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Recent Advances in the Understanding and Management of Asthma

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Abstract

Asthma is a chronic disease characterized by symptoms of intermittent shortness of breath with wheezing and airflow obstruction, affecting some 10 million persons in the United States. Both the prevalence and the mortality rates appear to be rising not only in the U.S. but throughout the world. Recent research has shown that asthma is initiated by complex interactions involving many different cell types with the release of a variety of mediators. This causes a particular type of inflammation in which the eosinophils predominate. There is epithelial damage, microvascular leakage and activation of neural mechanism. The inflammation is believed to be the underlying basis for bronchial hyperreactivity which is associated with the severity of the disease and the need for treatment. Understanding in these mechanisms has led to new emphasis on the control of inflammation in the approach to management. The most significant advance is the development of inhaled topical steroids with little systemic effects. In mild, intermittent asthma, inhaled 3-adrenergic agonist remain the first line of treatment. Chronic asthma should be managed with inhaled steroids in addition to 0-adrenergic agonists. Other anti inflammatory agents such as cromolyn and nedocromil have a role in some patients. This strategy should greatly reduce the need for systemic steroids thus limiting their use and their unwanted side-effects to only a few very severely affected patients.

Epidemiology

Despite the intensive efforts in research in asthma over the last 20 years resulting in a better understanding of the pathophysiology of the disease and the availability of improved and more potent medications, asthma morbidity and mortality, after showing a trend of falling, are now on the rise. Between 1980 and 1987, the prevalence rate of asthma in the United States increased 29 percent and death rates with asthma as the first-listed diagnosis increased 31 percent. It is now estimated that approximately 5% of the United States population or more than 10 million Americans suffer from asthma. It should be noted that these increases are not uniform across all ages but predominately affect children and young adults especially in inner cities. Additionally, the increase in asthma prevalence appears worldwide and has been reported as far apart as Britain, Taipei, Australia and New Zealand. In Hong Kong, rates of hospitalization were more than doubled for children 1-14 years of age between 1977 and 1987.

Comparison of asthma prevalence between various populations of the world is difficult because of difference in the definition of asthma, methodology of survey and even the use of different designations for prevalence (current or cumulative) in the reported studies. In recent surveys in children in developed countries, the prevalence of wheezing ranges

widely from 11.5% up to 23.1%. Rates for actual asthma are lower and are in the 5-10% range. In Chinese children, the prevalence appears to be somewhat lower. It affects 2.4% of 11-17 years olds in Guangzhou, 5.1% of 7-15 years olds in Taipei and 8.0% of 8-10 year olds, 8.6% of 10-18 year olds in two surveys in Hong Kong. The finding of a strong correlation between the level of particulate air pollution and asthmatic hospital admissions for young children 1-4 years of age suggest environmental factors may have an important role.

Pathophysiology

Asthma is a disease of the airways. It is characterized by intermittent episodic and reversible airflow obstruction. In severe, chronic cases, obstruction is persistent and prolonged. Bronchial obstruction is due to a combination of bronchoconstriction, edema of the bronchial mucosa and the presence of increased and viscid bronchial secretions. Until recently, treatment of asthma emphasized the use of bronchodilators to overcome the obstruction. The most important new development in asthma is the recognition that the underlying abnormality is a distinct and characteristic inflammatory process in the airways. Biopsies of bronchial walls and bronchoalveolar lavage studies in asthmatics have demonstrated the presence and the infiltration of bronchial walls by inflammatory cells even in mild asthmatics. These include mast cells, alveolar macrophages and lymphocytes; but the most characteristic feature is the predominance of eosinophil and relative lack of neutrophil. The role of airway inflammation is further strengthened by the demonstration of an increase in the number of these cells in bronchoalveolar fluid after antigenic challenge. There is injury to the epithelium with disruption of the lining cells but with remarkably little fibrosis and scarring or distortion of the airways.

The pathophysiologic event leading to the development of airway inflammation are complex. The mast cell is thought to play a key role in the initiation of the reaction. When stimulated by appropriate allergens or other non-allergenic stimuli, the mast cells degranulate releasing histamine and a number of mediators including prostaglandins, leukotrienes, platelet activating factor, bradykinin as well as eosinophil, and neutrophil chemotactic factors. In addition, other mediator releasing cells with low affinity IgE receptors such as macrophages may also be activated. These potent biologically active chemicals can cause both an immediate response and a late phase cellular reaction. The immediate response includes bronchoconstriction, increased microvascular leakage with mucosal edema and increased mucus production. The late phase which involves migration of inflammatory cells such as the eosinophils, neutrophils and T lymphocytes may take many hours to develop. It is associated with the activation of intercellular adhesion molecules (ICAM) for the continued recruitment and retention of inflammatory cells to the region. Eosinophils are known to contain proteins such as cationic protein and major basic protein which are toxic to the airway epithelium. The damage and denudation of the epithelium not only destroys membrane-bound epithelial enzymes (endopeptidases) which are important in degrading mediators but also exposes sensory nerve endings which have been shown to release neuropeptides through an axon reflex. The peptides released from these non-adrenergic, noncholinergic nerves include substance P, calcitonin-gene-related peptide and neurokinin A. They have been shown to increase microvascular permeability and mucus production, dilate bronchial vessels and induce bronchoconstriction, thus amplifying the inflammatory response in the airways.

Strategies in therapy

There is mounting evidence to suggest that the extent of airway inflammation correlates with the degree of bronchial hyperreactivity. Bronchial hyperreactivity has been shown to be related to the severity of asthma and the need for therapy. A key element in the treatment of asthma should therefore include the reduction and reversal of airway inflammation. B-adrenergic agonists, long established as potent bronchodilators, do not inhibit the late phase response or the bronchial hyperreactivity. They will, however, relax airway smooth muscle and produce bronchodilation irrespective of the cause of bronchospasm including airway inflammation. Inhaled B-adrenergic agonists with their rapid onset of action remain the treatment of choice for the short-term relief of acute asthma.

Use of steroids

If inflammation is the underlying pathogenetic mechanism for airflow obstruction in asthma then it is logical that antiinflammatory agents should be the mainstay of treatment of chronic disease. It has long been known that corticosteroids are highly effective in chronic asthma. Steroids do not inhibit the release of mediators from mast cells and do not prevent the immediate response in bronchoprovocation challenges. They do abolish the late phase response and reduce bronchial hyperreactivity. The molecular mechanism of action of steroids is still incompletely understood. It is known that steroids upon entering the cell bind to a cytoplasmic steroid receptor. This steroid-receptor complex is taken into the nucleus where transcription of a specific messenger RNA occurs. This results in the production of a new protein, lipomodulin, whose split product macrocortin, is responsible for the action of steroids. Because of the requirement of the synthesis of a new protein for its actions, steroids have a delayed onset of action and some beneficial effects may take weeks or months to manifest. The well recognized steroid actions include:

1. an increase in the expression of P-adrenergic receptors and their sensitivity,
2. inhibition of phospholipase A2 and decrease in the synthesis of leukotrienes, prostaglandins and platelet activating factor,
3. prevention of cytokine release and the migration and activation of inflammatory cells to the lung,
4. inhibition of the mediator release from macrophages, monocytes and eosinophils,
5. a decrease in circulating lymphocytes and suppression of the late phase reaction.

Although steroids are highly effective in the control of asthma, their systemic side effects are the main reason for poor acceptance by both patients and physicians. The most significant recent advance in asthma therapy has been the development of inhaled steroids. These preparations are characterized by their very high topical potency plus their rapid inactivation if swallowed. The high topical potency allows use of a very small effective dose thereby greatly minimizing the steroid side effects or hypothalamicpituitary axis suppression. What is not sufficiently emphasized is that inhaled steroids do not provide immediate relief of bronchospasm. It takes several weeks to exert their beneficial effects and may take even longer to reduce bronchohyperreactivity. Therefore, they are intended for long-term use in asthmatics with persistent symptoms not readily controlled by inhaled B-adrenergic agonists.

Guidelines in management

With the understanding that inflammation is the underlying pathogenetic mechanism for asthma and the availability of potent topical steroids with little side-effects, certain new guidelines for the management of asthma can now be formulated. It is obviously important to avoid known allergens and other inciting factors including environmental pollutants and infections. Patients with mild asthma with intermittent symptoms should be treated with and usually respond well to inhaled B-adrenergic agonists. Patients with more persistent symptoms should be placed on long-term inhaled steroids. Other medications including theophylline, cromolyn sodium and nedocromil sodium may be useful in some patients. Although the vast majority of patients will attain satisfactory control with these measures, some patients will have severe and unpredictable episodes of airflow obstruction and require systemic intravenous and oral steroids. Exacerbations are particularly com-mon in association with viral respiratory infections. Although inhaled steroids are ineffective during these acute episodes, they should be resumed as early as possible to allow withdrawal of systemic steroids and minimize their side effects.

"Little drops of water, little grains of sand, Make the mighty ocean and the pleasant land. So the little moments, humble though they be, Make the mighty ages of eternity." -- Julia A. Carney, "Little Things"