OCCUPATIONAL ASTHMA: WHAT ARE THE MECHANISMS?

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Occupational asthma may be defined as asthma induced by acquired hypersensitivity to an agent inhaled at work. A lot of agents in the workplace have been shown to cause asthma and the list is growing as new materials and processes are introduced. There are two major types of occupational asthma. Sensitizer-induced asthma is characterized by specific responsiveness to the etiologic agent. The mechanism of irritant-induced asthma is unknown, but there is no clinical evidence of sensitization. Two other mechanisms by which variable airway obstruction due to workplace exposure can occur are reflex and pharmacological bronchoconstriction. Occupational asthma can be a challenging diagnosis to make and to prove. Tests which are used and are helpful include nonspecific pulmonary function tests, specific or bronchoprovocative pulmonary function test, serial pulmonary function tests (most commonly using the peak flow meter), and immunologic tests. Each test has its own drawbacks and none is perfect. Early diagnosis of occupational asthma and early removal of patients from exposure are important. *Acta Medica Medianae 2003; 42 (3): 53-57.*

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Introduction

Asthma is characterized by airway obstruction that is reversible either spontaneously or with treatment, airway inflammation, and increased airway responsiveness to variety of stimuli. In occupational asthma, there is variable airway obstruction and/or airway hyperresponsiveness due to workplace exposure(s). Work-related variable airway obstruction can be caused by several mechanisms, including type I-immune reactions, pharmacological effects, inflammatory processes, and directs airway irritation. Many agents in the workplace have been shown to cause asthma and the list is growing as new materials and processes are introduced. Work-aggravated asthma occurs when workplace exposures lead to exacerbation's of preexisting nonoccupational asthma.

There are two major types of occupational asthma. Sensitizer-induced asthma is characterized by a variable time during which "sensitization" to an agent present in the work site takes place. Irritant-induced asthma occurs without a latent period after substantial exposure to an irritating dust, mist, vapor, or fume. Reactive airways dysfunction syndrome (RADS) is a term used by some to describe irritant-induced asthma caused by a short-term, high-intensity exposure.

Sensitizing agents known to cause occupational asthma can be divided into high-molecular weight (> 1000 Dalton) and low-molecular-weight compounds

Table I. Some agents causing occupational asthma

Mechanism	Examples
Without "sensitization" Anticholinesterase effect Endotoxin effects Airway inflammation Airway irritation	Organophosphate pesticide (agricultural workers) Cotton dust (textile workers) Acids, ammonia, chlorine (custodial workers, paper manufacturing workers) Dusts, fumes mists, vapors, cold (construction workers, chemical workers)
With "sensitization" High-molecular-weight agents IgE-mediated (complete allergens) Low-molecular-weight agents IgE-mediated (haptens) Mechanisms undefined	Animal and plant proteins (laboratory workers, Bakers) Antibiotics, metals (pharma-ceutical workers, metal plating workers, Acid anhydrides, di-socyanates, plicatic acid (epoxy plastics and paints, polyure-thane foams and paints, western red cedar products)

High molecular-weight compounds tend to cause occupational asthma via type I immunoglobulin E-mediated reactions, whereas the mechanism(s) of low-molecular-weight compounds is currently unknown. Sensitizer-induced asthma is characterized by specific responsiveness to the etiologic agent. The mechanism of irritant-induced asthma is unknown, but there is no clinical evidence of sensitization. Irritant-induced asthma involves persistent nonspecific airway hyperresponsiveness but not specific responsiveness to an etiologic agent. While there is no doubt that irritant-induced asthma can be caused by a single intense exposure (i.e., RADS), it appears that lower-level exposure over a longer duration of time (months to years) can also cause the disease (1,2).

Pathophysiology

Airway inflammation is now recognized as the paramount feature of asthma. Asthmatic airways are characterized by (1) infiltration with inflammatory cells, especially eosinophils; (2) edema; and (3) loss of epithelial integrity. Airway obstruction in asthma is believed to be the result of changes associated with airway inflammation. Airway inflammation is also believed to play an important role in the genesis of airway hyperresponsiveness (2,3,4).

Most of the research on mechanisms that mediate airway inflammation in asthma has focused on high-molecular-weight allergen-induced responses. In a previously sensitized individual, inhalation of specific allergen allows interaction of the allergen with airway cells (mast cells and alveolar macrophages) that have specific antibodies (usually IgE) on the cell surface. This interaction initiates a series of redundant amplifying events that lead to airway inflammation. These events include mast cell secretion of mediators, lymphocyte interaction, and eosinophil recruitment to the airways. The generation and release of various cytokines from alveolar macrophages, mast cells, sensitized lymphocytes, and bronchial epithelial cells are central to the inflammatory process (figure 1).

Cytokine networking, with both enhancing and inhibitory feedback loops, is responsible for inflammatory cell targeting to the bronchial epithelium, activation of infiltrating cells, and potential amplification of epithelial injury. Adhesion molecules also play critical roles in the amplification of the inflammatory process. The expression of various adhesion molecules is unregulated during the inflammatory cascade, and these molecules are essential for cell movement, cell attachment to the extracellular matrix and other cells, and possibly cell activation. As noted above, the mechanism of low-molecular-weight sensitiyer-induced asthma is not well understood, although bronchial biopsy studies of affected workers have clearly demonstrated that airway inflammation is present.

Inhalation of the specific etiologic agent in a worker with sensitizer-induced asthma will often trigger rapid-onset but self-limited bronchoconstriction. In many sensitized workers, a delayed reaction will occur 4-8. hours later, called the late response. Airway

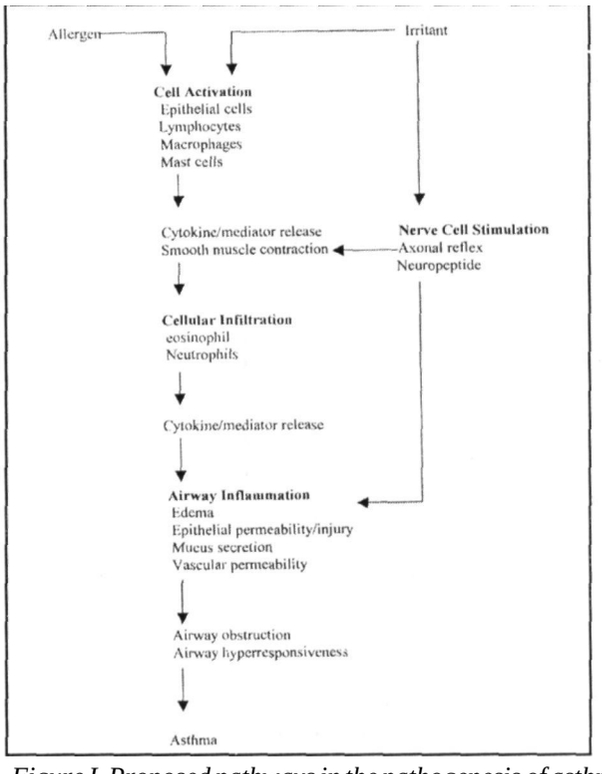

Figure I. Proposed pathways in the pathogenesis of asthma

inflammation, persistent airway obstruction, and airway hyperesponsiveness characterize the late response. In some workers there is a dual response, and in others, only an isolated late response. Mast cell degranulation and release of mediators such as histamine are believed to be responsible for the early response. The role of the mast cell in the genesis of the late response is more controversial, but the release of chemoattractant substances such as leukotrienes and cytokines (i.e., interleukin (IL)-3, IL-4, and IL-5) may be involved in the influx of neutrophils and eosinophils into the airway epithelium. The eosinophil can release proteins (e.g., major basic protein, eosinophilic cationic protein, eosinophil-derived neurotoxin, and enzymes), lipid mediators, and oxygen radicals that can cause epithelial injury. There is increasing evidence that lymphocytes, especially a CD4+ subset known as TH2 cells, are involved in the release of cytokines that may activate both mast cells (IL-3 and IL-4) and eosinophilis (IL-5). In IgE-mediated allergic asthma, Th2 cells may be responsible for the maintenance of chronic airway inflammation.

Although the mechanisms by which airway inflammation occurs in irritant-induced asthma are not well understood, neurogenic pathways may be involved. The axonal reflex involving C-fiber stimulation and the release of neuropeptides have been implicated in models of irritant-induced airway inflammation. With high-level irritant exposure direct chemical injury can lead to an inflammatory response. The important unanswered question is what causes this response to persist in certain individuals.

As the senitizer or irritant-induced airway inflammatory process proceeds, mucosal edema, mucus secretion, and vascular and epithelial permeability all

increase, leading to a reduction of the caliber of the airway lumen and resultant airflow obstruction. The level of airway obstruction in patients with asthma is a marker of the severity of disease. With mild asthma, there may be no evidence of obstruction between acute exacerbation's, but nonspecific airway hyperresponsiveness is likely to be present. With more severe asthma, there is increased airway hyperresponsiveness and airways obstruction is present between attacks.

Two other mechanisms by which variable airway obstruction due to v/orkplace exposure can occur are reflex and pharmacological bronchoconstriction. In reflex bronchoconstriction, agents such as cold air, dusts, mists, vapors, and fumes stimulate neuroreceptors in the airway. The reaction does not involve immunology mechanisms and does not lead to airway inflammation. In most cases, the patient has a history of preexisting nonoccupational asthma with nonspecific airway hyperesponsiveness so that this is primary mechanism of work-aggravated asthma. Pharmacological bronchoconstriction occurs when an agent in the workplace causes the direct release of mediators (e.g. Cotton dust in textile mills) or a direct effect on the autonomic regulation of bronchomotor tone (e.g. Organophosphate pesticides inhibit cholinesterase) (2,6).

Interestingly, biopsies from patients with atopic allergic asthma show very similar histological appearances to biopsies from patients with nonallergic (intrinsic) asthma (7), from patients with occupational asthma due to low molecular weight chemicals, in which immunoglobulin E (IgE) is not thought to be important (8,9), and even from irritant-induced asthma (10). This suggests that the histological appearances of allergic inflammation in asthma represent a final common response to a variety of inciting agents. Despite the huge research effort over the past 10 year, there are a number of important questions that remain to be answered. Chief among these is the need to establish which of the inflammatory changes are primary, and which are secondary events, which follow the primary insult. Secondly, we need to define which of the parameters that we can measure are important to the process that initiates asthma, and which are important to disease persistence and progression. Some may be relevant to both processes while others may operate only at certain phases of the disease. Finely, is inflammation an essential part of the disease, or are there forms of occupational asthma witch have different pathophysiological mechanisms and, therefore, show different relationships to biomarkers of disease severity?

Diagnosis

Diagnosis of occupational asthma depends greatly on the occupational hystory. Many people with occupational asthma have a history of atopy, especially when the exposure is to high-molecular-weight compounds. However, those without such a history may become sensitized after exposure to specific environmental agents such as disocyanates. Suspicion of this diagnosis should be aroused even when a worker has had no previous history of asthma. Often the worker reports wheezing, chest tightness, shortness of breath, or severe cough developing in the evening or at night with recovery overnight or over a weekend away from work. However, if exposure and its effects have been prolonged, the symptoms may persist at home or over the weekend. Specific questioning about nocturnal symptoms may elicit responses otherwise not volunteered. The physical examination of an acutely ill worker reveals wheezing and rhonchi.

Many patients with occupational asthma have normal pulmonary function test results at the time of presentation. A particularly useful test for bronchoconstriction of occupational origin is the FEV1 before and after a work shift. A drop of at least 300 mL, or 10% of the FEV1 (measured as the mean of the two best of three acceptable result each time) between the beginning and end of the first shift of the work week suggest a work-related effect. An acute drop in FEV1 as large as 1,8 L has been measured without the worker reporting symptoms. Serial measurements of peak flow, such as four times daily, both on days at and days away from work, with a simple, inexpensive peak-flow meter can be extremely valuable in detecting work-associated declines in airflow. Peak-flow monitoring has also become a mainstay of asthma management. Excessive eosinophils in the sputum or blood may distinguish asthma from bronchitis. Allergy skin tests with common aeroallergens can be used establish whether or not the worker is atopic. Atopy is a risk factor for high-molecular-weight sensitizer - induced asthma. When high-molecular-weight compounds are responsible for occupational asthma, skin tests with the appropriate extracts may help identify the etiologic agent. Extracts of materials such as flour, animal proteins, and coffee will give positive skin tests in specifically sensitized individuals. Skin testing may also be helpful for a few low-molecular-weight compounds such as platinum salts. IgE antibodies assayed by the radioallergosorbent test (RAST) or by enzyme-linked immunoabsorbent assay (ELISA) may confirm exposure to allergens such as flour, animal proteins, acid anhydrides, plicatic acid, or isocyanates. However, the presence of positive skin reactions and/or specific antibodies is not always correlated with the presence of occupational asthma. Measurement of nonspecific bronchial hyperreactivity is carried out by bronchial provocation test with histamine or methacholine. Approximately 95% of asthmatic patients develop symptoms and significant airflow obstruction after inhalation of these agents. Such testing can be particularly valuable if it demonstrates an increase in airway responsiveness on returning to work or a decrease when away from work. The most specific diagnostic information is provided by an inhalation provocation test using the suspected industrial agent. Identifying and purifying the agent, administering into the patient, and monitoring the concentration achieved are often technically difficult. Provocation tests are time consuming and potentially dangerous. Hospitalization is advisable, since late reactions can only be detected with continuous monitoring, and severe broncho&pasm may require urgent treatment.

Clinical guidelines for diagnosis of occupational asthma have been formulated recently and published (11):

1. Symptoms suggestive of asthma, such as wheezing, dyspnea, cough, or chest tightness, which are variable or intermittent.

2. Documentation of significant reversible or variable airways obstruction.

3. Evidence of an association between the pattern of airways obstruction and some workplace exposure. Anyone of the following types of evidence are sufficient:

a. Documented workplace exposure to an agent known to cause occupational asthma and an association between symptoms patterns and work.

b. Significant work-related changes in spirogram or peak flow.

c. Positive response to bronchial provocation testing with agent to which patient is exposed to work.

Once the diagnosis of occupational asthma is made, the primary intervention is to reduce or eliminate the worker's exposure to the offending agent.

Prognosis

The course of occupational asthma is quite variable. Many patients recover completely, with no long-term sequel. Others develop chronic asthma that is triggered either by specific antigens or nonspecific irritants. In some cases, bronchial hyperreactivity is so severe that the patient can never again be exposed to dust or fumes.

Studies in which individuals who recovered completely were compared with individuals who had persistent asthma have shown that the latter had diminished expiratory flow rates, a significantly longer duration of simptoms before diagnosis, and a greater degree of bronchial hyperreactivity. Thus, early diagnosis of occupational asthma and early remowal of patients from exposure are important (12,13).

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PROFESIONALNA ASTMA: KOJI JE MEHANIZAM?

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Profesionalna astma se može definisati kao astma izazvana izlaganjem agensu u radnoj sredini. Mnogi agensi iz radne sredine su prikazani kao uzročnici astme a njihov broj se stalno uvećava sa upotrebom novih materijala i procesa proizvodnje. Postoje dva glavna tipa profesionalne astme. Senzitivno indukovana astma se karakteriše specifičnom preosetljivošću na etiološki agens. Mehanizam iritantno indukovane astme je nepoznat, ali nema kliničkih pokazatelja senzibilizacije. Druga dva mehanizma koji dovode do varijabilne opstrukcije disajnih puteva na radnom mestu su refleksna i farmakološka bronhoopstrukcija. Dijagnoza profesionalne astme nije jednostavna. Testovi koji su od pomoći u dijagnostičkom postupku uključuju nespecifični i specifični bronhoprovokacioni test, serijsko praćenje plućne funkcije (upotrebom peak flow metra) i imunoloski testovi. Nijedan test nije dovoljno specifican. Rana dijagnoza profesionalne astme i uklanjanje bolesnika od uzročnog agensa su najvažniji. *Acta Medico. Medianae 2003; 42 (3): 53-57.*

Ključne reči: profesionalna astma, patofiziologija, dijagnoza, prognoza