

Defining phenotypes in rhinitis: A step toward personalized medicine

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Key words: *Phenotype, genotype, endotype, personalized medicine, allergic rhinitis, allergic asthma, environment, children*

The estimated prevalence of allergic rhinitis in the general population is 30%, making it the most common chronic disease in children. Allergic rhinitis is a serious public health problem because it is associated with high morbidity and heavy socioeconomic burden. In about one third of cases, it occurs with allergic asthma, constituting “united airway disease.”¹

After the revolution of evidence-based medicine supporting the development of many disease management guidelines, we are experiencing the revolution of personalized medicine. These 2 paradigms are not antagonistic but rather complementary. Personalized medicine is based on the principle that external stimuli (the environment) induce diverse clinical manifestations (phenotypes) mediated by distinct pathophysiologic processes (endotypes) in different subjects (genotypes).

Sir William Osler (1849-1919), renowned for his contributions to medicine, stated that “Medicine is both a Science and an Art.” To develop evidence-based guidelines is to practice medicine as a science. To apply such guidelines while treating individual patients with their various phenotypes, comorbidities, and social situations in a personalized manner is to practice medicine as an art. Guidelines are drawn based on scientific evidence generated by studies and are intended to unify the knowledge about a particular disease, standardizing disease management. They are important because they guide medical care and are applicable to a considerable proportion of patients. However, even in the context of well-controlled trials, drug response varies to a great extent among subjects,² and in the office not every patient matches the characteristics of those who participate in clinical trials. Therefore the physician needs to individualize management.

Rhinitis and asthma are currently regarded as syndromes or, at least, as diseases presenting several phenotypes. The 2 principal phenotypes are allergic and nonallergic airway disease, the former being most common and affecting 60% to 70% of adult patients and more than 90% of children. In patients with allergic airway disease, disease onset is early, progress is benign, other allergic comorbidities are usually present, the rate of hypersensitivity to

nonsteroidal anti-inflammatory drugs is lower, and inflammation is mediated by T_H2 inflammation and IgE to airborne allergens. The allergic phenotype can be further divided into local and systemic allergic disease. A recent follow-up study of local allergic rhinitis showed it to be a consistent entity not evolving to systemic allergic rhinitis.³ In those with nonallergic airway disease, neutrophilic infiltration is more common, but its pathophysiology is not completely understood and might include distinct subtypes. The classification of allergic and nonallergic airway diseases is not merely conceptual but has implications for prognosis and treatment.

Several classifications of rhinitis and asthma in phenotypes have been proposed. However, there is a high degree of subjectivity and little scientific basis in the description of some phenotypes, and not all of them have clinical relevance. Cluster analysis has been used to overcome these problems and better understand the different subtypes of the disease in asthmatic patients.⁴⁻⁶ In this approach an extensive list of clinical and laboratory characteristics are analyzed together through computerized mathematic algorithms, generating groups (clusters) of subjects with similar characteristics.

In this issue, for the first time, Kurukulaaratchy et al⁷ describe a cluster analysis without observer bias of young adults with rhinitis from the Isle of Wight Birth Cohort to identify phenotypes.⁸ This whole population birth cohort was established on the Isle of Wight (United Kingdom) in 1989 to study the natural history of allergic disease. Cluster analysis for rhinitis was performed when participants reached the age of 18 years, and 4 clusters were identified: moderate childhood-onset rhinitis, mild adolescent-onset female rhinitis, severe earliest-onset rhinitis with asthma, and moderate childhood-onset male rhinitis with asthma. Therefore the characteristics that distinguished the young adults with rhinitis and separated them into clusters were sex, the presence of asthma, and the severity and age of onset of rhinitis. Seasonal allergic rhinitis predominated in all clusters, and atopy was a marker of increased disease severity.⁷ In contrast, in asthmatic patients atopy or total serum IgE levels are associated with asthma severity only in children, whereas in adults disease severity is associated with nonatopic asthma.^{9,10}

In the study of Kurukulaaratchy et al,⁷ more severe and earlier-onset rhinitis was associated with asthma. Furthermore, asthma onset consistently predated rhinitis onset, as described in the atopic march.¹¹ These findings are important and relevant, and it must be emphasized that rhinitis is still poorly recognized by patients and physicians. Patients with early-onset rhinitis should be indentified during childhood to reduce morbidity and prevent the development of more severe airway disease.

However, the results of this study cannot be extrapolated to all ages or to different geographic regions with different levels and types of aeroallergens. For example, in older adults there are higher prevalence rates of other airway disease phenotypes and

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Disclosure of potential conflict of interest: P. Giavina-Bianchi declares that he has no relevant conflicts of interest.

Received for publication October 13, 2014; accepted for publication October 14, 2014.

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J Allergy Clin Immunol 2015;135:151-2.

0091-6749/\$36.00

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<http://dx.doi.org/10.1016/j.jaci.2014.10.029>

endotypes, such as nonallergic airway disease, chronic rhinosinusitis with and without nasal polyposis, and aspirin-exacerbated respiratory disease.^{12,13}

Medicine has evolved into a proactive discipline more focused on maximizing wellness for each patient rather than simply treating diseases. P4 medicine is a systems approach to medicine that includes predictive, personalized, preventive, and participatory features. Rhinitis and asthma are heterogeneous diseases, reflecting distinct pathophysiologic processes that likely result from different environmental exposures and cause different disease manifestations with varying therapeutic responses and prognoses. Recognition that earliest-onset and severe types of rhinitis are associated with more severe young adult airway disease allows early treatment that might reduce later development of severe adult rhinitis and asthma. Additional research, such as the report by Kurukulaaratchy et al,⁷ is needed to continue to advance our understanding of airway disease subtypes and pathophysiology, with the eventual goal of developing new treatments for more effective personalized medical management.

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