Inflammation in Childhood Asthma and Other Wheezing Disorders

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ABSTRACT. It has become clear in the last few decades that the primary underlying pathology of asthma is airway tissue inflammation. In asthma, airway remodeling occurs during chronic inflammation, even in very young children. One of the key goals in treating asthma is to identify those young children with an asthmatic phenotype and initiate early treatment to avoid irreversible airway remodeling. Distinguishing asthma from other conditions that induce wheezing is a daunting but critical step in the appropriate treatment of asthma. In some children, hallmark mediators of inflammation, such as increased eosinophil levels, may distinguish asthma from other causes of wheezing, such as viral infections. Although progress has been made in the differential diagnoses of asthma in young children, more research is needed to define unique markers for distinguishing asthma from other respiratory conditions that produce wheezing. Pediatrics 2002;109:368–372; asthma, phenotype, wheezing, inflammation.

ABBREVIATIONS. BAL, bronchoalveolar lavage; IgE, immunoglobulin E; NO, nitric oxide; CF, cystic fibrosis; VAW, viral-associated wheezing.

Although wheezing is an outward sign of asthma and most asthmatic patients wheeze, not all wheezing is asthmatic. It is now clear that in asthma, inflammation and irreversible airway remodeling occur at an early age. Biopsy specimens from adult patients with atopic or allergic asthma reveal a consistent, marked thickening of the laminar reticularis—a potential marker for chronic inflammation and airway wall remodeling—in patients with asthma.

Indeed, airway remodeling and inflammation are fundamental and interrelated pathogenic processes in asthma (Fig 1). Inflammatory cells, which include mast cells, eosinophils, and lymphocytes, are present even in the Airways of young patients with mild asthma. The release of cytokines by eosinophils and other inflammatory infiltrates plays a pivotal role in asthma pathophysiology by the active recruitment of a wide array of inflammatory mediators, the stimulation of mucus secretion, and the promotion of airway remodeling. The precise relationship between the presence of inflammatory infiltrates and airway remodeling is complex. Even in mild asthma, evidence exists for epithelial cell degradation, thickening of the laminar reticularis, and hyperplasia of the mucus-secreting goblet cells. Additionally, the actions of myofibroblasts may provide an important link between airway inflammation and airway remodeling. Stimulated by inflammatory mediators, myofibroblasts continually produce extracellular structural matrix components and secrete matrix metalloproteinases, which, when elevated in asthma, accelerate airway remodeling, including smooth muscle hypertrophy and hyperplasia.

The inflammation that occurs in asthma can be broken down into 3 stages. First, during the acute response, exposure to stimuli such as allergens or viruses leads to edema, smooth muscle contraction, and increased mucus production in the lungs. This early stage is usually complete within a few hours. Second, a residual stimulus leads to the chronic phase, characterized by epithelial cell denudation and the influx of inflammatory cells into airway tissue. Finally, chronic airway remodeling, which results from an increase in extracellular matrix proteins and vascular changes, may lead to a progressive loss of lung function.

In patients with chronic asthma, acute exacerbations can follow allergen exposure or viral infection. Prolonged acute exposure to allergens can lead to chronic inflammation of the airway and an acceleration of ongoing airway remodeling, further reducing airway patency and increasing wheezing. The persistent wheezing phenotype described by Martinez suggests that the airway remodeling process may be initiated early in life. Thus, an indispensable step in determining the most appropriate course of treatment would be identifying whether the wheezing seen in children with respiratory distress is related to the inflammation underlying asthma or to some other respiratory disease.

After reviewing some of the methods for detecting airway inflammation in children, this review will examine the role of inflammation in asthma and in wheezing associated with other respiratory ailments.

MEASURES OF AIRWAY INFLAMMATION IN CHILDREN

Several methods are available for identifying the presence of airway inflammation in children. Commonly used procedures include sputum induction, bronchoalveolar lavage (BAL), and bronchial biopsy. Because directly examining bronchial tissue is obviously difficult, a number of surrogate markers have been used to assess airway inflammation including measures of eosinophils or eosinophilic cationic pro-

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tein and immunoglobulin E (IgE) levels in peripherally collected blood. Additionally, nasal washings help in exploring the inflammatory response to many viruses, particularly the respiratory syncytial virus. These washings can be examined for markers of inflammation including eosinophilic proteins as well as antibodies to several viruses. Used for many years, methacholine bronchoprovocation is a surrogate tool for evaluating an ongoing inflammatory response in asthma.5–14

The measurement of expired nitric oxide (NO), a relatively new method for evaluating inflammation in the airway, is a noninvasive technique that not only may provide a reliable measure of lower airway inflammation, but also may be useful in evaluating airway inflammation in children. NO is formed by the enzyme NO synthase, which occurs in 3 isoforms including 1 that is inducible in the presence of inflammation. Rapidly induced by proinflammatory cytokines in a variety of cells including macrophages, NO—and hence, exhaled NO—can be an accurate marker of ongoing inflammation within the airway. Increased NO synthase immunoreactivity has been observed in the airway epithelium of asthmatic patients, and exhaled NO concentrations are higher in those patients with asthma as opposed to those without. Moreover, NO levels have also been shown to decrease during the treatment of both acute and chronic asthma.15–18

Some precautions must be taken before using NO levels as an outcome measure in asthma, however. The level of NO will decrease during airflow obstruction such as that induced by bronchoprovocation tests. Conversely, a bronchodilator test may artificially increase NO levels. Additionally, the NO evaluation procedure, which requires the patient to sit with a nose clip in place and breathe against pressure through a controller, may be difficult to perform with young children.

INFLAMMATION IN CHILDHOOD ASTHMA

During the last several decades, a compelling body of evidence has accumulated that implicates inflammation as the principal pathophysiology in asthma. In 1978, data were presented from the first histopathologic examination of lung tissue taken from children with ongoing asthma.6 Lung biopsies from 2 children with asthma in remission were compared with those from 2 children who were dying in status asthmaticus. Both sets of tissue contained striking changes—goblet cell hyperplasia, mucus plugging, and collagen deposition—that provided clear evidence of persistent inflammation. A larger number of submucosal eosinophils and much more extensive denudation of the epithelium were, however, clearly evident in the children who died in status. These differences suggest that the intensity of the inflammatory response was more pronounced in those children who succumbed to the disease. Most remarkable, perhaps, was the finding that signs of airway damage were present even in the 8- to 10-year-old children in remission.

Several studies have been completed using sputum induction to evaluate the role of inflammation in asthma. In a study that included children with asthma up to 4 years of age, pharyngeal aspiration was performed after a coughing episode, and the number of eosinophils in a portion of the sample was counted in 5 different microscopic fields.19 If the sample from a patient was found to contain 11 or

Fig 1. Airway inflammation and remodeling in asthma. During the acute response, exposure to an allergen leads to edema, smooth muscle contraction, and increased mucus production in the lungs. A residual stimulus from an allergen leads to the chronic phase, characterized by epithelial cell denudation and the influx of inflammatory cells into the airway. Chronic remodeling of the airway tissue results in irreversible structural changes and the progressive loss of pulmonary function.
more eosinophils in 5 fields, that patient was scored as positive for inflammation. In children younger than 1 year of age, 33% were positive; by 1 year of age, 55% were positive; and by 2 to 3 years of age, the percentage of children found positive for inflammation had risen to 80%. Additionally, the infiltration of eosinophils into the airway in these children (a physiologic hallmark of an inflammatory response) was detected before the appearance of IgE antibodies to house dust mite protein in the blood. Clearly, inflammatory events were occurring—at least in the upper airways of these children—before an antigen-specific IgE immune response could be detected.

In another study, which included children 8 to 15 years of age who presented with symptoms of an acute asthma attack, sputum samples were collected within 1 hour of arrival in the emergency department. Additional sputum was collected 14 days later, after the children had recovered from the attack. Found in the samples collected during the acute attack was an intense cellular infiltrate composed of eosinophils, neutrophils, and mast cells. In contrast, during the recovery period, eosinophil and neutrophil levels in the sputum dropped significantly. These results underscore the important role that the inflammatory process plays during an acute asthma attack.

A separate study included 42 children 8 to 17 years of age who visited the emergency department because of an acute asthma attack. These children underwent albuterol-protected sputum induction. Subsequently, the sputum was examined for the presence of inflammatory cells. Three different inflammatory cell patterns were recognized: 43% of the samples were found to be eosinophilic; 35% both eosinophilic and neutrophilic; and the remaining 22%, noneosinophilic. These results seem to suggest that there might be multiple phenotypes presenting with acute asthma attacks. Moreover, sputum eosinophil levels increased in association with the clinical severity of the asthma attack and decreased in response to steroid treatment. Nevertheless, eosinophilia did not correlate well with either the speed of the asthma attack onset or the exacerbation outcome. Eosinophilia, therefore, seems to be a marker for disease severity and the effect of the medication that the child takes. Although eosinophilia does not reflect how quickly children will respond to therapy or how fast the acute attack will happen, its presence can be a predictor of some aspects of asthma.

**INFLAMMATION IN WHEEZING DISORDERS**

Using the BAL technique, the role of inflammation in wheezing children with or without asthma was investigated, focusing on the role of alveolar macrophages and the inflammatory mediators that can be released from these cells. Thirteen wheezing infants underwent flexible bronchoscopy during an asymptomatic interval, and the results were compared with a control group that included 6 nonwheeze, nonasthmatic children with other airway problems. Alveolar macrophages from wheezy infants released larger amounts of thromboxanes A2 and leukotriene B4 under resting conditions. Thromboxanes A2 were also released when the calcium ionophore A23187 stimulated the alveolar macrophages. Treatment with dexamethasone induced a significant dose-dependent decrease in both ionophore-stimulated and spontaneous thromboxane release. The results suggest that in the lungs of wheezing children, the alveolar macrophage may be upregulated to produce mediators of inflammation amenable to certain interventions, such as glucocorticoids.

BAL was performed in 4 groups of children with respiratory disease (asthma, chronic cough, infantile wheeze, or cystic fibrosis [CF]), and the results were compared with those obtained from a control group having no identifiable respiratory disease. The highest total cell eosinophil and neutrophil counts were found in children with CF. Elevations in these cell types were somewhat surprising but may reflect that many CF patients also have allergies. The cell profile of children with chronic cough was similar to that of children in the control group. The children in the asthma and the infantile wheeze groups had a high median ratio of eosinophils (3%) and neutrophils (12%), as well as elevated levels of epithelial cells. Intriguing differences were detected in T-cell populations when the asthma and wheeze groups were compared. Asthmatic children had a higher proportion of CD8+ cells (58%) than did children in the wheeze group (40%), resulting in a significantly (P = .02) lower CD4/CD8 ratio in children with wheeze.

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**Fig 2.** Heterogeneity of inflammation in childhood asthma: eosinophils. No significant differences were detected in the level of eosinophils in the exudates from children with persistent or episodic asthma, but children with VAW had significantly lower levels of eosinophils than did the children with atopic asthma or those without asthma. Adapted from Stevenson et al. Used with permission.
Fig 3. Heterogeneity of inflammation of childhood asthma: eosinophils according to age. In both older and younger children, higher levels of eosinophils were seen in those with atopic asthma relative to those with VAW or those with atopy and without asthma. Over all age groups, eosinophil \( (P \leq .005) \) percentages were significantly elevated in the group with atopic asthma compared with the other groups. Considering the 5-year-old children only, eosinophil numbers were significantly elevated \( (P < .001) \) in the atopic asthma group compared with the group with VAW. Adapted from Stevenson et al.\(^{12}\) Used with permission.

asthma \( (0.27) \) than with infantile wheeze \( (0.45) \). In addition, one third of the children with asthma and half of the infantile wheezers had a proportion of neutrophils >10%, which was related to symptom severity. These results imply that neutrophil-mediated inflammation may contribute to asthma symptomatology in children. That increased neutrophil levels were related to the symptom severity highlights the importance of these inflammatory cells in airway disturbances in both asthmatic children and infantile wheezers.

Whether inflammation plays a role in atopic and nonatopic wheezing was the focus of a study in children with viral-induced wheezing and persistent allergic asthma.\(^{12}\) Data were collected voluntarily from children hospitalized for elective surgery. During the surgery, a nonbronchoscopic lavage was performed through a suction catheter inserted in the endotracheal tube and wedged in a distal airway. The study group included a total of 95 children: 52 with atopic asthma, 23 with atopy and no asthma, and 20 with wheezing associated with viral upper respiratory infections (mean: 8 years old for asthmatic and nonasthmatic children; 3 years for children with wheezing associated with upper respiratory infections). No significant differences were detected in the level of eosinophils in the exudates from children with persistent or episodic asthma (Fig 2). Nevertheless, children with viral wheezing had significantly lower levels of eosinophils than either the children with atopic asthma or those without asthma.

Eosinophil levels in the lavage were reexamined after the children were further subdivided into groups of those older or younger than 5 years of age. In both older and younger children, higher levels of eosinophils were observed in those with atopic asthma relative to those with viral-associated wheezing (VAW) or those with atopy and no asthma (Fig 3). These data suggest that the phenotype for asthma may be different from other wheezing conditions. Moreover, this separation appears to begin rather early in life. These data are another clear sign that inflammation is important in early asthma development.

CONCLUSION

Unquestionably, inflammation plays a critical role in asthma pathogenesis. Distinguishing asthma from other wheezing disorders remains daunting, however. Elevated markers of inflammation, although characteristic of asthma, are not always unique to this condition and may be present in other wheezing conditions such as CF. In very young children, and in the absence of infection, wheezing may be a precursor of asthma warranting increased vigilance, or it could be a symptom of asthma requiring immediate treatment. Nevertheless, in children with asthma, key markers of inflammation are present early in life, highlighting the importance of early intervention to prevent the irreversible remodeling that may underlie this chronic disease.

Many important questions regarding the role of inflammation in airway obstruction still need to be answered: Are there several asthmatic phenotypes? When does inflammation begin in childhood asthma? Clearly, some key inflammatory events begin in children with asthma as young as 6 months of age. When do eosinophils and neutrophils begin to increase in the airway? When does the deposition of extracellular matrix material begin to occur? Does wheezing in young children share a common phenotype with asthma? At present, these questions cannot be answered satisfactorily. Until they are, the goals of easily identifying young children at high risk for asthma, and distinguishing asthma from other wheeze-inducing disorders, will remain a major focus for guiding research efforts throughout the world.

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*Pediatrics* 2002;109;368

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