



Bronchial asthma – from psychosomatic illness to proinflammatory cytokines and asthma phenotypes

Bronhijalna astma – od psihosomatske bolesti do proinflamatornih citokina i fenotipova astme

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Bronchial asthma is a chronic inflammatory heterogeneous disease of the airways that is clinically manifested in episodes of heavy breathing, especially at the phase of expiration, shortness of breath accompanied by wheezing, and cough and expectoration of a thick, tough and sticky secretions¹. Pathogenically, asthma is characterized by chronic inflammation of bronchial mucosa and bronchial hypersensitivity, which result in the appearance of the variable, predominantly obstructive disorder of pulmonary ventilation, or by reducing the air flow rate while breathing²⁻⁴. Asthma was known in ancient times, in Egypt and in ancient Greece, as evidenced by the writings of Hippocrates (460–370 BC; *ἀσθμα* - gasping). It is present in 1–18% of the population, depending on the countries and regions¹. During 2004, it was estimated that asthma affects about 300 million people worldwide of all age structure, and it is estimated that by 2025 some 100 million people more will have this disease^{5,6}.

Knowledge of the etiology and pathophysiology of events in asthma has evolved with the progress of medical science: from data of “hay fever” from the 19th century through the theories of “psychosomatic disease” from the first half of the 20th century^{7,8} to the present knowledge of inflammation and bronchial hypersensitivity and hyperreactivity.

Risk factors for the onset, development and exacerbations of asthma are divided into host factors and environmental factors. Host factors are predisposing factors for the development of inflammation, which in conjunction with other factors can lead to the clinical manifestations of the disease. They are: genetic predisposition, atopic constitution, airway hyperreactivity, gender and race/ethnic factor. Environmental factors are usually responsible for the manifestation of the disease: allergens indoors and outdoors as well as in the workplace, smoking, air pollution, respiratory infecti-

ons, parasitic infections, socio-economic status, drugs, food additives and obesity.

Bronchoconstriction is responsible for both bronchospasm and increased mucosal secretion and mucosal edema of the airways for the occurrence of symptoms of asthma¹. The main underlying pathophysiological mechanism of asthma is the airway inflammation, and occasionally variable airway obstruction and bronchial hyperreactivity are its feature manifestations. Inflammation of the airways includes interaction of a large number of mechanisms: hyperresponsiveness, mucosal edema of the respiratory tract, bronchial gland hypersecretion and increased production of mucus, hypertrophy of the smooth muscle cells and airway remodeling which represents an irreversible process due to collagen deposition.

In the development and maintenance of chronic inflammation in the airways following factors are participating: inflammatory and structural cells, neuroregulatory substances and mediators (histamine and chemotactic factors, leukotrienes and many cytokines [granulocyte macrophage stimulating factor, tumor necrosis factor, interleukins (IL) - 1, 2, 3, 4, 5, 6, 8, 11, 13, 17 and others]⁹⁻¹⁷.

For the inflammation in asthma, the most important cells are activated mast cells, activated T-lymphocytes as regulatory cells and eosinophils. In the early asthmatic reaction, in sensitized persons, upon exposure to the allergen and its binding to specific antibodies, activated mast cells secrete mediators of the acute phase (which include leukotrienes and inflammatory cytokines) which have a role to maintain the inflammatory phase¹⁷. They also release IL-5, leading to a Th2 lymphocyte differentiation, chemotaxis and differentiation of eosinophil leukocytes, modification of basophil activity, and activation of the enzyme tryptase, which results in the further development of the inflammation in the airways^{14,15}. Mobilized and activated eosinophils play a central effector role in the development and

maintenance of inflammation in asthma by producing a number of mediators, including the major basic protein, eosinophil cationic protein (ECP), eosinophilic neurotoxin and eosinophil peroxidase^{12, 13}. A ribonuclease and ECP, act on the respiratory epithelium and pneumocytes leading to damage of the epithelial barrier and activation of adhesion molecules, mobilization of other inflammatory cells, and stimulation of fibroblasts¹⁶⁻¹⁹.

The diagnosis of asthma is based on the clinical examination (complete physical examination, medical history of difficulty in breathing, and a complete history of the disease, with a very significant abnormal physical findings in the lungs), lung function tests (spirometry, the peak expiratory flow, bronchodilatory and bronchial provocation tests - specific or non-specific) that can confirm the existence of asthma and the existence of the variable flow restriction of air through the airways and allergy tests (determination of IgE specific antibodies and skin prick tests) which can identify the atopic constitution and a factor that is the cause of the attack of asthma. In some patients, radiologic diagnostics is used, which is important as a method which can exclude the existence of any other pulmonary disease. In the diagnosis of asthma, for research purposes, and today in many centers during routine analysis, the measuring of certain inflammation markers is used (in a sample of sputum or induced sputum, nasal swabs, biopsy specimens of the bronchus or after the bronchoalveolar lavage inflammatory cells and cytokines are determined as well as measurement of the mediators and their metabolites in blood and urine and measuring the concentration of nitric oxide (NO) in the exhaled air]^{1, 16, 20-24}. Variability of disorders of the pulmonary ventilation is determined by the spontaneous evolution, bronchodilatory tests and proving of hypersensitivity^{1, 25, 26}.

For testing of pulmonary function in patients with asthma, spirometry is the most often used test to determine the values of the parameters of lung ventilation: forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), and the ratio of FEV1/FVC. In the manifested asthma, we most often register the obstructive ventilatory impairment (decrease in FEV1) and in such cases a bronchodilatory test is routinely performed in order to verify variability of the disorders. In the diagnosis and monitoring of asthma other methods may be used such as flow-volume curve, peak expiratory flow measurement peak expiratory flow – (PEF), body plethysmography, lung compliance, determining the value of the transfer factors of the lungs, arterial blood gas analysis with acid-base status and pulse oscillometry^{1, 24-28}.

Asthma is a chronic, incurable disease based on a continuing inflammation in the airways, which varies in intensity and clinical manifestations, either spontaneously or as a result of the applied treatment. Therefore, clinicians are

recommended the classification of asthma by the level of disease control in mild, moderate, severe and very severe, depending on the value of FEV1 and FEV1/FVC²⁹.

For the scientific and research purposes asthma is classified according to the frequency of symptoms into intermittent and persistent. In intermittent asthma patients have occasional complaints, spirometry test out of episodes of attacks shows no disorders and bronchial provocation tests are usually negative^{1, 30}. Problems occur less than once a week, exacerbations are short lasting, and the values of PEF and FEV1 are greater than 80% of the predicted ones with the variability of less than 20%. Persistent asthma can be mild, moderate, and severe. Mild persistent asthma is characterized by the onset of symptoms more than once a week, night attacks more than twice a month, and the values of PEF and FEV1 greater than 80%, with a variation of 20–30%. In severe stages the symptoms are constantly present, there are frequent exacerbations and nocturnal seizures, limited physical activity, and the PEF and FEV1 values less than or equal to 60%, while the variability is greater than 30%.

Based on the clinical and functional characteristics, inflammatory-immune profiles and capabilities for the treatment and control of diseases with medicaments and other methods, the population of patients with asthma is divided into the following phenotypes: allergic bronchial asthma with early onset and dominant eosinophilic inflammation – responds well to anti-inflammatory therapy of glucocorticoids; non-allergic asthma – characterized by inflammation with of neutrophil and eosinophil leukocytes involvement; late-onset asthma - needs high doses of inhaled glucocorticoids for the control; asthma with fixed airflow limitation; asthma associated with obesity²⁹.

Treatment of asthma is focused on relief of symptoms and alleviating chronic inflammation and bronchial hyperreactivity. Combining multiple pharmacological substances, either in terms of anti-inflammatory drugs, bronchodilators or specific drugs that act on particular inflammation mediators provides better control of symptoms and improves the quality of life. At the same time, it reduces the risk of severe asthma attacks with suffocation and a sense of lack of air as well as the chance of a fatal outcome. The therapy starts when the disease is confirmed by pulmonary function tests along with a history of typical symptoms.

For clinical practice, asthma will continue to be a challenge in patients with a history of chronic symptoms and who have a normal pulmonary ventilation determined by the spirometric test and negative tests to bronchial hyperreactivity because some of them already have intermittent asthma (which due to the spontaneous variability of symptoms, inflammation and hypersensitivity remains undiagnosed and untreated)^{31, 32}.

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