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Allergy and the nose

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Summary

Allergic rhinitis (AR) is the most common immunological disorder and is characterized by an immunoglobulin E (IgE)-mediated inflammation induced by the allergen exposure. This review will consider some issues concerning pathophysiological aspects of AR: impact on asthma, response to decongestion, link with infections, response to specific immunotherapy, relationship with adiposity, effects on quality of life (QoL) and allergic inflammation. AR, even though not a serious illness, may be a clinically relevant disorder as it may present numerous complications and affect QoL, as reported in this review. Therefore, the management of AR patients should be rigorously careful and multi-disciplinary.

Keywords: allergic rhinitis, asthma, decongestion, infections, inflammation, immunotherapy, obstruction

Introduction

Allergic rhinitis (AR) is the most common immunological disorder and is characterized by an immunoglobulin E (IgE)-mediated inflammation induced by allergen exposure. Infiltrating cells, including T cells, eosinophils, mast cells and basophils, release several mediators, that cause the symptoms occurrence, and cytokines, that promote and amplify the inflammatory cascade. Therefore, AR triggers both a local and a systemic inflammatory process.

The main symptoms are the so-called irritative ones, such as itching, sneezing and rhinorrhoea, that are histamine-dependent, and obstruction, that is inflammation-dependent.

This review will consider some issues concerning pathophysiological aspects of AR: impact on asthma, response to decongestion, link with infections, response to specific immunotherapy, relationship with adiposity, effects on quality of life (QoL) and allergic inflamamtion.

Impact of AR on asthma

In this regard, a bidirectional relationship between the nose and the bronchi has been demonstrated recently by elegant experimental models: the allergen nasal challenge induces a bronchial response as well as bronchial stimulation, resulting in a nasal reaction [1]. Therefore, respiratory airways constitute a single anatomical–functional unit. This concept is based on the presence of numerous similarities existing between upper and lower airways, as follows:

(1) epidemiology: several surveys report the association between AR and asthma;
(2) anatomy: the respiratory epithelium is substantially the same from the nasal cavities to the bronchioles;
(3) physiology: nose and bronchi share the same adrenergic and vagal innervation;
(4) immunopathology: mast cells, T lymphocytes and eosinophils may infiltrate both upper and lower airways;
(5) pathophysiology: airflow limitation is the main functional consequence of both AR and asthma; and
(6) therapy: anti-histamines, anti-leukotrienes, corticosteroids and specific immunotherapy may be prescribed both for AR and asthma.

AR is a risk factor for asthma. Two recent studies provided convincing confirmation that AR is an independent risk factor for asthma onset. Settipane *et al.* reported that patients with AR are at three times the risk of developing asthma compared with those without AR [2]. In addition, a cross-sectional study of representative samples of young adults, who completed a detailed questionnaire and underwent lung function tests, bronchoprovocation challenge, IgE measurement and skin prick test, has been performed in Europe [3]. The results demonstrate and confirm that AR is a main risk factor for asthma onset.

There is a close epidemiological link between AR and asthma, as reported by several surveys. Among them, a recent European multi-centre, cross-sectional survey evaluated respiratory symptoms in the young adult population [4]. About 60% of asthmatics suffered from AR; on the other hand, AR

patients presented an eightfold risk of having asthma compared to subjects without AR. Further, Downie *et al.* showed that the most severe nasal symptoms were associated significantly with bronchial symptoms in patients with perennial allergic rhinitis (PAR) [5].

As bronchial hyperresponsiveness (BHR) is a paramount component of asthma, BHR may also be observed in a high proportion of rhinitics. In this regard, it has been hypothesized that a positive bronchial challenge to methacholine could be considered as predictive for those rhinitics would progress to develop asthma [6]. Moreover, BHR was reported to be an important risk factor for asthma development in patients with both PAR and seasonal allergic rhinitis (SAR) [7]. On the basis of these considerations, it was hypothesized that rhinitics may present different spirometric and BHR patterns concerning both aetiology and allergen exposure. To confirm this theory, a large group of patients with AR was analysed. Thus, 2347 patients were enrolled, subdividing them into three groups: patients with PAR, SAR or mixed allergic rhinitis (MAR) (such as polysensitized) [8]. Most AR patients were polysensitized (up to 80%) and BHR affected 82·2% of PAR subjects, 73·6% of MAR subjects and 53·5% of SAR subjects, confirming previous reports. Therefore, these different patterns are related to specific sensitizations. In addition, a seasonal variability of BHR degree was significantly present in SAR and MAR patients.

Moreover, nasal inflammation significantly affects bronchial function, as there is a direct relationship between eosinophil numbers and spirometric performance. Therefore, two studies were performed to analyse the structure/function relationship between the nose and the bronchi. The first study was performed in a group of patients with SAR and asthma [9]. Nasal airflow and forced expiratory volume in 1 s (FEV_1) were correlated significantly with nasal eosinophils, and nasal airflow was correlated significantly with FEV_1. The second study investigated a group of patients with PAR and asthma [10]. Significant positive relationships were demonstrated among nasal eosinophil infiltration, nasal airflow and FEV_1, thus confirming the previous study.

Therefore, both studies constituted the first evidence of a relationship between T helper type 2 (Th2)-related nasal inflammation and nasal and bronchial airflow in patients with AR associated with asthma. These findings constitute formal and objective proof concerning the close link between nasal and bronchial function. Moreover, these data are consistent with the concept of the so-called rhinobronchial cross-talk, such as a bidirectional relationship between structural (i.e. inflammatory phenomena) and functional (i.e. airflow) events. In other words, nasal obstruction through different pathophysiological mechanisms, including oral respiration, systemic absorption of mediators and cytokines, post-nasal drip and nervous reflex, significantly affects the bronchial airflow.

Response to decongestion

Nasal obstruction is actually related to allergic inflammation. Nasal obstruction may be approximately evaluated subjectively, by the perception of air passage through the nose, and objectively, by measuring the nasal airflow through rhinomanometry. Recently, the relationship between nasal obstruction, eosinophils, Th2-dependent cytokines and airflow limitation has been described in patients suffering from AR [10,11]. Specifically, nasal eosinophils may be considered as the best marker of allergic inflammation and their evaluation should be included in the work-up of patients with AR.

The nasal decongestion test consists in evaluating the percentage of reversibility of nasal airflow obstruction after administering an intranasal vasoconstrictor (such as α-adrenoreceptor stimulant). Some studies have shown that there is a relationship between allergic inflammation and recovery to decongestion test, and it is possible to relate responder to test [12,13].

Link with infections

Allergic rhinitis and asthma share common immunological mechanisms characterized by Th2-dependent inflammation. As a consequence, allergic subjects have typically Th2-polarization and a reduced Th1-response. Interferon (IFN)-γ, a typical Th1-derived cytokine, is deputized for fighting infections. Thus, it has been pointed out that allergic subjects could present a higher susceptibility to contracting respiratory infections (RI) than non-allergic subjects [14]. This hypothesis could be reinforced by evidence that rhinovirus infections are the most common [15]. The main receptor for rhinovirus is intercellular adhesion molecule-1 (ICAM-1) [15]. ICAM-1 expression on nasal epithelial cells is related strictly to allergen exposure in allergic subjects [16]. Thus, there is a clear link between allergen exposure, ICAM-1 expression, allergic inflammation and RI. In addition, treatments with drugs able to reduce ICAM-1 expression diminish both the number and severity of RI in allergic children [17].

Infectious diseases (ID) of RI and the gastrointestinal (GI) system are frequent and constitute a demanding challenge for the physician [18]. Moreover, ID represent a social problem concerning both the pharma-economy and the impact on the social milieu of the subject, mainly during journeys or conducting heavy work. Recently, it has been shown that allergic children have more numerous and severe RI diseases than non-allergic children [19]. More recently, these data have also been confirmed in adults with AR [20].

Response to specific immunotherapy

AR is characterized by inflammatory reaction displaying a predominant Th2 cell profile with greater interleukin (IL)-4

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production than IFN-γ expression by Th1 cells: the so-called Th2 polarization. AR management includes patient education, allergen avoidance, drug therapy and, when appropriate, allergen-specific immunotherapy (SIT) [21]. SIT is the practice of administering gradually increasing doses of the causal allergen in order to reduce allergic symptoms and the need for medication. Treatment efficacy depends upon achieving clinical tolerance of the causal allergen. There is evidence that SIT is effective in patients with allergic rhinitis and mild forms of asthma, as stated in a World Health Organization (WHO) position paper [22].

SIT is based classically on the subcutaneous administration of allergen extracts (SCIT) sublingual (SLIT). The rationale of SLIT is that oral administration of high-dose allergens may reduce and prevent IgE responses. Methodologically, the extract is kept under the tongue for a few minutes and then swallowed: the 'sublingual-swallow'.

The exact SIT mechanism of action is not understood completely [23]. SCIT has been in practice for many years, and several studies have shown that subcutaneous administration of the allergen induces hyposensitization by redirecting peripheral and mucosal Th2 responses to a prevalent Th1 polarization. However, regarding SLIT, only few studies have demonstrated that it was able to increase allergen-driven IFN-γ production. Moreover, a number of recent studies indicate that regulatory T cells (T_{regs}) play an important role in controlling the Th2-biased response [24]. Indeed, a defect in T_{regs} has been proposed by one study in allergic subjects [25]. Very recently, also with regard to SLIT, it has been found that the appearance of allergen-specific tolerance induction is shown by restored allergen-specific IL-10 and IFN-γ production [25]. On the other hand, only two studies have reported decreased allergen-induced Th2-dependent cytokine (IL-4 and IL-13) production after SLIT [26,27].

Relationship with adiposity

There is evidence that the prevalence of allergic disorders, such as rhinitis and asthma, has increased globally in developed countries. Even though several environmental factors have been hypothesized to be involved in the development of allergic diseases, none could explain fully the rapid increase in prevalence. However, some lifestyle factors, including diet, alcohol consumption, physical inactivity and obesity, have recently gained recognition. Indeed, the increase in affluence, typical of western societies, may result in the increased availability of foods and decreased physical activities, both of which may contribute to promote the prevalence of obesity and overweight. In addition, there is evidence that obesity and overweight are linked with allergic diseases, probably because of the immunogical effects of adipose tissue on the development of allergies. Obesity has been associated with an increased risk of asthma both in children and adults [28,29]. However, the real association between obesity and allergic disorders is unclear. Many cross-sectional surveys have pointed out that obesity is a risk factor for asthma, but prospective studies to define the chronological relationship between obesity and asthma are lacking. Moreover, a gender-dependent influence was observed and a significant association between body fat and asthma in women, but not in men, was found [30].

Furthermore, only two studies have investigated the effects of obesity on allergic rhinitis. The first study, conducted on a large cohort of 1 247 038 Swedish military conscripts, reported that obesity was not associated with allergic rhinitis in patients with only nasal symptoms [31]. The second study showed that the risk of allergic rhinitis increased with increasing body mass index (BMI) among women, but not among men [32].

On the other hand, the association between obesity and respiratory allergy may, at least partially, depend upon decreased immunological tolerance to allergen as a consequence of immunological changes induced by adipokines, such as adiponectin and leptin, and some proinflammatory cytokines, including IL-6 and TNF-α, secreted by white adipose tissue (WAT). Therefore, an increase in WAT is characterized by chronic inflammation that skews the immune system towards a Th2 polarization, typical arrangement of allergic patients.

Effects on QoL

QoL evaluation represents an important step in the study of allergic rhinitis concerning both clinical and therapeutic trials [33]. However, the impact of clinical, immunological and functional aspects on QoL has been investigated recently in a study by Ciprandi *et al.* [34]. QoL values are associated with many aspects of allergic rhinitis, concerning mainly allergic inflammation (eosinophils and recovery to decongesting), immune response to allergens (sensitizations) and individual clinical status (symptom severity).

Differences in QoL or strength of the association between patient characteristics and QoL is generally largest for the eye symptoms scale. This aspect highlights the importance of eye symptoms associated with allergic rhinitis, as they are frequently most annoying and irritating.

Moreover, multivariate analysis has identified that a number of sensitivities and eosinophils count as independent determinants of QoL (globally and for some scales) and baseline nasal flow as an independent determinant of the eye symptoms scale. Therefore, QoL appears to be dependent upon the degree of immune response to allergens.

Allergic inflammation

Allergic rhinitis is characterized by a Th2-polarized inflammation. Th2-derived cytokines, such as IL-4 and IL-13, are the primary pathogenic factors in inducing, maintaining and amplifying inflammatory allergic inflammation. IL-4 and IL-13 orchestrate allergic inflammation promoting IgE

synthesis, up-regulating adhesion molecules selective for eosinophil recruitment and causing increased mucus production and airway hyperreactivity [35].

On the other hand, there is accumulating evidence that Th1-related cytokines, such as IFN-γ and IL-12, may suppress and counteract this Th2 response, and vice versa, as there is a functional dichotomy between Th1 and Th2 cells [36]. Moreover, T_{regs} play a crucial role in the balance of T cells [37] as well as several cytokines exerting pathogenic activities [38].

Conclusions

AR, even though not a serious illness, may be a clinically relevant disorder because it may present numerous complications and affect QoL, as reported in this review. Therefore, the management of AR patients should be rigorously careful and multi-disciplinary.

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