The pathogenesis of asthma

Abstract

Asthma is a chronic inflammatory disease which is characterized by airway hyperresponsiveness with reversible bronchial obstruction, spontaneously or with treatment. Its development depends on interactions between external factors and genetic predisposition to atopy and bronchial hyperresponsiveness. Exacerbations are caused by allergens (antigens from dust mites, pets, cockroach and molds), viral infections and other irritants (tobacco, weather changes and medications). Bronchial inflammation is the major feature in asthma pathogenesis and results from complex interactions between inflammatory cells, structural bronchial cells, cytokines and inflammatory mediators. Some clinical comorbidities can be associated with asthma, contributing to its severity, such as rhinosinusitis, gastroesophageal reflux and broncopulmonary allergic fungal diseases.

Keywords: Asthma; Inflammation; Etiology.

Asthma immunopathogenesis

The development of bronchial asthma is associated with several external (environmental and occupational) and individual (genetic and psychosocial) factors, and depends on the interaction between these external factors and genetic predisposition to the development of bronchial hyperresponsiveness and atopy, i.e., genetic predisposition to the overproduction of immunoglobulin E (IgE) specific to common environmental antigens.

The main external factors associated with the development of asthma are inhalable allergens (substances from the body and excrement of domestic mites, insects like cockroaches, and pets, as well as fungal antigens and pollens) and respiratory viruses, particularly infections caused by respiratory syncytial virus (RSV) in the early years of life. Environmental pollutants such as cigarette smoke, gases, and particulates suspended in air pollutants such as particulates from the combustion of diesel oil also appear to act as advocates or facilitators of bronchial hyper-responsiveness in predisposed individuals.1,2

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In relation to occupational agents, about 300 substances have been identified as potential causative agents of occupational asthma, and it is believed that 10% of asthma initiated in adulthood is associated with these agents. In occupational asthma, there are well-defined occupational agents that induce asthma via allergic (IgE-mediated) mechanisms and other agents that induce non-allergic asthma. They are divided into high (>10 kd) and low molecular weight agents. The former include animal and vegetable proteins, the main examples of which are cereals, which cause asthma in bakers; latex, which affects health professionals; and epithelial cells, saliva, and urine of animals, which affect veterinary and laboratory workers. The second group includes chemicals such as isocyanates, which cause asthma in employees of the plastic and rubber industries, and acid anhydrides, which affect workers in epoxy resin, plastic, and insecticide industries.

Several candidate genes, at different levels of penetration and association, have been associated with different asthma phenotypes. Typically, the individual impact of these various genes on phenotypic manifestations of the disease is small; however, large effects can arise from the synergistic action of multiple genes in an environmental context. The wide phenotypic heterogeneity of asthma, which can start at any age, can be intermittent and mild, transitory, or persistent and extremely serious, and is associated with different intermediate phenotypes such as atopy, bronchial hyper-responsiveness, varying serum levels of IgE, and atopic dermatitis, among others, contributes to difficulty in characterization of the specific role of individual genes in the development of this disease.

More than 30 genes have been identified as candidates for susceptibility to the development of asthma, and are divided into 4 broad groups: (a) those associated with innate immunity and immunoregulation (e.g., CD14, toll-like receptor [TLR]-2, TLR-4, TLR-6, TLR-10, interleukin [IL]-10, transforming growth factor-beta [TGF-β], human leukocyte antigen [HLA]-DR, HLA-DQ, and HLA-DP); (b) those associated with atopy and T-helper type 2 (Th2) cell differentiation and function (e.g., GATA-3, IL-4, IL-4 receptor [IL-4R], Fc RI, IL-5, IL-5 receptor [IL-5R], and signal transducer and activator of transcription [STAT]-6); (c) those associated with epithelial biology and immunity of mucous membranes (e.g., the chemokines CCL5/RANTES, CCL11, CCL26, CCL24, and filaggrin); and (d) those associated with pulmonary function and bronchial remodeling (e.g., ADAM-33, DPP-10, and HLA-G).

The effects of fetal and early life exposure to maternal smoking, infectious diseases, diet, and breastfeeding on the risk of infant asthma can be modified by genetic susceptibility. Recent epigenetic studies suggest that expression of the asthma-related genes glutathione S-transferase (GST), methylenetetrahydrofolate reductase (MTHFR), gasdermin-like (GSDML), and orosomucoid 1-like 3 (ORMDL3) can be modified by environmental exposure to substances including tobacco. An increased risk of early onset asthma is associated with exposure to tobacco in early childhood due to genetic variations of the genes ORMDL3 and GSDML, among others. In addition, exposure to tobacco in fetal life seems to be associated with transient wheezing in childhood due to changes in GST.

Other individual characteristics are also associated with the development of asthma. Boys have twice the risk of developing asthma as girls of the same age, and obesity has been linked to increased risk of asthma.

Bronchial inflammation is the most important pathophysiological mechanism of asthma, and is the result of complex interactions between inflammatory cells, inflammatory mediators, and structural airway cells. Inflammation is present not only in severe asthmatics or those with long-term illness but also in patients with recent onset asthma, those with mild forms of the disease, and even asymptomatic individuals. The inflamed bronchial mucosa becomes over-reactive to several stimuli, whether they are allergic stimuli or not.
In allergic asthma, which represents the majority of cases of asthmatic disease, the IgE-mediated response causes immediate changes, minutes after exposure to the allergen(s), and late changes, which represent the chronic inflammatory response characteristic of the disease (figure 1).

Atopic individuals, who have a genetically determined predisposition to produce large amounts of IgE antibodies specific to environmental allergens/inhalants (substances from dust mites, fungi, insects, pets, and pollens) after previous exposure, i.e., those who are already producing IgE specific for one or more of these allergens, experience immediate IgE-mediated hypersensitivity of the airway mucosa when they inhale these substances. The binding of the allergen to IgE on the membranes of mast cells in the mucosa and submucosa leads to bronchial degranulation and activation of these cells, which release preformed mediators such as histamine and platelet-activating factor (PAF) from their granular stores, as well as newly formed mediators produced from arachidonic acid released by cell membranes, such as prostaglandins and leukotrienes. The immediate effects of these substances are vasodilation and vascular extravasation, subsequent swelling of the bronchial wall, mucus hypersecretion, and bronchoconstriction, which are responsible for the clinical manifestations of asthma crises (dyspnea, cough with viscous secretion, wheezing, and tightness of the chest).1,2

Activated mast cells also produce IL-3, IL-5, and granulocyte-macrophage colony-stimulating factor (GM-CSF) which, along with the leukotrienes, activate and attract other inflammatory cells to the bronchial wall, perpetuating the inflammatory process. Bronchial inflammation in asthma has other special features in addition to the activation and degranulation of mast cells, such as eosinophilic infiltration, interstitial and epithelial injury of the airway, and activation of Th2 lymphocytes that produce cytokines such

![Figure 1: Phases of the IgE-mediated response. (ABBA- Cellular and Molecular Immunology)](source: Kay AB. Allergy and allergic diseases. N Engl J Med, Vol. 344, No. 1 · January 4, 2001.)
as IL-4, IL-5, and IL-13, among others. These cytokines are responsible for amplification and worsening of the inflammatory process and act as a continued stimulus to produce more IgE specific to environmental allergens.

IL-4 has an important role in increasing both the production of specific IgE and the expression of high and low affinity receptors for IgE on inflammatory cells such as mast cells, basophils, and eosinophils. IL-5 is important in the attraction, activation, and increased survival of eosinophils, which act as the main effector cells of tissue injury through the release of cationic proteins that damage the extracellular matrix and epithelial cells. IL-13 acts synergistically with IL-4, increasing the production of specific IgE by B lymphocytes and differentiated plasma cells, both locally and at a distance.

Extracellular signal-regulated kinase (ERK) is a signaling protein that regulates the meiosis and mitosis of differentiated cells, including T lymphocytes, and also acts on various cellular processes such as proliferation, differentiation, growth, and secretion of cytokines. It has an important role in the differentiation of Th2 lymphocytes and disease development in experimental models of bronchial asthma.6

Various inflammatory mediators and cytokines are also released by other cells such as activated macrophages (tumor necrosis factor-alpha [TNF-α], IL-6, and nitric oxide), T lymphocytes (IL-2, IL-3, IL-4, IL-5, and GM-CSF), eosinophils (main basic protein [MBP], eosinophil cationic protein [ECP], eosinophil peroxidase [EPO], prostaglandins, leukotrienes, and cytokines), neutrophils (elastase), and epithelial cells (endothelin-1, nitric oxide, prostaglandins, and leukotrienes). In addition, the activated vascular endothelium plays an important role in the recruitment of inflammatory cells through increased expression of adhesion molecules such as intracellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM)-1.1,2,7 Through mediator release, these cells cause injury to the epithelium and changes in epithelial integrity, abnormalities in neural control and autonomic tonus of air flow, changes in vascular permeability, mucus hypersecretion, changes in mucociliary function, and increased smooth muscle reactivity of the airways, leading to bronchial hyper-responsiveness.7,8

Therefore, asthma is an inflammatory disease of the airways mediated by Th2 lymphocytes and eosinophils, involving tissue remodeling and bronchial obstruction. In addition, other T-cell phenotypes including Th17 cells and natural killer T (NK-T) cells also contribute to the pathogenesis of asthma.9,10 NK-T cells play a crucial role in the pathogenesis of asthma exacerbation in animal models. Koh et al11 have shown that serum levels of these cells are discriminated against during the exacerbation of asthma secondary to viral infection, suggesting that they are mobilized to the airways and lungs during these episodes.

In chronic inflammation, epithelial cells and myofibroblasts present below the epithelium are activated, undergo proliferation, and carry out interstitial deposition of collagen and proteoglycans in the lamina reticularis (basal membrane), resulting in the apparent thickening and irreversible damage that can occur in patients with severe asthma or long evolution of this disease. Other changes, including smooth muscle hyperplasia and hypertrophy, an increased number of Goblet cells, proliferation of the glands and submucosal blood vessels, and changes in deposition/degradation of extracellular matrix components, occur to cause the remodeling that interferes with the architecture of the airway and may lead to irreversibility of bronchial obstruction. All these structural changes are induced by activation and dysregulation of the normal activity of the epithelial-mesenchymal trophic unit, which is represented by bronchial epithelium, myofibroblasts, and bronchial smooth muscle. Recent studies have also demonstrated the ability of the muscle cell itself to become a cell with pro-inflammatory activity, producing cytokines and acquiring the ability to express several surface molecules important in chronic inflammation.7,8
Viral respiratory tract infections are the primary triggering factor of asthma crises in both adults and children. Respiratory viruses have the ability to greatly enhance bronchial hyper-responsiveness by stimulating the inflammatory process and elevating local, autonomic dysfunction with significant increases in the production of neuropeptides (e.g., substance P, neurokinin A, and neurokinin B, etc.) from the nonadrenergic noncholinergic (NANC) nerves of the submucosa. In addition, this causes easier contraction of atopic viral infection, particularly by the rhinoviruses, since these viruses infect cells by using adhesion molecules such as ICAM-1, which show increased expression in the inflamed bronchial epithelium. Therefore, viruses may be important factors in the elevation and maintenance of bronchial inflammation as well as worsening of the disease, particularly in children.12

Anatomopathological changes, previously identified in severe cases of asthma-related death, are currently demonstrated by available methods for the collection and study of bronchial biopsies. In asthma, there is hypertrophy and hyperplasia of the bronchial smooth muscle, which correlates with the severity and duration of illness. These changes, associated with vascular proliferation and the increase of submucosal gland size, collaborate to induce progressive thickening of the bronchial wall, known as bronchial remodeling, and reduced airflow obstruction reversibility.7,8 Fibrosis can be present in varying degrees and is identified in all individuals with asthma, even before the appearance of symptoms. With the progression of the inflammatory process and consequent damage to the bronchial epithelium, areas of epithelial cells are lost and sensitive nerve endings are exposed to irritants, inflammatory cells, and allergens. In cases of asthma-related death, there is a large amount of mucus in bronchial eosinophils, the presence of Charcot–Leyden light crystals (eosinophilic cation protein aggregates) and Curschmann spirals (clusters of eosinophils), extensive epithelial damage, extensive infiltration of lymphocytes and eosinophils in the submucosa, an exaggerated increase in the bronchial smooth muscle of the bronchial submucosal glands, and extensive fibrosis with sub-epithelial thickening, i.e., extensive lower airway remodeling (figure 2).

Triggers of asthma attacks

The bronchial asthma feature of hyper-responsiveness is triggered by several factors, which can be specific (allergic) or nonspecific (non-allergic). Specific factors include inhaled drug allergens, substances derived from domestic mites, animals such as dogs and cats, and cockroaches, and mold in the air. In the southern region of Brazil, as well as in the northern hemisphere, where pollination occurs at certain times of the year, pollen is also an important trigger of asthmatic symptoms. In Rio de Janeiro, pollen does not trigger symptoms, although there are individuals sensitized to pollen in this region.

Nonspecific factors include viral infections (RSV, rhinovirus, adenovirus, parainfluenza, and influenza), which are the most frequent cause of asthma attacks in infants and children (up to 90% of crises). About 40% of adult asthma attacks are associated with viral infection, whereas about 10% are caused by subclinical bacterial infection.12

Viral infections and allergens interact to increase the risk of exacerbations. Rhinoviruses are the most frequently detected viruses, except in infants hospitalized due to bronchiolitis, in whom RSV is the main cause of asthma attacks. Influenza is a common infection during the winter. After the pandemic of influenza A (H1N1) in 2009, several studies highlighted that asthma was an important comorbidity in this infection, whose severity markers, such as hospitalization, intensive care unit admission, and mortality, were associated with the diagnosis of asthma.13

Other nonspecific triggers include climate change, cold and dry air, and environmental pollutants, including tobacco and strong odors (detergents, perfumes, and paints). Smoking induces a non-eosinophilic inflammation
pattern with resistance to corticosteroids. The emergency care and hospitalization of asthmatic adults are more frequent in smokers than in nonsmokers. There is also evidence that smoking is a risk factor for fatal and near-fatal asthma.2,7,13

Physical exercise can trigger asthma attack, which are often expressed by a dry cough and low tolerance to stress only, especially in children and adolescents. In these cases, mast cells are activated directly by cooling and an increase in the osmolarity of the airway due to hyperventilation caused by physical exertion. These changes may also occur during prolonged laughter.14,15

About 10% of asthmatics are sensitive to acetylsalicylic acid (AAS) and nonsteroidal anti-inflammatory drugs (NSAIDs), which can trigger crises if used systemically or topically. Some of these patients develop severe allergic asthma that is not primarily associated with rhinosinusitis and nasal polyposis (now called aspirin-exacerbated respiratory disease [AERD] or Samter syndrome). In AERD, blockade of the cyclooxygenase (COX) enzymes (primarily COX-1) by the action of AAS or NSAIDs with consequent increased production of cysteinyl leukotrienes by lipoxygenase, increased expression of receptors for leukotrienes on target cells, and reduction of inflammatory modulators by prostaglandin E2 and the lipoxins are the main mechanisms responsible for the development of respiratory disease. Characteristically, asthma in AERD tends to have a severe evolution, with eventual crises requiring intensive treatment. In these cases, airway disease persists even after suspension of the use of AAS or NSAIDs.1,2,8,16

Rarely, foods may trigger asthma crises. In patients with food allergy, bronchospasm may occur with other manifestation, including anaphylaxis, urticaria, angioedema, and hypotension.

Beta blockers may trigger bronchospasm in patients with subclinical bronchial hyper-
-responsiveness or exacerbate the condition in those with pre-existing asthma; thus, beta blockers are contraindicated in these patients. Reduction of kinase activity related to the use of angiotensin-converting enzyme (ACE) inhibitors can cause the loss of control of asthmatic symptoms, but is rarely an isolated cause of bronchospasm.

Exacerbations occur in about 20% of pregnant asthmatic patients. They can occur throughout pregnancy; however, they are more frequent at the end of the second trimester. The main risk factors for exacerbations during pregnancy are severe asthma, viral infections, and interruption of treatment as a result of the belief that treatment would harm the fetus. In clinical practice, one should never underestimate the influence of emotional factors on chronic diseases, and it is not uncommon to observe their action as triggers or, at least in part, aggravating factors for asthma attacks.

**Conditions aggravating the development of asthma**

Some medical conditions may be associated with asthma and contribute to its worsening, thus increasing the need for the use of medicines. These conditions include rhinosinusitis (acute or chronic), gastroesophageal reflux disease (GERD), and allergic bronchopulmonary mycoses. When asthma does not respond to properly instituted maintenance treatment and there are signs/symptoms of these conditions, they should be properly investigated and dealt with. However, prior to this, it should be kept in mind that asthma is a complex disease pathogenesis, which is influenced by several external factors, and adherence to the various therapeutic measures for asthma is difficult. Therefore, therapy should be re-evaluated in every patient who does not display the expected response to treatment.

**Rhinosinusitis**

Epidemiological studies and clinical practice draw attention to the important association between rhinosinusitis and asthma. Up to 80% of asthmatics have associated allergic rhinitis, which can be combined with allergic and chronic sinusitis, a predisposing factor for sinusitis. On the other hand, about 40% of individuals with allergic rhinitis have some degree of bronchial hyper-responsiveness, which is often sub-clinical, or asthma itself. The same genetic and environmental factors known to predispose patients and/or trigger symptoms act in a similar way in the upper and lower airway, leading to the clinical manifestations of rhinitis and allergic asthma, respectively. Moreover, even in non-atopic asthma phenotypes, e.g., aspirin-induced asthma or respiratory disease exacerbated by aspirin, naso-sinus inflammation coexists with familial asthma, which is usually of severe evolution. The upper and lower airways have several similar anatomical features such as epithelial cells lining a mucous membrane, a lamina propria, and an extracellular matrix submucosa, which is populated by cells with immuno-inflammatory potential. There are also a few differences, including the presence of the large venous plexus of the nasal submucosa, which is absent in the bronchial submucosa, and, conversely, the presence of myofibroblasts in the bronchial submucosa and smooth muscle surrounding the bronchial tree.

Studies show that the presence of sinusitis worsens the clinical evolution of asthma and is associated with a higher frequency of severe asthma. In addition, the treatment of allergic rhinitis alone improves the control of asthma and reduces bronchial hyper-responsiveness. More than 33% of patients with chronic rhinosinusitis and nasal polyps have bronchial hyper-responsiveness (with or without history of wheezing).

**Gastroesophageal reflux**

GERD also worsens asthma, mainly in patients at the extremes of age, i.e., in infants, young children, and the elderly, and occurs more frequently in asthmatics when compared with
the general population.

Cholinergic vagal reflexes cause repeated esophagobronchial microaspirations, which seem to be the main factor involved in the interrelationship between GERD and asthma. Therefore, clinicians should pay attention to their presence when cough and/or bronchospasm occur as a result of or are intensified by decubitus and/or meals, even with adequate treatment of asthma. In addition, it should be remembered that in these cases, the xanthines can aggravate symptoms by relaxing the lower esophageal sphincter, worsening reflux.1,2,8

Allergic bronchopulmonary mycoses

This group of diseases are characterized by type I (IgE-mediated) and type III (mediated by immune complexes) hypersensitivity, which leads to chronic asthma, transient pulmonary infiltrates, proximal bronchiectasis, very high levels of serum IgE (up to 1000 IU/dL), and the need for systemic corticosteroids for disease control. The first illness described in this group, which is also the most frequently encountered, was bronchopulmonary allergic aspergillosis (ABPA), but other fungi have been described as causative agents in this class of diseases.

In ABPA, fungal spores adhere to the bronchial walls and bronchioles, perpetuating the local inflammatory response mediated by IgE and IgG. Via activation of the complement system and attraction of neutrophils, the fungus then promotes greater damage to the airway already affected by allergic asthma.21,22

Obesity

Asthma and obesity are conditions that are considered as public health problems, and obesity is currently thought of as a risk factor for asthma. Several studies have shown the relationship between the percentile of body mass index (BMI) and asthma.23 In 2011, a Brazilian study associated obesity with uncontrolled asthma.24,25 The authors showed that obesity doubles the risk of asthma in children of school age.31,32 In addition, overweight asthmatic children and obese women used more beta-adrenergic agonists and oral corticosteroids than patients of normal weight.25

Changes in respiratory mechanics with decreased functional residual capacity and tidal volume secondary to obesity can cause worsening of asthmatic symptoms. Obesity also increases the risk of gastroesophageal reflux, which can lead to asthmatic hyper-responsiveness.26

Adipose tissue produces a number of cytokines such as TNF-α, IL-6, adiponectin, and resistin, which have important roles in the modulation of local and systemic metabolism. The production of TNF-α is markedly increased in the adipose tissue of obese subjects and high levels of TNF-α are also found in asthma, where they are associated with the production of Th2 cytokines (IL-4 and IL-6) in the bronchial epithelium.

Several cross-sectional studies have shown a significant association between BMI and asthma in women but not in men. A plausible hypothesis is that female sex hormones play an important role in the pathogenesis of asthma and that these hormones are affected by obesity. Progesterone increases the expression of β2 receptors. One theory is that obesity reduces progesterone levels, reducing the function of β2 receptors, which in turn decreases the relaxation of bronchial smooth muscle.27

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