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# Pediatric bronchial hyperresponsiveness and asthma phenotypes

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Dr. Lee and colleagues have examined the intersection of 2 relevant aspects of asthma, bronchial hyperresponsiveness (BHR) and clinical patterns of childhood asthma.[1] Using the novel approach of considering different patterns of BHR as characteristic phenotypes, Dr. Lee demonstrated a relationship between the BHR phenotypes and the clinical patterns of asthma in children. These investigators had previously demonstrated a relationship between atopic phenotypes and the development of BHR and asthma.[2] These are both interesting contributions that relate to important components that make up asthma.

Dr. Lee and colleagues state, "BHR is one of the key characteristics of asthma and correlates with severity." Although that is certainly true, many assume that BHR is unique and even diagnostic of asthma. That is an oversimplification. For example, cystic fibrosis patients without asthma have BHR from histamine that is reversed with ipratropium aerosol, an anticholinergic agent that has little effect on histamine-induced bronchospasm for asthma. Some patients with allergic rhinitis, but no asthma, also have BHR.[3] Bronchial hyperresponsiveness is also seen in nonasthmatic parents of children with asthma, suggesting that BHR is an inherited trait necessary but not sufficient to cause asthma.[4] Thus, BHR is characteristic of but not unique to asthma.

In a study of BHR to methacholine in 547 nine-year-old children with no history of symptoms consistent with asthma, 41 (7.5%) had BHR.[5] When reevaluated at various ages as adolescents and adults, an increased risk of asthma was found among those with BHR to methacholine at age 9, compared with those without BHR. By age 26 years, 24% with BHR at age 9 had asthma, whereas only 9% of those without BHR had asthma. That risk increased to 50% if BHR to methacholine was seen during repeat examinations at later ages. The results of this and previous studies suggest that rather than considering BHR as diagnosing asthma, BHR appears to be a pathologic process that is associated with a substantial risk that clinical asthma may eventually occur.

Although BHR to methacholine approaches 100% in patients with currently active asthma, the sensitivity decreases substantially for episodic asthma when the patient has been asymptomatic for an extended time when tested.[6] Bronchial hyperresponsiveness can vary in an individual over time and under different circumstances, and thus measurements must be viewed as relevant to the current status and not necessarily to remote or future events.

Dr. Lee and colleagues refer to both BHR and atopy in children as phenotypes that relate to the development and clinical patterns of asthma.[1,2] But what does it mean to be a phenotype? Phenotype has been defined as an observable characteristic resulting from the interaction of the genotype with the environment. Since about the year 2000, the number of publications addressing asthma phenotypes has increased substantially, reflecting increasing interest in this expanded concept of asthma. The definition of asthma must adjust to this increasing recognition that asthma consists of multiple disorders with different clinical characteristics. The term *asthma* now is regarded as including several phenotypic disorders that share a common end-organ pathway characterized by an increased responsiveness of the trachea and bronchi to various stimuli and manifested by a widespread narrowing of the airways that changes in severity either spontaneously or as a result of therapy.

Bronchial hyperresponsiveness and atopy are components of the more readily observable clinical phenotypes of asthma. Those are identified by patterns of asthma encountered from a detailed history. Several of these readily observable phenotypic clinical patterns are seen in children with asthma. The most common clinical phenotype begins in infancy and is prominent throughout the preschool-age period. Symptoms of asthma only occur in children with this phenotype when they are infected with a viral respiratory infection (VRI). Between the episodic illnesses, neither symptoms nor chronic inflammation of the airway is present.[7] For many, that clinical phenotype persists into adulthood, although progressively fewer VRIs with age frequently make this phenotype less troublesome. A minority of children who begin with that clinical pattern manifest evidence of a different phenotype because of atopy with sensitivity to environmental allergens; they then may develop persistent asthma.[8] In contrast to the nonatopic children with episodic VRI-induced exacerbations, those with atopy have chronic inflammation of the lower airways even during periods free of symptoms.[9]

A classical phenotype of asthma is known as the atopic triad. In addition to eczema, this clinical pattern is commonly associated with atopy, including allergen-specific immunoglobulin E antibody to foods in infancy; inhalant allergy follows with a likelihood of eventual persistent asthma. Another distinct phenotype, although rare in the pediatric age group, is asthma associated with aspirin-exacerbated respiratory disease.

Other observable phenotypes can be seen in clinical practice, such as the child with atopy who begins with allergic rhinitis and progresses in later childhood to have allergic asthma. A less common nonallergic asthma is the young girl who around menarche develops persistent asthma. During childhood, asthma is more prevalent in boys; however, the frequency of asthma in girls increases markedly during adolescence and adulthood. Another phenotypic variation that occurs in adult women and occasionally during adolescence is known as catamenial asthma, which is characterized by often severe exacerbations during menses.

An alarming pattern of sudden asphyxic asthma is another unique phenotype. Fatalities associated with this phenotype appear to be associated with neutrophilic rather than eosinophilic inflammation.[10]

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Obesity also has been suggested as being associated with a unique phenotype of asthma. Adult-onset asthma has various phenotypes not generally present in the pediatric age range.

The recognized challenge with all phenotypes is the relationship to endotypes. An endotype is a specific biological pathway that explains the observable properties of a phenotype. New biologic preparations decrease the activity of specific bioactive cytokines, with varying degrees of improved asthma outcome. Understanding the mechanism by which viral respiratory infections activate asthma may eventually provide a means for treating or even preventing VRI-induced exacerbations. However, efforts at further improvements of asthma outcome are still limited by the complexity of the multiple asthma phenotypes and the still not fully understood endotypes.

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