

Allergy and asthma: from the bedside to the bench and international actions

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Abstract: The interdependence of the bench to the bedside has been demonstrated for many years. The example in allergy and asthma has been used to show how clinical observations can be dissected by epidemiologic and basic scientific studies leading to a better concept of rhinitis, asthma and their comorbidities. From research, public health programs can be designed.

Key words: Allergic Rhinitis and its Impact on Asthma, allergy, asthma, Global Alliance against chronic Respiratory Diseases

The interdependence of the bench to the bedside has been recognized for a long time [1]. Many important discoveries in medicine have been driven by clinical questions and basic and clinical research are mutually synergistic. To achieve the greatest benefits, observations must flow both ways. However, it is also of importance to expand the knowledge obtained from these interactions to international public health actions.

In the present paper, the interactions between rhinitis and asthma will be developed to show how a clinical observation lead to a better understanding of comorbidities and to an international program.

The clinical observation

In 1990, a 59-year old woman with severe asthma (forced expiratory volume in one second [FEV₁] 50% predicted values) was treated by 60 mg prednisolone for 7 days, beclomethasone dipropionate (1000 µg daily) and salbutamol prn. A month later she came back for reassessment. She had no asthma symptoms and her FEV₁ was 90%. However, she complained "I am not satisfied because, now, I have rhinitis". A few other examples similar to this one lead us to think that rhinitis was a disease with a life style impact and that there was a link between the nose and the lower airways.

Clinical and basic research

Firstly, quality-of-life was studied in patients with asthma or rhinitis and quality of life has been found to be impaired

both in patients with asthma and in patients with allergic rhinitis [2,3]. The relative burden of these diseases has been studied using the generic SF-36 questionnaire in the European Community Respiratory Health Survey (ECRHS), a population-based study of young adults [4]. Patients with both asthma and allergic rhinitis experienced more physical limitations than patients with allergic rhinitis alone, but no difference was found between these two groups for concepts related to social/mental health. Subjects with asthma without rhinitis could not be studied since their number was too low. However, it seems that impairment in social life in asthmatics may be attributable to nasal symptoms.

Epidemiologic studies have consistently shown that asthma and rhinitis often co-exist in the same patients [5]. The majority of patients with asthma present seasonal or perennial allergic rhinitis symptoms. However, it has been shown that perennial rhinitis was a factor independent of allergy in the risk for asthma. Rhinitis usually occurs in over 65% of patients with allergic asthma and in over 80% of patients with non allergic asthma (for review see [5,6]).

Nasal and bronchial inflammation were studied in patients with asthma. The recent progresses achieved in the cellular and molecular biology of airways diseases has clearly documented that inflammation plays a critical role in the pathogenesis of asthma and rhinitis. The same inflammatory cells appear to be present in the nasal and bronchial mucosa. A growing number of studies show that the inflammation of nasal and bronchial mucosa is sustained by a similar inflammatory infiltrate, which is represented by eosinophils, mast cells, T-lymphocytes and cells of the monocytic lineage [7,8].

For more than 70 years, the coexistence of asthma and rhino-sinusitis has been noted in the medical literature [9,10]. The debate still remains as to whether rhinosinusitis is a precipitating factor for bronchial asthma. In light of current knowledge, it seems that rhinosinusitis and asthma are linked by a common process that is mainly inflammatory, and, central to the pathogenesis is the role of eosinophils and airway

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epithelium. In a study comparing mild-moderate asthmatics with corticosteroid-dependent asthmatics, the proportion of patients with symptoms of rhinosinusitis was similar in both groups (74% in corticosteroid-dependent asthma and 70% in mild-moderate asthma) [11]. The clinical and CT-scan scores were higher in severe asthmatics.

These studies and many others have led to the concept that the nasal and bronchial mucosa present similarities and most patients with asthma also have rhinitis [12] suggesting the concept of "one airway one disease". However, not all patients with rhinitis present with asthma and there are differences between rhinitis and asthma [8,10]. Thus, a large information and dissemination concerning these links was proposed by ARIA (Allergic Rhinitis and its Impact on Asthma).

ARIA

In 1999, during the ARIA World Health Organization (WHO) workshop, an evidence-based document was produced using an extensive review of the literature available up to December 1999 [5]. The statements of evidence for the development of ARIA have followed WHO rules and were based on those of Shekelle et al [13].

The ARIA document was intended to be a state-of-the-art for the specialist as well as for the general practitioner and other health care professionals to update their knowledge of allergic rhinitis and to highlight the impact of allergic rhinitis on asthma. An update of the ARIA guidelines was, however, needed because:

- a large number of papers have been published within the past 7 years extending our knowledge [14-19]
- the ARIA classification was proposed by an expert group and needed to be validated in terms of classification and management [5]. New studies showed consistently that "intermittent" and "persistent" are not synonymous of "seasonal" and "perennial" [20,21]. There are now several reports which have validated this classification [22,23] although some authors proposed to extend the severity of allergic rhinitis to three levels [24,25]. However, since this would not lead to a difference in treatment, the ARIA experts proposed to continue to classify the severity of rhinitis into "mild" and "moderate/severe"
- moreover, there were gaps in our knowledge in the first ARIA document which were more recently approached. These include:
 - some aspects of treatment like complementary and alternative medicine [15]
 - sports and rhinitis in athletes [16,26,27]
 - rhinitis and its links with asthma in children [28-32].

The ARIA update was started in 2004. Several chapters of ARIA were extensively reviewed using the Shekelle evidence-based model, and papers published in peer-reviewed journals: tertiary prevention of allergy, complementary and alternative medicine, pharmacotherapy and anti-IgE treatment, allergen-specific immunotherapy, links between rhinitis and asthma and mechanisms of rhinitis [14-19]. There was then

a need for a global document which would highlight the interactions between the upper and the lower airways including diagnosis, epidemiology, common risk factors, management and prevention. Moreover, the allergy perspective should also be targeted to developing countries [33,34]. The ARIA 2008 has been recently published [35].

The grading of evidence and recommendation for management evidence-based system of the ARIA 2008 update does not use the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach [36,37]. It is expected that some of the recommendations offered by the ARIA 2008 may differ when the GRADE approach will be achieved.

However, ARIA only considered the links between rhinitis and asthma and a more global program was needed in chronic respiratory diseases.

GARD

Chronic respiratory diseases (CRD) are chronic diseases of the airways and the other structures of the lungs. Major preventable CRD include asthma and respiratory allergies, chronic obstructive pulmonary disease (COPD), occupational lung diseases and pulmonary hypertension.

Preventable CRD are a major global health problem. Over 1 billion people of all ages, in all countries throughout the world, are affected by preventable CRD. More than half live in developing countries or deprived populations. The prevalence of preventable CRD is increasing everywhere and in particular in children and old age people.

The burden of preventable CRD has major adverse effects on the quality of life and disability of affected individuals; they cause premature death; create large adverse and underappreciated economic effects on families, communities and societies in general. The WHO and the World Bank have estimated that 4.6 million people with CRD will prematurely die in 2005, and they have projected that the global burden of CRD will considerably increase in the future.

Many risk factors for preventable CRD are identified and efficient preventive measures can be proposed. Tobacco smoking in both developed and developing countries, indoor air pollution particularly in developing countries, allergens, occupational agents, some diseases such as schistosomiasis or sickle cell disease cause preventable CRD. Prevention of these risk factors will have a significant impact on patient's morbidity and mortality.

Yet, preventable CRD and their risk factors receive insufficient attention from the health care community, government officials, patients and their families as well as the media.

The Fifty-Third World Health Assembly recognized the enormous human suffering caused by chronic diseases and requested the WHO Director General to give priority to the prevention and control of chronic diseases, with special emphasis on developing countries (WHA resolution 53.17, May 2000, endorsed by all 191 WHO Member States). This led to the formation of the WHO Global Alliance against Chronic Respiratory Diseases (GARD) [38,39].

The goal of GARD is:

- to propose a stepwise and integrated program on the prevention and control of preventable CRD and respiratory allergies taking into account co-morbidities
- by improving the collaboration between the fragmented WHO and non-WHO programs
- in order to increase awareness on CRD, to decrease the burden of CRD, and to foster country focused initiatives according to the special needs of each country
- with a special emphasis on developing countries and deprived populations
- in addition, there is an important need to assure the availability of low cost, affordable medications and spirometry for all CRD patients, and appropriate training of health care providers is essential.

The health priorities, the geographic variability in risk factors and CRD, the diversity of national health care service systems and variations in the availability and affordability of treatments require that any recommendation should be adapted to ensure their appropriateness in the community they are applied.

Clinical observations are essential to better understand diseases. The recognition of the links between rhinitis and asthma have lead to clinical, epidemiological and basic research which confirmed that patients with asthma should be considered for rhinitis and patients with rhinitis should be considered for asthma. However, these links, when demonstrated, need to be publicized and this was done through ARIA and subsequently GARD. These initiatives have a single goal: to improve patient's care.

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