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Editorial

The nose – from symptoms to evidence-based medicine

J. Mullol[1,2], A. Valero[3] I. Alobid[1]

[1]Unitat de Rinologia i Clínica de l'Olfacte, Servei d' Otorinolaringologia, Hospital Clínic i Universitari. Barcelona; [2]Unitat d'Al.lèrgia, Servei de Pneumologia I Al.lèrgia Respiratòria, Hospital Clínic i Universitari. Barcelona; [3]Immunoal.lèrgia Respiratòria Clinica i Experimental, IDIBAPS, Barcelona, Spain

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Introduction

Rhinologic inflammatory diseases affecting the nose and paranasal sinuses, mainly rhinitis and rhinosinusitis, constitute a global health problem causing major illness and disability in Europe and worldwide. Patients from all countries, ethnicities and age groups suffer from these diseases, affecting their quality of life and causing important socioeconomic impact. Two main guidelines have recently been produced and disseminated: Allergic Rhinitis and its impact on Asthma (ARIA) (1) and the European Position Paper on nasal Polyps and rhinoSinusitis (EP^3OS) (2) which will be updated in 2007 (Fig. 1).

The current issue of *Allergy* reports five papers in the rhinology field that will be evaluated and discussed below. Three original articles discuss (i) the importance of scoring rhinitis severity by the visual analog scale (VAS) (3); (ii) the role of asymptomatic skin sensitization in developing allergic rhinitis (4), and (iii) rhinoconjunctivitis epidemiology in children (5). One meta-analysis strengthens the evidence (from Ib to Ia) of desloratadine in allergic rhinitis (6); and one magnificent review reports on the cellular mechanisms in nasal polyposis and their therapeutic implications (7).

Assessment of rhinitis severity by VAS

The ARIA guidelines (1) classify allergic rhinitis as intermittent or persistent, based on the duration of symptoms, and as mild or moderate/severe, based on both impairment of quality of life (sleep, work/school productivity, daily activities, and leisure) and bothersome symptoms. Since its first publication, several studies have been conducted to validate the ARIA classification, both in duration (8–10) and severity (11, 12). However, investigators and clinicians are still searching for a simple and sensitive tool to enable the classification of the severity of patients with allergic rhinitis.

The VAS has been used to quantitatively measure the intensity of symptoms as well as disease severity. Using VAS, patients are asked to cross a line of 10 cm (or 100 mm), 0 being the lowest and 10 (or 100) the highest level of the assessed variable (symptom or disease). VAS scales have been extensively validated for a variety of chronic diseases such as anxiety (13) or pain (14). In the rhinology field, the European Consensus on Rhinosinusitis and Nasal Polyps (15) and the American Taskforce on Practice Parameters (16) have recently proposed the use of a VAS to classify the severity of rhinosinusitis and allergic rhinitis, respectively.

In the present issue of *Allergy*, Bousquet et al. (3) present a study where the severity of rhinitis is quantitatively evaluated by VAS and by quality of life (RQLQ). After studying 3052 rhinitis patients in a primary care setting, the authors report a higher impact of rhinitis severity than symptom duration on VAS levels. Severity of rhinitis, both treated and untreated, could be classified as 'mild' when VAS scored under 5 cm and 'moderate/severe' when VAS scored over 6 cm. The study also confirms a strong correlation of rhinitis severity measured by VAS and its impact on the quality of life. The authors finally propose a VAS cut-off point of 5 cm to discriminate between 'mild' and 'moderate/severe' allergic rhinitis patients, concluding that VAS is a simple, quantitative, and reliable tool that can be used in primary care to assess the severity of treated and untreated allergic rhinitis patients.

Asymptomatic sensitization and allergic rhinitis development

The skin prick test is considered to be a sensitive, inexpensive test that simply and safely diagnoses IgE sensitization to aeroallergens (17). It is common for

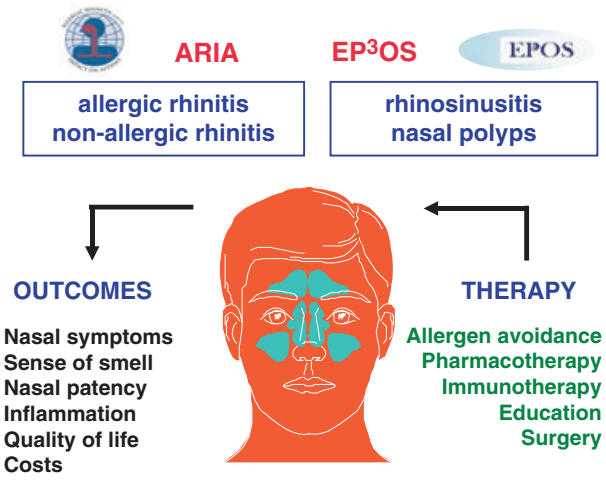

Figure 1. Potential diagnostic and research outcomes, and treatment options for inflammatory diseases of the nose and paranasal sinuses. Two recent guidelines cover the field of rhinology for both rhinitis (ARIA) and rhinosinusitis (EP^{3}OS).

subjects with a positive skin test or serum-specific IgE to aeroallergens to present symptoms of rhinitis and/or asthma. However, one group of sensitized subjects remains asymptomatic while others, sensitized to various allergens, only present symptoms when exposed to a specific allergen (18). It has been hypothesized that those patients could belong to an intermediate clinical entity, somewhere between nonatopic and clinical allergy.

Patients with asymptomatic skin sensitization are frequently found in both epidemiological studies and clinical life, but few studies have addressed this problem. Using a standard panel of aeroallergens, asymptomatic subjects with skin sensitization range from 8% to 30% (19). It has been demonstrated that AS subjects have a greater risk of developing respiratory symptoms and this risk increases as the years pass (18–20).

Research is being carried out on the characteristics and mechanisms in order to explain why sensitized subjects do not present respiratory symptoms by means of skin tests and specific positive IgE tests (21, 22). Nonsymptomatic subjects have a reduced papular response to skin tests and a lesser degree of specific IgE. They need a greater concentration of allergen in conjunctival provocation to produce positive results. They also present a smaller amount of allergen-specific T cells, a decreased allergen-induced $CD4^+$ memory T-cell proliferation, as well as a diminished number of chemokine receptors that needs to be carried out in order (CCR4), IL-8 receptor (CXCR1), and L-selectin (CD62L)-positive memory T cells. A change in immunological sensitivity, as indicated by allergen-induced memory T-cell proliferation, could be an early and strong predictor for the subsequent development of allergy in asymptomatic sensitized individuals.

Assing et al. (4) have studied the appearance of clinical manifestations using a symptom registry card. This study was carried out during the pollination period of grasses and birch on asymptomatic sensitized patients who had not reported any symptoms during the previous year. The study illustrates the difficulties involved in evaluating symptoms in a specific season without a daily record, as a retrospective evaluation of symptoms is neither a reliable and accurate method, nor the right way to evaluate the conversion of asymptomatic sensitized subjects into symptomatic patients. The recording of symptoms resulted in a fivefold reduction in the conversion of asymptomatic subjects into symptomatic patients (14.1–2.6%). In conclusion, it is of great importance to determine the intervention that needs to be carried out in order to prevent asymptomatic sensitized subjects from developing symptoms. The potential role of allergen avoidance should also be determined.

Rhinoconjunctivitis epidemiology in children

The prevalence of allergic rhinitis is 10–30%. The greatest frequency is found in children and adolescents, 70% of cases beginning before the age of 30. In recent years, its prevalence has increased in the pediatric population (1, 23, 24). Few studies have been carried out to investigate its distribution, risk factors, and natural history in the first decade of life.

The interrelationship between rhinitis and asthma has been demonstrated from the physiopathological, clinical, and therapeutic viewpoints (25). In an 8- to 11-year follow-up study on 154 children aged 3–17, Linna et al. (26) reported that 19% of the cases developed asthma. Frequency was higher in children with perennial (34%) as compared to seasonal (13%) allergic rhinitis. Arshad et al. (27) found that 50% of 4-year-old children sensitized to mites had asthma, while the percentages were 44%, 42%, and 32% for those sensitized to cat, grasses, and alternaria, respectively. Masuda et al. (28) also demonstrated the comorbidity between rhinitis and asthma in children, showing that rhinitis usually precedes the appearance of asthma. They found that 82% of the children with asthma suffered from persistent nasal symptoms, with an average onset age of 3.2 and 4 years, respectively.

Marinho et al. (5) report the prevalence and risk factors for suffering from rhinitis and rhinoconjunctivitis at the age of 5. The reported prevalence is 26% for rhinitis and 12% for rhinoconjunctivitis, suggesting a significant coexistence with the presence of asthma and eczema. Half the children with rhinoconjunctivitis were not sensitized to aeroallergens. In contrast to other studies (29, 30), rhinitis did not seem to affect the severity and frequency of sibilants or bronchial hyper-reactivity, neither did the presence of sibilants affect the severity of rhinitis. These findings suggest that at this age there is no association between nasal and bronchial symptoms. In light of these data, there is a need for research to ascertain whether the interrelationship and natural history of rhinitis and asthma may differ according to the age of onset of symptoms.

Evidence Ia for desloratadine in allergic rhinitis

Shekelle et al. (31) established the basis for categorizing the levels of evidence-based medicine with the main objective of developing guidelines. The two main levels of evidence are Ib (evidence from at least one randomized controlled trial, RCT) and Ia (evidence for meta-analysis of RCT). Although RCT and meta-analysis are the designs of choice for evaluating the effectiveness of health care interventions, they are not immune to bias (32, 33).

Nonsedating second-generation antihistamines constitute a first-line therapy for both intermittent and persistent allergic rhinitis while first-generation antihistamines are not recommended by guidelines (34). Desloratadine, a second-generation nonsedating antihistamine, improves allergic rhinitis symptoms, including nasal congestion (35), also produces further antiallergic properties (36).

In this issue, Canonica et al. (6) report a meta-analysis of the desloratadine profile on allergic rhinitis by measuring five different outcomes – total symptom score, total nasal symptom score, nasal airflow, nasal eosinophils, and nasal IL-4. Other outcomes, including quality of life, were not included due to an insufficient size of the patient population. From the potential 57 relevant trials on desloratadine in allergic rhinitis, only 13 (3108 patients) parallel-group, randomized, controlled, and double-blinded trials were included in the meta-analysis, rated using the Jadad scale (37), and scored out of a maximum of 5. Desloratadine was associated with significant improvement in total symptom and total nasal symptom scores as well as nasal airflow. Concerning inflammatory markers, desloratadine was associated with an improvement in nasal eosinophilia but not in nasal IL-4. No differences were found when desloratadine was compared with other second-generation antihistamines in all the measured outcomes of allergic rhinitis. In conclusion, this meta-analysis strengthens the evidence for the existing profile of desloratadine in allergic rhinitis from Ib to Ia.

Implications of inflammatory mechanisms in nasal polyp therapy

Inflammatory mechanisms

Although insights into the pathophysiology of nasal polyps (NP) have largely expanded over the last decades, Rinia et al. (7) conclude in their review that the exact etiology and mechanism of persistence is still unrevealed. IL-5 may represent an important cytokine responsible for the delay of the death process in eosinophils in NP (38). IL-5 was found to be increased in NP compared to healthy controls, and the concentration of IL-5 was independent of the atopic status of the patient (39). It has also been demonstrated that other cytokines such as GM-CSF, TNF-alpha, IL-8, RANTES and eotaxin may also be involved in the promotion of eosinophil chemotaxis, survival, and degranulation (40). Cheng et al. recently reported the relationship between oxidative stress and eosinophils, concluding that free radical levels in PN tissues are associated with severity and with bronchial hyperresponsiveness/asthma (41). Pérez-Novo et al. showed that the presence of specific IgE to *Staphylococcus aureus* enterotoxins (SAEs) is related to the severity of eosinophilic inflammation (42). Analysis of specific IgE revealed a multiclonal IgE response and IgE antibodies to SAEs in about 30–50% of patients and in about 60–80% of NP subjects with asthma. The expression of different mucin profiles may also be of importance in NP inflammation (43).

Therapeutic options

Intranasal corticosteroids can be used, as a long-term therapy, alone in mild cases or together with systemic corticosteroids and/or surgery in severe cases to improve nasal symptoms and patients' quality of life (15, 44). It has recently been reported that a short course of oral corticosteroids causes clinical improvement in NP patients (45), and that this effect can be maintained by long-term intranasal steroids (46). Intranasal corticosteroids are safe and significantly efficient compared to placebo, in reducing polyp grade and in improving nasal symptoms and may delay the need for surgery (47). While some studies stated that intranasal amphotericin B may benefit patients with NP (48), a European multicentric, randomized, and placebo-controlled study has recently demonstrated that amphotericin B nasal lavages are ineffective in the treatment of patients with NP (49). In addition, a recent study has demonstrated that anti-IL-5 treatment reduces NP size and nasal IL-5 levels (50).

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