Clinical Commentary

The Allergic Asthma Phenotype

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Date of Original Release: November 2014. Credit may be obtained for these courses until December 31, 2015.

Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

Target Audience: Physicians and researchers within the field of allergic disease.

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List of Design Committee Members: Michael Schatz, MD, MS, and Lanny Rosenwasser, MD

Activity Objectives

1. To appreciate the characteristics of the allergic asthma phenotype.
2. To identify patients with the allergic asthma phenotype.

Recognition of Commercial Support: This CME has not received external commercial support.

Disclosure of Significant Relationships with Relevant Commercial Companies/Organizations: L. Rosenwasser is president of the World Allergy Organization. M. Schatz declares that he has no relevant conflicts of interest.

Allergic asthma is the most common asthma phenotype. It usually is defined by the presence of sensitization to environmental allergens, although a clinical correlation between exposure and symptoms further supports the diagnosis. The average age of onset of allergic asthma is younger than that of nonallergic asthma. Although the spectrum of allergic asthma may vary from mild to severe, studies have reported that allergic versus nonallergic asthma is less severe. There is an increased prevalence of allergic rhinoconjunctivitis and atopic dermatitis in patients with allergic asthma. Total IgE levels usually are higher in allergic versus nonallergic asthma, but levels substantially overlap between the 2 groups. Increased Th2 cytokines have been demonstrated in secretions and peripheral blood of patients with allergic asthma. Atopy has been reported to be inversely associated with persistent airflow obstruction and airway remodeling. Clusters with a high prevalence of early onset atopic asthma have been frequently reported in statistical phenotyping studies, but the various clusters of patients with atopy were quite heterogeneous in terms of symptom severity, pulmonary function, and tendency for exacerbations. Implications for future research regarding the allergic asthma phenotype are described. © **2014 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2014;2:645-8)**

Key words: *Asthma; Allergic asthma; Asthma phenotypes; Allergic sensitization*

Allergic asthma can be defined clinically by identifying (1) allergic sensitization and (2) a correlation between allergen exposure and asthma symptoms. The first criterion is more objective and straightforward, whereas the second depends on whether or not appropriate questions are asked of the patient and the patient's ability to accurately link exposures to the onset of symptoms. Literature that compares allergic to nonallergic asthma, and thus identifies the specific characteristics of this phenotype, usually uses only the first criterion, although inclusion of the second criterion would increase the specificity of the definition. A positive antigen inhalation challenge could be considered to further confirm this phenotype, but this is not clinically practical and has not been used in the allergic asthma phenotype literature.

DEMOGRAPHICS

Allergic asthma is probably the most common asthma phenotype in the general population of patients with asthma.[1] Allergic asthma may present at any age, but cohorts of patients

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No funding was received for this work.
Conflicts of interest: L Rosenwasser is president of the World Allergy Organization. M. Schatz declares that he has no relevant conflicts of interest.
Received for publication July 7, 2014; revised September 9, 2014; accepted for publication September 10, 2014.
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2213-2198

http://dx.doi.org/10.1016/j.jaip.2014.09.004

Abbreviation used
FENO- Fraction of exhaled nitric oxide

with allergic asthma are younger than those with nonallergic asthma.[1-4] Allergic asthma is more common in male patients, whereas nonallergic asthma is more common in female patients.[1] There is no difference in smoking prevalence in these 2 phenotypes.[1,2]

CLINICAL CHARACTERISTICS

The onset of allergic versus nonallergic asthma occurs at a younger age.[1,2,5,6] In 1 study, the mean age of onset was 15.8 years of age in allergic versus 32.2 years of age in nonallergic asthma.[1] Conversely, atopy is less common in later-onset asthma.[7] Analysis of some data suggests that a family history of asthma is more common with allergic versus nonallergic asthma,[2] whereas other studies do not confirm this observation.[8] Patients with allergic asthma may have either intermittent or persistent asthma and may or may not be more "brittle" or prone to exacerbations.[9,10] They are more likely than those with nonallergic asthma to report seasonal variations of their symptoms.[1] Patients with allergy and with asthma may be classified as having "few, moderate, or high" symptoms,[11] and cohorts of difficult-to-control or severe asthma include individuals with allergy.[12-14] However, studies of patients with varying degrees of asthma severity report that allergic versus nonallergic asthma is less severe[1,2,5,15-18] or that there is no association between severity and atopic status.[19-22] Other reports suggest that patients with allergic versus nonallergic asthma have less need for oral glucocorticosteroids.[1,2] In contrast, a study of severe asthma in school-age children demonstrates that those with severe asthma have significantly greater sensitization to aeroallergens than children with mild-to-moderate asthma.[23] Exercise-induced bronchospasm is reported to occur more frequently and be more severe with allergic versus nonallergic asthma.[24]

COMORBIDITIES

There is an increased prevalence of allergic rhinoconjunctivitis and atopic dermatitis in patients with allergic asthma.[1] However, there are no differences in the prevalence of rhinitis symptoms between patients with allergic versus those with nonallergic asthma, the latter of whom presumably have nonallergic rhinitis.[1] Nasal polyps and chronic rhinosinusitis are less common with allergic versus nonallergic asthma.[1]

BIOMARKERS

Most persons with asthma, regardless of phenotype, have a predisposition toward Th2 inflammation in the airway due to innate factors, such as thymic stromal lymphopoietin, IL-25, and IL-33.[25] Subjects with allergic asthma, by definition, demonstrate allergic sensitization (allergen-specific IgE), although allergic sensitization probably represents a more important factor in triggering exacerbations than in induction of disease. Total IgE levels usually are higher in allergic versus nonallergic asthma,[2,24] but separation of these 2 phenotypes cannot be solely based on total serum IgE levels because of substantial overlap between the 2 groups.

Peripheral blood eosinophilia may be seen in allergic or nonallergic asthma and may correlate with airway obstruction[26] and predict exacerbations.[27] Some studies have demonstrated higher levels of peripheral eosinophilia in patients with allergic versus those with nonallergic asthma.[28] Th2-polarized responses, measured as higher mean IL-5 and IL-13 production and lower ratios of INF-γ and IL-12 to 3 Th2 cytokines (IL-4, IL-5, or IL-13), were reported in the peripheral blood of participants with allergic asthma in the Detroit Childhood Allergy Study.[28] Secretions from the airways of patients with allergic asthma also contain increased Th2 cytokines as well as eosinophils and mast cell mediators.[3] Positive allergen challenges are associated with an increase in fraction of exhaled nitric oxide (FENO). Some studies report no association between atopy and persistent airflow obstruction[29] or excessive FEV_1 decline,[30] but another study shows less atopy in patients with versus those without persistent airflow limitation.[31] Similarly, a 2014 study shows a greater decline in pulmonary function in a less atopic, late-onset group compared with an early onset, atopic cohort.[32] Less remodeling by computerized tomography in allergic versus nonallergic patients is also reported.[33]

RELATIONSHIP TO STATISTICALLY DEFINED PHENOTYPES

Statistical attempts to define asthma phenotypes usually have identified at least 1 allergic phenotype.[1-14,31,34-39] In these studies, early onset disease and atopy typically go together,[12,14,34,35,37-39] and atopy did not distinguish the phenotypes identified in a cohort with adult-onset asthma.[37] The reported studies describe various associations with the atopic phenotypes. Haldar et al[34] studied primary and secondary care cohorts and identified an early onset, atopic cluster in both samples. Those in the atopic cohorts demonstrated more FEV_1 reversibility, higher sputum eosinophil and FENO levels, and more exacerbations in the past year compared with the other clusters. Siroux et al[35] identified clusters in 2 large European epidemiologic studies conducted with adults. They identified 2 atopic cohorts, 1 that was being actively treated and manifested increased IgE levels, bronchial hyperreactivity, and exacerbations, and the other that was characterized as "inactive-mild untreated."

Boudier et al[11] conducted a 10-year follow-up of cluster-based phenotypes in a pooled analysis of 3 adult cohorts and identified 4 atopic clusters, distinguished each from the other primarily by the severity of symptoms. The most symptomatic atopic cluster also demonstrated higher levels of IgE, increased bronchial hyperreactivity, and an increased frequency of exacerbations compared with the other clusters. Howrylak et al[40] reported the application of spectral clustering to clinical data from 1041 children with asthma who participated in the Childhood Asthma Management Program study. Four of the 5 clusters were moderately to highly atopic. These clusters differed from each other in their level of airway obstruction and rates of exacerbations.

Four studies applied statistical methods to identify clusters in patients with severe or difficult-to-treat asthma. Moore et al[12] presented a cluster analysis of participants ages 12 years old or older in the Severe Asthma Research Program, which includes some individuals with mild and moderate asthma. More than 75% of the subjects were atopic in 3 of the 5 clusters. Two of these clusters had normal pulmonary function and low health care utilization, whereas the third atopic cluster was more likely