

Phenotyping of Allergic Rhinitis

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Abstract Allergic rhinitis (AR) is characterized by immune-mediated inflammation of the nasal mucosal lining. Although this chronic disease is not fatal, it is associated with many debilitating symptoms. Like many other chronic diseases, AR has a wide range of clinical aspects, and comorbidities such as asthma, rhinosinusitis, dermatitis, and conjunctivitis may accompany the disease to different degrees. These comorbidities and features determine the clinical phenotypes of AR. Different phenotypes and other characteristics of AR are discussed in this review. It is important for clinicians to be aware of these variable clinical phenotypes of AR to diagnose and treat the disease properly.

Keywords Allergic rhinitis · Nonallergic rhinitis · Mixed rhinitis · Asthma · Phenotypes · Quality of life · Genetic · Environmental · Prevalence · ARIA · Treatment

Introduction

Allergic rhinitis (AR) is characterized by an IgE-mediated inflammation of the nasal mucus membranes [1]. Triggering allergens vary in a wide spectrum from house dust mites to ragweed [2]. Once a patient is sensitized by the allergen,

repeated exposures result in allergic symptoms. Symptoms are related to the inflammatory edema of the nasal mucosal linings and stimulation of the nerve endings by preformed or newly produced chemicals, which are degraded by the inflammatory cells. Watery nasal discharge, nasal obstruction, sneezing, and itching of the nose are the main symptoms. Among these symptoms, the most debilitating is nasal obstruction [3]. Nasal obstruction is also related to sleep disturbance, which results in poor quality of life (QoL). The economic burden of AR also has importance due to its biological and social impacts. In the wide spectrum of allergic diseases, AR has unique characteristics and may be the most bothersome of all. Like many other chronic diseases, AR has multifactorial etiologic aspects. Various genetic and environmental factors give rise to the pathophysiologic mechanisms of AR. In the pathophysiologic pathway of AR, each step has its own molecular and structural properties. Although those biological molecules (eg, immunoglobulins, chemokines) and inflammatory cells are not different among sensitized individuals, the manifestations of AR differ from patient to patient, and eventually, AR expresses various clinical phenotypes. From a clinical point of view, many questions must be answered. For example, why do some AR patients have bronchial hyperresponsiveness (asthmatic reactions) and have primarily nasal obstruction instead of having a runny nose? On the other hand, AR can appear at a younger age in some individuals than others, so why is the age at onset different? The indicators of QoL can be worse in some patients. This means some of the AR patients have more serious debilitating symptoms than others. Why are these clinical phenotypes different among the affected patients? To answer these questions, first we have to explain what phenotype means. A phenotype of an organism is its observable characteristics that, basically, are influenced by genetic and environmental factors. To identify the reasons (ie, genetic and environmental) is not the primary goal of this article, because previous studies indicated and future studies are likely to

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indicate responsible “specific” genes and other factors in the future. In this review, we aim to educate physicians (otorhinolaryngologists, primary care physicians, pulmonologists, allergists, family doctors, dermatologists) who are interested directly or indirectly in AR about the different clinical phenotypes of the disease.

Prevalence of Allergic Rhinitis by Age and Gender

In adults, the prevalence of AR may vary according to geographical areas. A recent prevalence study indicated different results (eg, Italy, 17%; Belgium, 29%; Spain, 21.5%) across Europe [4]. The increasing prevalence of allergic diseases is attributed to civilization and industrialization. Food additives, chemical agents, vast shifts in lifestyle, diet and consumer products, as well as air pollutants are the major causative factors for this relative increase during the past century, especially after World War II [5]. AR can manifest at any age, but most patients develop the condition before the age of 30 [6]. AR is not common in preschool children. The prevalence of the disease has been reported to be 5% to 9.6% [7, 8] and 7.2% to 8.5% [9, 10] at ages of 4–5 and 6–7 years, respectively. In a prospective cohort study, Crump et al. [11] concluded that prematurity is associated with a decreased risk of AR later in life, possibly because of a protective effect of earlier exposure to environmental pathogens. Results of another prospective cohort study point out that some phenotypic features, such as “positive allergy test, recurrent wheeze, eczema, heredity and male gender” are independent risk factors for AR at 4.5 years of age [12]. Another spectacular finding of this study is the protective effect against AR of the early introduction of fish (at preschool age). This finding is supported by previous reports of a reduced risk of allergic disease following a high fish intake during pregnancy and infancy [8, 13, 14]. Among adults, males and females are equally affected, but a male preponderance exists among the pediatric population. As mentioned previously, Alm et al. [12] showed the male preponderance of AR at preschool age [12]. In a prospective cohort study, Bertelsen et al. [15] observed a female preponderance, especially to indoor allergens. In this study, cat and dog allergens were the major ones found to have significant association with girls rather than boys. The authors suggested that a higher allergen level could be related to the tendency of girls to decorate their bedrooms with plush animals, fluffy pillows, and carpets, which may act as reservoirs [16, 17].

Subtypes of Allergic Rhinitis Patients

From the symptomatic perspective, AR patients may be subdivided into “runners” and “blockers,” according to the characteristics of their nasal complaints. Although some of them

have nasal blockage predominantly, others have nasal discharge. Various clinical trials have reported the direct relationship of these phenotypic varieties with poor QoL in AR patients [18, 19]. The pathophysiologic mechanism of nasal obstruction in AR is primarily related to a combination of early- and late-phase inflammatory reactions [20•]. In early response, histamine is the major inflammatory molecule that dominates the vascular leakage and early mucosal swelling. In addition, leukotrienes, prostaglandins, tumor necrosis factor- α , and interleukin-4 have a role in this congestive process [21]. During the late-phase inflammatory response, cellular infiltration mainly exacerbates the mucosal congestion [20•]. When examining “runners” (the patients who have nasal discharge or rhinorrhea), evaluation of the ultrastructural properties associated with this symptom point out differences between healthy and allergic individuals (perennial). Riccio and Proud [22] have shown the different effects of bradykinin stimulation in healthy, nonallergic, and allergic rhinitis subjects. In this study, investigators showed increased lactoferrin levels in the increased secretions of patients with perennial AR [22]. This finding suggests that there is enhanced glandular secretion in patients with AR compared with healthy individuals.

Classification of Allergic Rhinitis and Therapeutic Approaches

With considerable variations in clinical practice and phenotypes, clinicians are faced with the uncertainty of different therapeutic options. During the past few decades, the classification of AR has changed to solve this problem. Traditional classification of disease (“perennial” and “seasonal” AR) has some insufficiencies. Thus, a new “functional” classification of AR was formulated by Bousquet et al. [23] as the ARIA (Allergic Rhinitis and its Impact on Asthma) system (Table 1). These different phenotypes (mild or moderate/severe) also determine the therapeutic approach directed toward the patient. With this new system, a focus on both severity and duration of symptoms has become sentinel. The validation of the ARIA system has been studied in various clinics for adults [24–26] and pediatric population [27•]. In this classification system, AR patients are subdivided based upon the duration/chronicity of symptoms as “intermittent” (symptoms <4 d/wk or for <4 wk/y) or “persistent” (symptoms >4 d/wk and for >4 wk/y) as well as the severity of the symptoms as “mild” (symptoms do not affect sleep status, normal daily activities, or work and school performances, and symptoms are not troublesome) to “moderate to severe” (symptoms impair sleep status, daily activities, or work and school performances, and symptoms are troublesome). This classification has a direct relationship to the patient’s QoL.

Table 1 ARIA (Allergic Rhinitis and its Impact on Asthma) classification system

Symptom severity		Symptom duration	
Mild	Moderate/severe	Intermittent	Persistent
No sleep disturbance	Sleep disturbance	Symptoms appearing <4 d/wk or for <4 wk	Symptoms appearing >4 d/wk and for >4 wk
Daily activities and school performance not affected	Impairment of daily activities		
No bothersome symptoms	Impairment of school performance		
	Bothersome symptoms		

Asthma and Other Comorbidities

Probably the most important aspect of AR is its comorbidities, such as asthma, sinusitis, dermatitis, and conjunctivitis. Among these comorbid diseases, asthma has a unique importance because of its morbidity and effects on QoL. Although these two diseases often occur together, the exact cause of this common state is still a matter of debate. In fact, during the past several decades, many researches have tried to answer this question. Answers could present an opportunity to clinicians to prevent asthma development. Prevalence studies reveal that approximately 15% to 40% of rhinitis patients have an asthmatic phenotype. The risk is higher (~25%–40%) if the patient has more severe (or persistent) disease; however, risk is less (~10%–15%) when the patient has mild (or intermittent) disease [28]. A recent genetic study regarding this issue highlighted the molecular basis of this relationship. In this study, Ku et al. [29•] suggest that the CC16 38A/38A (Clara cell secretory protein- CC16, secretoglobin 1A1) genotype plays a role in the development of early asthma in children with AR. It is likely that more genetic variables are waiting to be described. In another cohort, Rochat et al. [30] observed 1,314 healthy newborns from birth to 13 years of age. They found that “children who have AR in preschool age are at risk for developing wheezing between the ages of 5 and 13” [30]. On the other hand, a genetic aspect is not the only reason, as environmental factors also influence this relationship—the so-called gene–environment phenomenon. For example, patients who are sensitized to perennial allergens have a greater risk of developing asthmatic phenotype than patients who are sensitized to seasonal pollens [31]. However, it is still unclear whether polysensitized (sensitized to more than one allergen) patients have a more severe phenotype and more comorbidities than those who are sensitized to one allergen. Precise description of the relationship between AR and asthma has an important role in adequate treatment of allergic airway diseases. These studies that are attempting to determine the risk of developing an asthmatic phenotype in AR patients are also critically important. In the future, the opportunity to determine which AR patients will have the asthmatic phenotype will allow physicians to potentially intervene to prevent disease development.

Allergic, Nonallergic, and Mixed Rhinitis

As a major group of chronic rhinitis, AR is a common chronic respiratory problem that is associated with significant health care costs to society. However, we have limited knowledge of the clinical characterization of these rhinitis subtypes. The Joint Task on Practice Parameters in Allergy, Asthma and Immunology reports estimated that 43% of chronic rhinitis patients have AR, 23% have nonallergic rhinitis (NAR), and 34% have mixed rhinitis (MR) [32]. MR, which refers to patients with AR and NAR, is a distinct phenomenon and should be included in the differential diagnosis of all physicians when approaching the rhinitis patient because this AR phenotype has a different treatment modality than IgE-mediated AR alone. In general practice, physicians also tend to diagnose all rhinitis patients as having AR because they usually have more knowledge about AR than MR or NAR. Moreover, media advertising has an important effect on this bias. Actually, we have limited clues as to how to make a precise distinction between these phenotypes. For example, the main complaints of rhinitis are nasal congestion, postnasal drainage, and rhinorrhea, and physical examination findings are generally not useful in making a distinction. For this purpose, the physician must ask about detailed patient history, specifically onset of complaints, duration, severity, and frequency of symptoms; indoor and outdoor triggers; and previous history about medication, comorbidities such as asthma, and family history of allergy. This inquiry is the key to aid in differentiation between AR and the mixed phenotype. The relationship between symptoms and nonallergic environmental triggers such as perfumes, smoke, fragrances, and cleaning agents is a typical feature of MR [33]. An index score was developed to help clinicians make this distinction by examining possible nonallergic environmental irritants [34]. This scale has 21 questions regarding irritants and was completed by 650 individuals as part of a study. In this study, each participant was assessed by questioning for the rate of severity of his or her upper respiratory symptoms after exposure to specific irritants. Results showed that 15% had the pure AR phenotype, 15% had the pure NAR phenotype, and up to 70% had the MR phenotype [33]. These results also have

importance because of their objectivity regarding the impact of nonallergic triggers on upper respiratory symptoms [33].

Conclusions

AR is an important health problem in many ways. Various clinical phenotypes point out the diversity of its nature, which is basically formed by various genetic and environmental factors. Clarification of these factors is going to inform us more about it so that we may have the opportunity to treat AR patients properly. Not only do the symptoms that are associated with AR determine the sobriety of disease, but the comorbidities, such as asthma and rhinosinusitis, also have a serious impact on an individual's health status. The close relationship of AR with asthma carries the disease from simple upper respiratory tract abnormality to another important level according to the possible serious morbidities due to asthma. Various molecular, genetic, and clinical studies of AR are trying to define this relationship and thus trying to determine who specifically is at risk of developing asthma in the future. To predict those risky phenotypes is going to decrease all unwanted effects of AR on public health. From the clinical perspective, being aware of various phenotypes of AR will help clinicians treat this chronic respiratory problem appropriately.

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- Of major importance

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