increased thickness of the nasal mucosa. There are several important messages raised by the paper.

First, the authors use an interesting model of chronic exposure which probably mimics more the chronic allergen exposure of allergic patients than an acute allergen challenge.

Secondly, it is shown that in spite of a predominant deposition of inhaled allergen in the upper airways, the magnitude of the inflammatory response is greater in the bronchi, at least in terms of eosinophilic inflammation. This evidence further supports the concept of a link between biological events occurring in the upper and lower airways and raises the need to understand the mechanisms by which this link is established. Post-nasal mucus drip and/or the release of mediators in the nose, which are subsequently able to affect the lower airways (or vice versa), have been proposed as possible causes of the association between

nasal and bronchial inflammation [31]. However, the data provided by Hellings *et al.* [30] support the concept of a systemic link between biological events occurring in the nose and in the bronchi. Such a link is established by the release of cytokines, such as IL-5, the levels of which increase after acute allergen provocation and are followed by an increase of eosinophils in broncho-aveolar lavage fluid (BALF). Interestingly, the peak level of IL-5 in serum coincided with that of eosinophils in BALF, suggesting that allergen-stimulation of the nasal mucosa elicits a systemic allergic response sustained by the release of cytokines which in turn are able to promote an inflammatory response in the airways. These data accord with the recent study of Braunstahl *et al.* [29]. Moreover, the importance of IL-5 in nasal eosinophil recruitment is confirmed in animal studies and confirms studies carried out in the lower airways [32].

Even though these important data provided by Hellings *et al.* are convincing, there are still a number of unanswered questions which need to be addressed in further studies.

The first question deals with the systemic nature of the eosinophilic inflammation following allergen stimulation of the nasal mucosa. Two major mechanisms have been demonstrated to contribute to the increased number of eosinophils in the inflamed airways of allergic subjects. In patients with allergic diseases, allergen provocation can activate a systemic response that provokes inflammatory cell production by the bone marrow [33]. After release and differentiation of progenitor cells, eosinophils, basophils and mast cells are typically recruited to tissues in atopic individuals. An understanding at the molecular level of the signalling process that leads to these systemic responses between the target organ, especially the airways, and the bone marrow may open up new avenues of therapy for allergic inflammatory disease [34,35]. Studies that support the critical involvement of the bone marrow in the development of eosinophilic inflammation of the airways point out the systemic nature of these conditions.

The second important mechanism, termed '*in situ* haemopoiesis' [36] depends on the production of haemopoietic cytokines by inflamed tissues from patients with allergic rhinitis [37–39] and nasal polyposis [40] that, generating a particular local 'microenvironment', promote the differentiation and maturation of eosinophil progenitors that populate the nasal or the bronchial mucosa [41,42]. It is therefore likely that a truly 'systemic' response to the application of inflammatory stimuli to the nasal mucosa should be associated with an activation of the aforementioned mechanisms. Thus the hypothesis put forward by Hellings and coworkers of a 'systemic link' between nasal and bronchial eosinophilic inflammation, though plausible, has to be confirmed by further investigations supporting the involvement of the bone marrow and/or of local airway progenitor cells in the allergen-driven airway responses.

These local cytokines can also reduce apoptosis and delay cell death [43] and such an *in vivo* study should also be carried out.

Another important unanswered question is: Can bronchial inflammation influence the inflammatory response in the nose? Recent findings support this 'bidirectional' relationship between nasal and bronchial inflammation [29]. This very important study raises the point that biological events occurring in the nose or in the lung are not 'compartmentalized' but tend to promote more widespread responses involving 'downstream' (following nasal inflammation) or 'upstream' (following airway inflammation) target organs. Such links may be studied in animals using an acute intratracheal allergen administration and will provide another very important mechanism. However, such a study may require a sophisticated methodology.

Third, the authors found that there is an increase in the nasal mucosa thickness. This finding was also observed in allergic patients during the pollen season and may be associated with oedema or with a true increase of the mucosa. Even though the authors used MRI, they could also have studied the size of the mucosa microscopically [44].

Thus, this paper raises several questions which are of great importance for the understanding of the relationships between the nose and the lungs in allergic individuals.

Conclusions

Rhinitis is a very common comorbidity of asthma and common mechanisms coexist. An initiative in collaboration with WHO (ARIA: allergic rhinitis and its impact on asthma) has been developed to assess the association between asthma and rhinitis and it has been recently proposed that physicians should consider the diagnosis of rhinitis in all symptomatic children and young adults with asthma [6].

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