

Differences between adult and childhood asthma

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During the last 2 decades, we have gained new insights into the pathogenesis of asthma; consequently, new therapeutic agents and approaches to therapy have emerged. Nevertheless, significant gaps remain in our understanding of this disease. Important new treatment issues affect childhood (the usual time of asthma onset), and researchers have recently described increases in asthma incidence in children. Yet, most clinical studies have been performed with adults, and our knowledge about major determinants of childhood asthma remains incomplete. Major challenges in pediatric asthma include methods of easily assessing lung function and noninvasive methods of assessing asthma's inflammatory nature. Research that addresses the mechanisms responsible for disease onset is also critical to decrease the prevalence of asthma. What we know about adult asthma cannot be used in the treatment of children without further study, but it is now clear that effective treatment should begin during childhood. (*J Allergy Clin Immunol* 2000;106:S153-7.)

Key words: *Asthma pathogenesis, airway function, airway hyperresponsiveness, airway inflammation, cytokines, leukotrienes*

During the last 2 decades, research has produced important insights into the pathogenesis of asthma. Consequently, new therapeutic agents have emerged, and many others are in development.¹ Important issues now being addressed concern asthma close to the time of onset, commonly during childhood, and yet most studies about basic mechanisms of disease or the safety and efficacy of newer therapies have been conducted in adults.² Important pathologic events occur at all ages, but clinical evidence has not been so universally studied. This article reviews the usual characteristics of asthma and the unique aspects of the disease in preschool-aged children as well as the physiologic and pathologic features of the disease in the youngest asthmatic patients. A lack of understanding concerning the clinical manifestations of asthma at all ages can cause possible delays in diagnosis and initiation of therapy.

CHARACTERISTICS OF ASTHMA

As noted in the 1999 Expert Panel Report³ from the National Institutes of Health, the characteristics of asthma

Abbreviation used

ICS: Inhaled corticosteroid

include physiologic and pathologic features. In terms of physiologic features, episodes of airway obstruction that recur are reversible either spontaneously or with therapy. The airways of asthmatic patients are also hyperresponsive, being obstructed when subjected to stimuli that do not produce such an effect in normal persons. Even when the disease is mild according to clinical criteria, the patient experiences chronic inflammation of the airways.^{4,5} These features of asthma have been extensively characterized in adults, which is appropriate, given the difficulty of studying young patients; but several issues unique to children must be kept in mind when asthma characteristics are applied to pediatric patients. Important features of asthma as a function of the patient's age and the challenges in the study of the disease are summarized in Table I.

UNIQUE ISSUES OF CHILDHOOD ASTHMA

The onset of asthma commonly occurs during the preschool years.^{6,7} A study from the Mayo Clinic documented significant increases in asthma incidence over approximately 2 decades; this increase was observed only in children and adolescents aged 1 to 14 years.⁷ The identification of children with asthma remains problematic, however. The clinical syndrome that we recognize as asthma does not develop in all infants and children with wheezing illnesses.⁸ For example, more than one half of all children who wheeze with viral infection during the first years of life have a transient condition that rapidly subsides during preschool and early school years. In the selection of patients for a study after an episode of wheezing early in life, then, some patients may be included who have another cause for this symptom. Another difficulty in identifying childhood asthma is that conducting pulmonary function tests for the documentation of airway obstruction and its reversibility in an objective and quantitative manner is not easy in young patients.⁹ This makes the identification of infants and young children for studies that address asthma pathogenesis and therapy far from an exact science. This does not mean the endeavor is not worthy of effort, however. The increased incidence of asthma in infants and children suggests just the opposite. We need more information on airway function and those factors that influence it, positively or negatively, close to the time of symptom onset.¹⁰ Thus, a major challenge for researchers

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TABLE I. Characteristics of asthma and the age of patients

Disease onset	Preschool children > > older children/adults
Increased incidence	Children > > adults
Pulmonary function tests (availability/use)	Adults/adolescents > older children > > infants
Pathologic information	Adults > > adolescents > children > infants

and clinicians who care for infants with wheezing is to develop tools that distinguish transient infant wheezing from the early onset of asthma. Cellular, biochemical, and genetic markers of risk could allow for the identification of wheezing infants who are at greatest risk for the development of asthma.^{11,12} This is the subset of infants who must be studied and followed as strategies are developed that more effectively treat and, possibly, prevent childhood asthma.

In an attempt to circumvent some of these difficulties and limitations, some researchers study models of airway dysfunction.¹³ They have observed that insults that occur early in postnatal development (such as aspiration, infection with the respiratory syncytial virus, or allergen sensitization) may alter the normal balance of neural control within an airway for prolonged periods of time.¹⁴⁻¹⁶ Thus, there may be critical periods during airway development when insults may have far-reaching consequences. To define the significance of such studies in humans, however, methods must be developed that can safely and noninvasively assess airway control and function in young patients in a time-efficient manner. When this is possible, we should be able to gain additional insights into asthma pathogenesis and determine whether early interventions can alter the course of asthma.

AIRWAY HYPERRESPONSIVENESS IN ADULTS AND CHILDREN

One of the physiologic characteristics of asthma is airway hyperresponsiveness, or the ease with which airways narrow in response to various nonallergic and nonsensitizing stimuli, including inhaled chemical mediators (such as histamine or methacholine) and natural physical stimuli (such as exercise or hyperventilation of cold air). Studies in both adults and older children suggest that the severity of asthma, as judged by clinical criteria, is loosely correlated with the level of airway responsiveness.¹⁷ This is important because the level of responsiveness is not static in either normal or asthmatic patients. Stimuli that produce inflammation within airways (such as viral infections, allergen exposure in atopic asthmatic individuals, and air pollutants) increase the level of airway responsiveness and also lead to the loss of control of the disease. Conversely, various therapies that decrease airway inflammation (such as inhaled corticosteroids [ICSs]) or the avoidance of relevant allergens decrease the level of responsiveness. When the effects of various therapies are assessed, it is common to measure changes in responsiveness over time to determine whether the therapy improves this fundamental abnormality of asthma.

Levels of airway responsiveness to drugs (such as his-

tamine and methacholine) can be measured in infants and preschool-aged children. One observation has been that the level of responsiveness, as defined by the drug concentration needed to significantly decrease airway function, can be quite marked even in normal infants. In other words, the concentration of drug needed to decrease lung function by a significant degree is quite dilute.¹⁸ This has led to speculation that the level of responsiveness is normally quite high and decreases with postnatal maturation. Although normal persons have an age-dependent variability in levels of airway responsiveness,¹⁹ in infants, higher levels of responsiveness may reflect the technical factors inherent in the administration of a bronchoconstricting agent to a small airway. Nevertheless, some evidence suggests that an insult to an airway at a young age may interfere with this normal age-related decrease in responsiveness.^{20,21}

In clinical practice, decisions regarding medications are usually based on history and conventional assessments of lung function. Measures of the level of airway responsiveness are not usually part of the decision-making process. A recent study has suggested, however, that better control of disease might result if airway responsiveness became part of the decision-making process. Sont et al²² reported on a 2-year study in adults in which medication decisions were made with the use of existing guidelines or a strategy that targeted reductions in airway responsiveness. Those patients in whom the level of airway hyperresponsiveness was factored into the decision-making process experienced fewer exacerbations of asthma, greater improvements in lung function, and greater reductions in the thickness of the subepithelial reticular layer. If additional studies substantiate this observation, important questions could then be raised about whether routine assessments of airway responsiveness should be made in caring for asthmatic adults and whether a similar approach to infants and younger children might lead to better control of asthma that could prevent or reverse any remodeling of airways that may be caused by chronic inflammation. Unfortunately, there are several problems in the assessment of airway responsiveness in young patients (including a lack of standardized methods, an absence of established normal values, and the difficulty of performing lung function in preschool-aged children). Normal changes in levels of responsiveness with age will have to be considered in any long-term study. Because of the variability of the test at any point in time, serial measurements will likely be of most value.

THE PATHOLOGIC FEATURES OF ADULT AND CHILDHOOD ASTHMA

That fatal asthma is associated with marked inflamma-

tion has been known for decades.²³ With the use of bronchoalveolar lavage and biopsy, it is now apparent that clinically mild asthma is also characterized by airway inflammation.^{4,5} The most frequently identified features of airway inflammation include an infiltration of airways by eosinophils, the activation of T cells within airways, an increase in mast cell numbers, and desquamation of airway epithelium.²⁴ These invasive studies have been performed primarily in adults, and although information about pediatric patients is limited, studies in older children suggest that the process in their lungs resembles that in adults.²⁵ The greatest gap in our knowledge concerns preschool-aged children in whom asthma develops. There are descriptions of the pathologic features of fatal asthma in preschool children,²⁶ but these observations were made over a long period of time and may include postmortem findings in children whose terminal event was bronchiolitis or bronchopneumonia. Studies that involve lavage in younger patients are now starting to appear in the medical literature. Based on findings in lavage fluid, 1 of these investigations suggests the possibility of 2 different forms of childhood asthma.²⁷ With a more complete analysis of lavage fluid or tissue from airways, additional subclasses might be identified.

Many studies have attempted to correlate the physiologic abnormalities of the disease with indices that reflect the inflammatory process. The relationship between cellular indices of airway inflammation and airway function (obstruction and hyperresponsiveness) has been varied in studies that were performed in older asthmatic patients.²⁸ It is possible there will be a closer relationship between these variables when studies are performed close to the age of onset in young patients because a young person's airways have not been remodeled to the same degree as an adult's. The most likely stimulus for remodeling is the inflammatory response, which is presumed to be present early and to be persistent even when the disease is mild.²⁹

MECHANISMS OF AIRWAY DYSFUNCTION

In the examination of the airways, several cells can be identified that interact with the environment to orchestrate an asthmatic response. In addition to lymphocytes and mononuclear phagocytes, mast cells and the airway epithelium can release products that alter airway structure in response to environmental stimuli. Products from these sentinel cells (cytokines and mediators) attract inflammatory cells (eosinophils, neutrophils, additional lymphocytes, and mononuclear phagocytes) into the airway wall and lumen. These infiltrating cells also release products that affect airway structures. Airway smooth muscle, vessels, neural elements, and the airway epithelium may be altered or injured by this inflammatory process; and the airway wall will thicken because of several factors that include the accumulation of fluid and cells within the wall and smooth muscle hypertrophy.

Many cells and their products contribute in some way to the asthma phenotype, but the primary focus of recent

investigations has been lymphocyte subsets and their products, including a complex network of cytokines that is believed to be responsible for maintaining asthma's chronic inflammation.³⁰⁻³² Concerns about the increasing incidence of asthma have served to focus attention on how immune responses mature early in life.³³ Nonallergic, normal persons have a T_{H1}-skewed immunity against soluble protein antigens, whereas the expression of a T_{H2}-skewed immunity against the same antigens is thought to be a primary cause of allergic inflammation in persons with atopy. Thus, attention is now focused on how this T_{H1}/T_{H2} balance is achieved early in life when asthma incidence is highest. Prescott et al³⁴ recently reported that T_{H2}-skewed responses to common environmental antigens (allergens), comprising IL-4, IL-5, IL-6, IL-9, and IL-13, are present in most newborns and are dominated by a high-level production of IL-10. These observations suggest that the key etiologic factor in atopic disease may not be the initial acquisition of allergen-specific T_{H2}-skewed immunity, but instead may be the efficiency of immune deviation mechanisms that normally redirect these fetal immune responses toward a T_{H1} cytokine phenotype. Additional work by Prescott et al³⁵ demonstrated rapid suppression of T_{H2} responses during the first year of life in nonatopic children, although the consolidation of T_{H2} responses that occurred in atopic children were associated with defective neonatal IFN- γ production. Stumbles et al³⁶ have argued that the observed T_{H2} polarity of the resting mucosal immune system may be an inherent property of resident dendritic cells. Employing rat respiratory tract dendritic cells, they found that mobilization of T_{H1} immunity may rely on a provision of appropriate microenvironmental costimuli such as TNF- α or CD40 ligand to the cells. A possible role in the maturation of antigen-presenting cells has also been proposed for CD14, a glycoprotein that functions as a high-affinity receptor for endotoxin and other structurally related components of microbial pathogens.^{33,37}

In terms of inflammatory mediators, leukotrienes have received much recent attention in terms of their contributions to the pathogenesis of asthma.³⁸ Published studies that deal with the use of leukotriene modifiers in young asthmatic patients are limited,^{39,40} and more information on the efficacy and safety of administering these agents early in the course of disease is needed. Studies that address the ability of leukotrienes to alter the underlying airway inflammation will particularly help define their antiinflammatory effects. Comparative long-term efficacy data with existing antiinflammatory agents will also determine the relative role of leukotrienes in therapy. Their effectiveness in optimizing disease control when combined with other drug classes, including corticosteroids, needs to be addressed in detail. Additional long-term safety information will be forthcoming as more experience is gained with these agents.

CLINICAL MANIFESTATIONS OF ASTHMA AS A FUNCTION OF AGE

A recent study by Zeiger et al⁴¹ argued that asthma

severity in school-aged children is related to the duration of disease. Using the extensive Childhood Asthma Management Program (CAMP) data base, the authors found that the duration of asthma was significantly associated with lower lung function, greater methacholine responsiveness, more asthma symptoms, and greater use of albuterol on an as-needed basis. Studies in adults and children suggest that the introduction of ICSs early in therapy produces better effects on lung function and airway hyperresponsiveness, compared with introducing them later. For example, Haahtela et al⁴² found that as little as a 2-year delay in starting ICS in adults with mild-to-moderate asthma was associated with blunted improvement in lung function. Agertoft and Pedersen⁴³ also argued that delays in the initiation of ICS therapy in children led to blunted improvements in lung function when antiinflammatory therapy was eventually introduced. Knowing that the highest incidence of disease occurs during the preschool years, these observations underlie the importance of establishing an early diagnosis and defining what constitutes the most effective therapy. One major difference between adult and childhood asthma may be that the disease is more amenable to therapy that preserves lung function and normalizes airway responsiveness when initiated close to the onset of disease during early childhood. To determine whether there is merit in this argument, studies that address this issue should include preschool-aged children.²

SUMMARY

In spite of a major impact on public health, our knowledge of the major determinants of childhood asthma remains incomplete. The highest incidence of disease occurs in preschool-aged children, and recently described increases in incidence have also occurred in children. Yet, most information on the pathogenesis and the effects of newer forms of therapy has been gathered in adults for whom the disease has likely been present for years or decades. A major goal in asthma therapy should be to develop methods for the assessment of lung function that can be easily and quickly used in the youngest patients. Methods that can noninvasively assess the inflammatory nature of the disease are also urgently needed. Emphasis on research that addresses the mechanisms responsible for disease onset and understanding the genetic and environmental interactions that lead to disease expression are critical if we are to decrease the prevalence of asthma.

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