Editorial

Asthma Phenotypes: An Approach to the Diagnosis and Treatment of Asthma

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The review articles in this issue of *The Journal of Allergy and Clinical Immunology: In Practice* focus on asthma phenotypes. These articles represent the completion of work begun several years ago by a task force convened by the National Health Lung and Blood Institute and composed of representatives from the American Academy of Allergy, Asthma & Immunology, American Thoracic Society, and European Respiratory Society. What I hope to accomplish in this editorial is to outline my approach to a patient with suspected asthma, a medical problem for which the treatment options are variable and for which the prognosis is excellent. Defining phenotypes is an important part of this process.

DEFINITION OF ASTHMA

To begin, what exactly is asthma? It has been defined in a variety of different ways; however, I define asthma as "a syndrome with various phenotypes ["the observable properties of an organism that are produced by the interaction of the genotype and the environment"] and endotypes."[1] It presents with recurrent cough, usually emanating from the chest, exacerbated by physical factors, such as exercise, laughing, and lying down; wheezing; tightness of the chest; and shortness of breath, both inspiratory and expiratory; but, with increased severity, the expiratory versus inspiratory phase of breathing becomes prolonged. Sputum production is variable, in most cases, nonexistent, but, in a few others, is a dominant characteristic. Its severity can vary from mild to very severe, even life threatening, and changes in the same individual from time to time with or without treatment. Its pathogenesis is associated with neurogenic and genetic abnormalities, and airway inflammation. Environmental factors, including viruses, naturally occurring allergens (eg, pollens, mites, cockroaches, animal danders, molds), and man-made pollutants (eg, nitric oxide, sulphur dioxide, cigarette smoke, diesel fumes), play a role in its onset and chronicity. The airway obstruction usually is reversible with β-agonists but not always. Comorbid and coexisting conditions, the most common of which is rhinosinusitis, contribute to its variability and severity ["conditions characterized by a specific pathological process"].[2]

IDENTICAL TWINS WITH DIFFERENT ASTHMA PHENOTYPES

The complexity of this disease first became apparent to me during one of my first research projects, which resulted in a 1973 publication, "Familial Occurrences of Asthma, Nasal Polyps, and Aspirin Intolerance."[3] Four members of a Mennonite family, 3 of whom were first cousins, had aspirin-exacerbated respiratory disease (AERD). One of the cousins, whose husband also was a member of the isolate, had a daughter with this same syndrome and an identical twin sister with allergic rhinitis and allergic asthma but not AERD (15 genetic loci tested were concordant with a probability that the twins were dizygotic rather than identical of only 0.0038). In an additional non-Mennonite family, 2 siblings had AERD, whereas a third sibling had nonallergic asthma. He did not have AERD. His asthma, for unexplained reasons, became asymptomatic in double-blinded controlled challenge with aspirin 300 mg versus placebo, 4 times a day. How could this occur? We concluded that genetic as well as environmental factors were casually involved in the differences observed in both of these families.[3] First, 1 individual with allergic asthma and an identical twin sister with AERD, and second, 2 siblings with AERD and 1 without AERD, who was able to discontinue all asthma medications if he took aspirin, 300 mg 4 times per day.[3] Epigenetics, known to be affected by environmental influences, also may explain these observations.

CLINICAL APPROACH TO A PATIENT WITH ASTHMA

How should a patient with suspected asthma be approached clinically? First and foremost, I always teach students, residents, and other health care professionals that "asthma is the most treatable of all chronic diseases known to mankind." I also say "properly treated asthma should rarely, if ever, result in an emergency department visit or hospitalization." Yet today, it remains one of the most common reasons for hospitalization in the United States.[4]

Detailed history and physical examination

First, as with any complex medical condition, a detailed history and physical examination is absolutely essential, mandatory, to best recognize the symptoms and signs of the disease, and to differentiate it from diseases often confused with asthma, some of which include vocal cord dysfunction, hyperventilation, restrictive lung diseases, and bronchiectasis. Sometimes, these and

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TABLE I. Asthma phenotypes

A. Major asthma phenotypes
1. Allergic
2. Nonallergic
3. Infection related
4. AERD
5. Childhood preasthma phenotype
B. Other asthma phenotypes
1. Trigger induced
a. Occupational
b. Cigarette smoke induced
c. Air-pollution induced
d. Exercise induced
2. Symptom based
a. Exacerbation prone
b. Asthma with persistent air-flow limitation
c. Cough variant
d. Adult onset
e. Obese
3. Biomarker based
a. Eosinophilic
b. Neutrophilic

other diseases are comorbid or coexisting conditions, which makes the diagnosis and treatment even more complex and difficult.[2] For example, symptoms of vocal cord dysfunction can mimic asthma, and patients with asthma can have concomitant vocal cord dysfunction. Whereas wheezing is thought of as being the most characteristic symptom of asthma, most often recurrent cough, which usually emanates from the chest and not from the upper airway, associated with tightness or a heavy feeling in the chest, is equally characteristic. The cough can be triggered by laughing, lying down, exertion, and other physical activities.[5]

Shortness of breath or difficulty breathing, both inspiratory and expiratory, also is characteristic of the disease. With increased severity, the expiratory phase becomes more difficult. Sputum production is variable, in most cases is nonexistent, but, in a few others, a dominant characteristic. A sensation of air hunger, or breathing in deeply because of a sensation of inadequate intake of air, is more characteristic of hyperventilation, whereas a delayed expiratory phase is more characteristic of asthma. Thus, the diagnosis of asthma is primarily made clinically and, when possible, confirmed by spirometry. Although 12% reversibility in the FEV_1 after the inhalation of a short-acting β-agonist remains the criterion standard, such reversibility is sometimes never demonstrated in some individuals with asthma, even though they have some or most of the other clinical characteristics of the disease and respond to appropriate treatment. The latter is especially true with those who have cough variant asthma, a common presentation of this disease, yet very poorly understood and not well studied.

Identification of phenotypes

Second, I try to decide which phenotype best fits each individual, by realizing that some individuals cannot be pigeonholed into one or another phenotype but have characteristics of several phenotypes as discussed in this issue of *The Journal of Allergy and Clinical Immunology: In Practice* (Table I). The concept of phenotypes and endotypes of asthma is not new, and every generation seems to revisit this issue.[6,7] For example, a 2012 article in *Nature Medicine* by Wenzel[6] speculates that asthma phenotypes can be differentiated into Th2 versus non-Th2 asthma; this differentiation has therapeutic implications. Why is phenotyping asthma so important? By identifying a phenotype, the clinician can better understand the pathophysiology and appropriate treatment unique to control asthma. For example, allergic asthma benefits from allergen immunotherapy; however, nonallergic asthma does not. Likewise, individuals with allergic asthma can be instructed about how to avoid allergen triggers, alter living habits, and increase medications during seasons of the year when an expected exacerbation is likely to occur secondary to tree, grass, or weed pollens in the air. Similarly, individuals can premedicate when they are going to be exposed to an animal or a dust mite–infested environment, which results in flares of their asthma. Individuals with AERD are potential candidates for improvement of their asthma and nasal polyposis with aspirin desensitization.[8] Those with infectious asthma can be treated at the very onset of a respiratory tract infection and until the infection resolves, and can prevent a severe asthma exacerbation. Oftentimes, treatment can be discontinued between infections both in children and adults with this phenotype. There also is some evidence that leukotriene antagonists decrease the number of infectious flares of asthma, particularly with children.[9,10]

Severity of asthma

Another clinical strategy is to define asthma severity when first diagnosed and over time. Severity over time is difficult to predict because, with treatment, severe asthma with some individuals can become mild, and, occasionally, mild asthma with some individuals can become severe. Thus, this characteristic should be reevaluated during routine visits, which enables appropriate "step-up" and "step-down" therapy, or even discontinuation of some or all therapies at times. Measuring peak expiratory flow routinely each time a patient is seen and obtaining an asthma control assessment, that is, Asthma Control Test or similar assessment, are essential to determine and monitor severity and control.[11] Spirometry used periodically and appropriately also can be helpful regarding assessing control, severity, exacerbation risk, and persistent airflow limitation.

Education

Individuals with any chronic disease, including asthma, need to be continually educated about their disease, not only by their physician but by other health care professionals as well. The appropriate use of medications, particularly inhalers, is crucial. Knowledge about the symptoms and signs of worsening asthma is vital information for good outcomes so that a secondary or even tertiary "emergency" treatment plan can be instituted by the patient when a flare of asthma occurs. At the same time, when instituting such a program, patients should be reevaluated by a physician. This kind of program not only helps decrease concomitant anxiety often associated with an asthma exacerbation but also is cost effective because it eliminates or minimizes missed work or school, and emergency department visits and hospitalizations. Having immediate access to care is essential for the well-being of these patients.

Comorbid conditions

Comorbid conditions also need to be identified. For example, asthma, gastroesophageal reflux disease, sleep apnea, and obesity,

when they coexist, are all interrelated and need to be collectively addressed to appropriately treat asthma.[12] Likewise, if a person has concomitant vocal cord dysfunction syndrome, that, too, has to be treated.[13] Perhaps the most common comorbid condition associated with asthma is rhinitis or rhinosinusitis.[2] In my experience, "as goes the nose, so goes the chest" and appropriate treatment of upper airway disease, as well as other comorbid or coexisting problems, is important for optimal asthma outcomes.

Reassurance

Last, but not least, patients with asthma should be reassured about the safety of their medications, especially when used chronically, and should be informed that their prognosis is excellent, particularly with appropriate treatment. A good tip is to compare the safety of asthma therapy versus being in a car or riding a bicycle. They should also be told that asthma does not usually lead to chronic obstructive lung disease, which is primarily associated with smoking, and should be encouraged to live a normal and active life, especially children, who are oftentimes unnecessarily restricted by what they are told they can and cannot do.

SEVERE ASTHMA

Severe asthma is reported to make up approximately 5% to 10% of all individuals with this disease.[14] My clinical impression is that this percentage is too high. Individuals with persistent asthma, particularly those with severe asthma, need an asthma specialist to evaluate, treat, and reevaluate them regularly, at least every 3 to 4 months. They also need immediate access to care and should not be compelled to use the emergency department or walk-in clinics when their asthma flares. Many times in large medical clinics individuals with asthma have to wait weeks or months to be seen by a specialist, particularly for an exacerbation, which can lead to severe asthma. With few exceptions, the earlier a flare of asthma is appropriately treated, the less severe it becomes and the quicker it resolves. Likewise, early treatment with increased use of inhalational glucocorticosteroids can often resolve the flare, which negates the necessity for systemic glucocorticosteroids, which are associated with many adverse effects.[15] Short- and long-acting β-agonists, anticholinergics, leukotriene modifiers, and theophylline as well as antibiotics, particularly for acute or chronic bacterial sinusitis when appropriate, also can be used.

A PERMANENT DISEASE?

One additional point is that asthma is not always a permanent disease.[16] Continuous treatment of asthma is recommended for anything other than mild intermittent asthma, but, typically, many individuals with asthma experience remission after appropriate treatment, especially with glucocorticosteroids. Some individuals will take their medications for an extended period of time and then stop them, and then they do not reappear in the clinic until their problem reoccurs years later. For example, I saw a patient with asthma this year who was treated for approximately 5 years with omalizumab. He stopped his treatment in 2009 and did not have recurrence of his allergic asthma, rhinitis, or conjunctivitis until the spring of this past year, 2014.

ASTHMA TRIALS

Even to this day, the primary criteria for subject entry into most drug studies of asthma is the prerequisite that participants must have 12% reversibility of their FEV_1 after inhalation of a short-acting β-agonist, sometime within the past year or so. Conversely, very few other criteria are necessary for entry into a study. With severe asthma, additional criteria, such as the number of hospitalizations, use of systemic glucocorticosteroids, and number of exacerbations or emergency department visits, also have been used with or without 12% FEV_1 reversibility. Although improvement in spirometric measurements are often important, other equally important data should be included for study entry to assess treatment outcomes. These include asthma phenotypes, the initial and ongoing severity of asthma, comorbid and coexisting conditions, and biomarkers. Providing such information will enable investigators to perform additional analyses of outcome data to determine whether or not 1 phenotype (or endotype) responds better to 1 treatment modality versus another.

SUMMARY

I teach that "Asthma is the most treatable of all chronic diseases known to mankind." Yet, outcome data from throughout the world (emergency department visits, hospitalizations, and quality of life) indicate that the diagnosis and treatment of asthma are not optimal and need improvement. Why? First, asthma is not thought of as a complex, heterogeneous disease or syndrome that consists of different phenotypes and endotypes. Second, asthma is variable, particularly in its severity, and is influenced by known, unknown, avoidable, and unavoidable environmental factors. Third, treatment usually requires complex inhalational devices that are difficult to understand and use, and with which adherence is suboptimal. Continued education on how to appropriately use medications, particularly inhaled medications, is absolutely essential, and knowledge and access to a backup treatment plan to be initiated by the patient for an asthma flare is necessary. Fourth, assessment of asthma is primarily based on symptoms, and, at times, all symptoms are due to asthma, but many times some or all symptoms are due to unrecognized and untreated comorbid or coexisting conditions. Too often, asthma is viewed as a disease that occurs in isolation, and comorbid and coexisting conditions are not appropriately identified and treated. Allergists/immunologists are well suited to provide the type of comprehensive care required to optimize asthma outcomes for the benefit of individual patients and society.

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