SEVERE BRONCHIAL ASTHMA, A DISEASE OR A SYNDROME?

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Abstract

Background. The World Health Organization defines asthma as a disease characterized by repeated attacks of dyspnea and wheezing, which vary in frequency from person to person. According to another definition, asthma is considered a complex syndrome that cannot be classified as a single disease but as a series of overlapping individual diseases and phenotypes, the expression of which is the result of a unique interplay between genetic and environmental factors. This conglomerate of diseases is more pronounced precisely in the severe form of asthma, which by definition is the most serious and life-threatening form, the adequate control of which often cannot be achieved even with high doses of medication.

Clinical experience and now genetic data are increasingly leaning towards the concept of asthma as a heterogeneous clinical syndrome; clinical cases erupt, progress and respond to treatments in different ways. Currently, the diagnosis of asthma is based on incisive clinical methods that rely on pulmonary function tests, which prove the reversibility of bronchial obstruction. But this approach alone is not enough to address the diagnostic and therapeutic challenges resulting from the heterogeneity of asthma; among others, regarding the management of asthma, current guidelines pay special attention to the identification of comorbidities and the role they play.

Methods. In this article, we briefly discuss some of the health conditions that coexist with severe bronchial asthma, following a systematic literature review approach.

Conclusion. Bronchial asthma coexists with many other comorbidities, which are often overlooked. In order to have a more comprehensive management of this pathology, a diagnostic and therapeutic approach of the contributing factors and comorbidities, should be taken.

Key words. severe asthma, comorbidity, syndrome, disease

ASTMA E RËNDË BRONKIALE, SËMUNDJE APO SINDROM?

Abstrakt

Hyrje. Organizata Botërore e Shëndetësisë e përkufizon astmën si një sëmundje të karakterizuar nga atake të përsëritur të dispnesë dhe fishkëllimave, të cilat ndryshojnë në frekuencë nga një person në tjetrin. Sipas një tjetër përkufizimi, astma konsiderohet si një

sindromë komplekse që nuk mund te klasifikohet dot si një sëmundje e vetme por si një seri sëmundjesh dhe fenotipesh individuale të mbivendosura, shprehja e të cilave është rezultat i ndërthurjes unike midis faktorëve gjenetikë dhe mjedisorë. Ky konglomerat sëmundjesh shoqëruese është më i theksuar dhe i ndërlikuar pikërisht në formën e rëndë të astmës e cila për definicion është forma më serioze dhe jetëkërcënuese, kontrolli adekuat i së cilës shpesh nuk mund të arrihet madje edhe me doza të larta medikamentoze.

Eksperienca klinike dhe tashmë edhe të dhënat gjenetike po anojnë gjithnjë e më shumë nga koncepti i astmës si një sindromë klinike heterogjene; rastet klinike shpërthejnë, progresojnë dhe i përgjigjen trajtimeve në mënyra të ndryshme. Aktualisht diagnoza e astmës bazohet në metoda klinike incizive që mbështeten në teste të funksionit pulmonar, që vërtetojnë reversibilitetin e obstruksionit bronkial. Por nuk mjafton vetëm kjo qasje për të adresuar sfidat diagnostikuese dhe terapeutike që vijnë si pasojë e heterogjenecitetit të astmës; ndër të tjera, sa i përket menaxhimit të astmës, udhërrëfyesit aktuale i kushtojnë një vëmëndje të veçantë identifikimit të komorbiditeteve dhe rolit që ato luajnë.

Metodologji. Për punimin e këtij artikulli, është kryer një rishikim sistematik i literaturës mbi gjendjet shëndetësore që bashkëekzistojnë me astmën bronkiale.

Konkluzione. Astma bronkiale bashkëshoqërohet me shumë sëmundje të tjera, që shpeshherë nuk u kushtohet vëmendja e duhur. Çdo faktori kontribues apo komorbiditeti, i duhet kushtuar një qasje diagnostike dhe terapeutike, me qëllim që të arrihet një menaxhim sa më optimal i astmës bronkiale.

Fjalë kyc. astma e rëndë, komorbiditete, sindromë, sëmundje

Introduction

Asthma is considered severe when adequate symptomatic control is not achieved with high doses of inhaled corticosteroids and additional medications (LABA, montelukast and/or theophylline) or with oral corticosteroids for at least 6 months, or when this control is lost after medication reduction. This form is present in 9.5% of all asthmatic patients and accounts for about 60% of the total medical costs of asthma. (1). Its features include hyperactivity, constriction and thickening of the bronchial smooth muscle, inflammation and subepithelial fibrosis, mucus hypersecretion and its clearance deficit, as well as an increase in the level of eosinophils and neutrophils.

Severe bronchial asthma should be differentiated from uncontrolled asthma. Although both are part of what is recently known as "difficult asthma", the second (difficult-to-treat-asthma) is related to poor inhalation adherence/technique and exposure to triggering factors, while severe asthma is related to worsening of the patient's condition, regardless of proper adherence to medication or effective avoidance of triggering factors. Numerous studies prove the connection of asthma with health conditions or other diseases such as: obesity, GERD, CRSwNP, hyperventilation, epiglottic dysfunction, psychopathologies, smoking and nicotine addiction, COPD, respiratory infections, atopic dermatitis, sleep apnea, hormonal disorders,

etc (2). The following will discuss some of the clinical entities that more often coexist with severe bronchial asthma.

Severe asthma and obesity

Researchers link the prevalence of obesity in asthmatics with the obesogenic effect of systemic corticosteroids, but there is evidence that obesity itself increases the risk of asthma and its severity. Hadar et al. first mentioned the concept of "obese asthma" regarding patients with common features such as late onset of asthma, female predominance, severe symptoms, sputum with insignificant eosinophils, low atopy, severe bronchial hyperactivity and low response to ICS (3).

The first common mechanism of obesity and severe asthma is thought to be vitamin D deficiency which is 35% higher in obese asthmatic patients, mainly in women(4). The higher the vitamin deficiency, the more frequent exacerbations of severe asthma; a reduction of the latter has been observed with increased exposure to the sun, which is related to an increase in vitamin D production.

The second mechanism is systemic inflammation, resulting from infiltration of cytokines from the hypoxic death of adipocytes increased in obesity. Production of IL-1, TNF alpha and IL-6 damage the lungs after entering the bloodstream. The higher the level of IL-6 and CRP, the higher the probability that the patient is obese, hypertensive, diabetic and has more frequent asthma exacerbations. (5)

The third mechanism is damage to the microbiome, mainly pulmonary and gastrointestinal (from early exposure to antibiotics, formula versus breast milk, cesarean versus vaginal delivery, exposure to domestic or farm animals) which increases the risk of developing allergic asthma, as well as the frequency of its exacerbations (6).

Severe asthma and cardiovascular disease

In a meta-analysis of cohort studies on 3700 individuals aged 17-77 years, from 1979 to 2014, it was found that severe asthma increases the risk of death from cardiovascular diseases, arterial hypertension, ischemic stroke (in contrast to patients with mild/moderate asthma, in whom no significant association was observed), coronary artery disease in females over 18 years of age, and myocardial infarction in hypertensive asthmatic patients, particularly in those treated with inhaled LABAs or systemic corticosteroids. (7)

The first mechanism that connects asthma with cardiovascular diseases is the chronic inflammation of the airways, the chronicity of which leads to increased vulnerability of blood vessels, activation of coagulability, dysfunction of vascular endothelial cells. The second mechanism is related to chronic airway obstruction, the hypoxemia caused by which leads to increased secretion of inflammatory mediators and accumulation of lipids in macrophages. Both of these mechanisms, aided by risk factors such as smoking, hypertension, diabetes and dyslipidemia, affect the progression of atherosclerosis and increased incidence of other cardiovascular diseases.

The following scheme (Fig. 1) (8) schematically shows the physio-pathological mechanisms that link severe asthma with cardiovascular diseases. Among other things, the study examines

the connection of IgE with FcεR1 receptors in lymphocytes, smooth muscles, macrophages, endothelial cells and mast cells, their activation (which is interrupted by medications such as omalizumab and glucocorticoids) as a result of the connection with this immunoglobulin and its impact on the pathogenesis of asthma, atherosclerosis and aortic aneurysms (9).

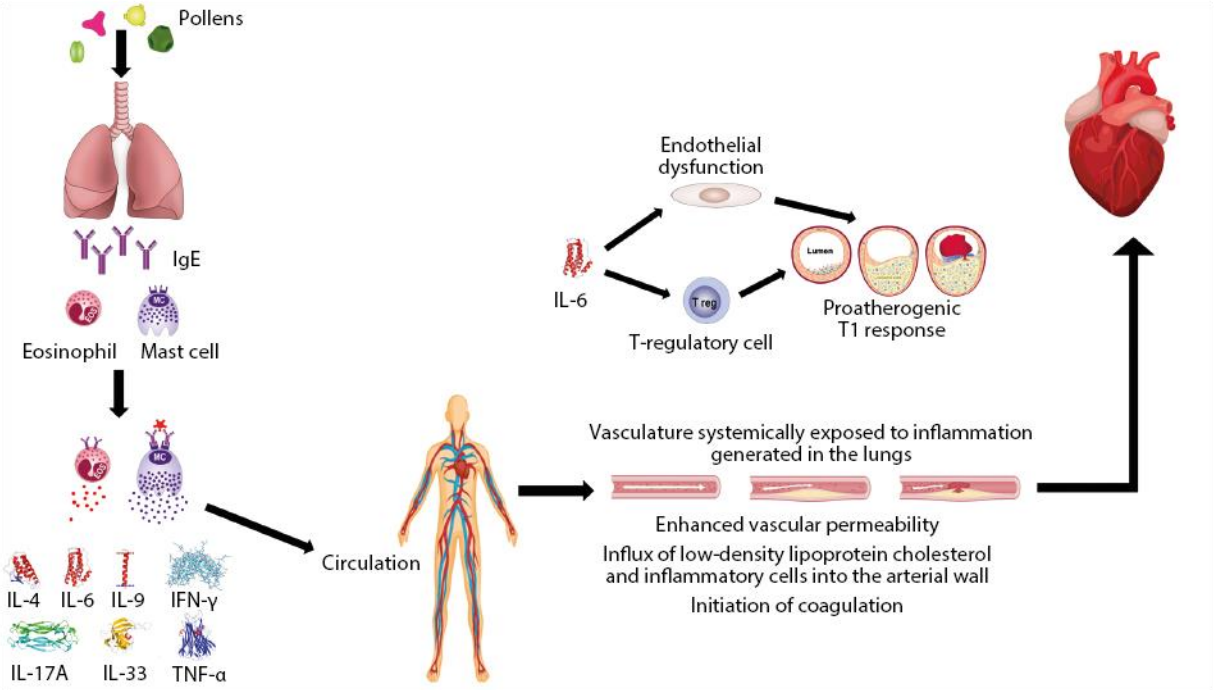

Figure 1. Pathophysiologic mechanisms connecting asthma with cardiovascular diseases (8).

Severe asthma and autoimmunity

Both asthma and autoimmunity result from a disorder of the immune system. Autoimmunity is an exaggerated TH1 response, while asthma is mainly a TH2 response. During the last decades, circulating autoantibodies against beta 2 adrenergic receptors, epithelial and nuclear antigens have been frequently reported, especially in patients with severe asthma, and are believed to be epiphenomena from chronic airway inflammation (10).

The hypothesis of autoimmunity (Fig. 2) is getting more and more attention, especially in intrinsic asthma (late onset in adult, non-atopic patients). It is based on three main mechanisms; the first consists of the classical TH2 cascade, with release of IL-5, Il-4 and IL-13., eosinophilic and lymphocyte recruitment and release of IgE-s, which together cause tissue damage (9). The second mechanism is chronic inflammation which increases the expression of IL15, IL16 BCA1 BAFF and CC17, which contribute to the formation of "B cell clusters" and autoantibodies. The third mechanism consists of increased levels of IgG, anti EPX and ANA, which cause cytolysis of eosinophils and increased exposure to autoantigens (11).

In patients with severe asthma, pulmonary infections cause the release of pro-inflammatory mediators such as IL-18 and neutrophilic degranulation (NETosis). Their consequences include tissue damage, accumulation of autoantigens, and production of autoantibodies (12).

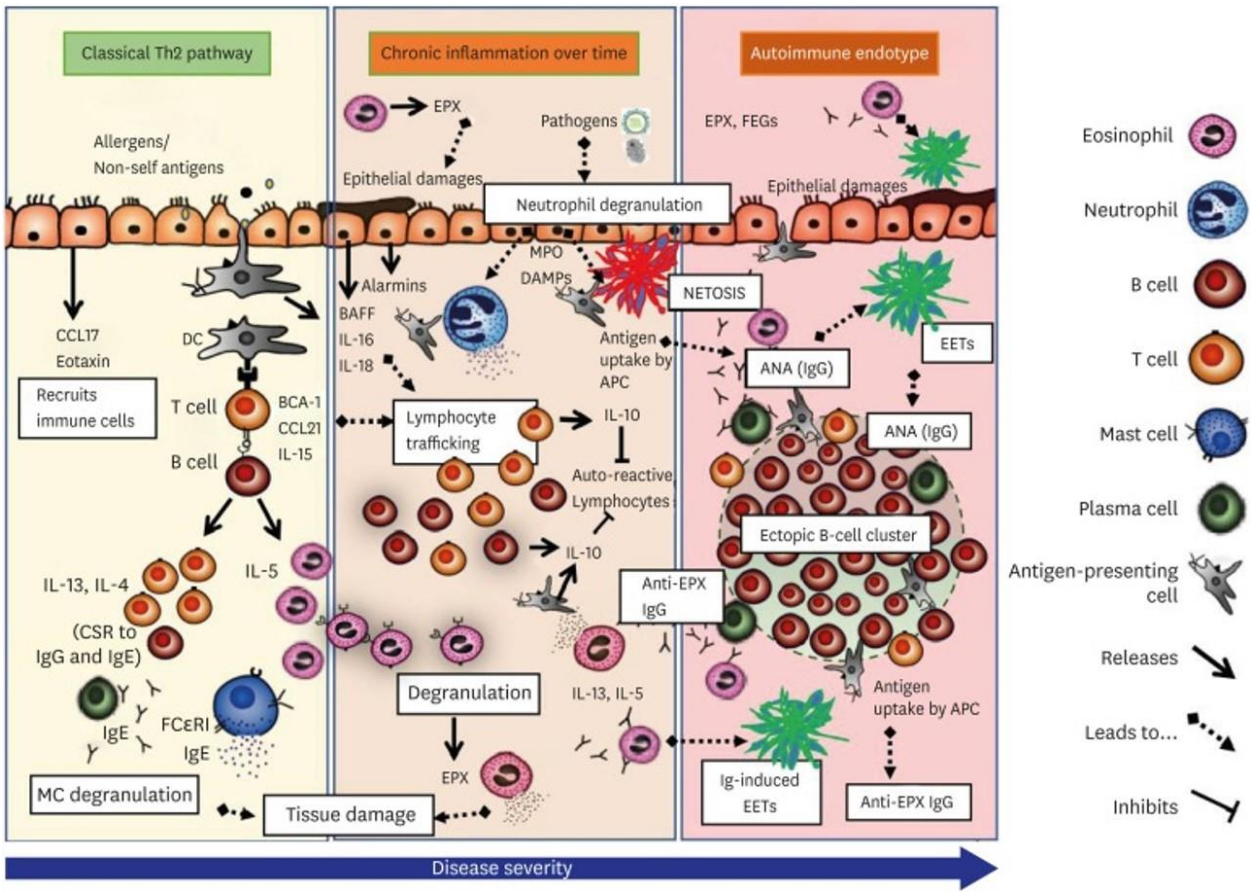

Figure 2. The hypothesis of autoimmunity in asthma (12).

Perimenstrual asthma

Perimenstrual asthma is defined as cyclic exacerbation of asthma symptoms during the luteal phase and/or during the first days of the menstrual cycle. The first case was reported in 1931, in a woman in whom, with the cessation of ovarian function, the symptoms subsided, and with its return, they reappeared. Coexistence of asthma with exacerbations during hormonal changes is reported in 19-40% of women with asthma. (13) These data, together with the evidence of gender differences in asthmatic patients, support the hypothesis that hormonal fluctuations (especially estrogenic ones) significantly affect asthma (14). Studies have concluded that the appearance of PMA correlates with increased emergency room presentations, which peak in the preovulatory and perimenstrual phase. Hospitalizations of asthmatic patients do not show gender differences in pre-pubertal ages and in those over 50 years old, while from the age of 13-50 years the ratio of hospitalizations is 3:1 in favor of women. (15)

It has also been noted that patients with severe asthma show clinical improvement when progesterone concentrations are increased. In these patients, unlike estrogens, free

testosterone correlated positively with pulmonary function. This can be explained by the fact that testosterone is derived from aldosterone, the precursor of which is progesterone (16).

Asthma with chronic rhinosinusitis and nasal polyposis

Patients with CRSwNP are characterized by eosinophilia and high local IgE, poor quality of life (especially when associated with asthma), frequent coexistence with severe bronchial asthma, accompanied by frequent exacerbations, chronic obstruction and 1more pronounced serum eosinophilia. Both of these pathologies, together with hypersensitivity to aspirin, constitute the Samter triad or AERD (aspirin-exacerbated respiratory disease). It is present in about 2.5% of the population, mostly in women, in 20% of patients with asthma and in 30% of those suffering from the severe form of asthma. (17)

GA²LEN (Global Allergy and Asthma European Network) data show that 67% of patients with CRSwNP have coexisting asthma, which in 62% of cases is of a severe form and, in many cases, may remain undiagnosed. In these patients, asthma has an adult-onset (early onset: 18-39 or late, after the age of 40) and is usually not associated with childhood asthma. (18)

The most frequent sequence (36%) of Samter's triad diagnosis starts with bronchial asthma, is followed by nasal polyposis and ends with aspirin hypersensitivity diagnosis, while the reverse sequence of the above is the rarest one (6%). (19)

Asthma and CRSwNP share a common pathophysiological pathway, which begins with the activation of TH2 cells by antigen-presenting cells. They then produce IL-4, IL-13, and IL-5, interleukins that are capable of recruiting mast cells, eosinophils, goblet cells, macrophages, and B cells. The result is a cascade of inflammatory responses shown in the picture below (Figure 3). (20)

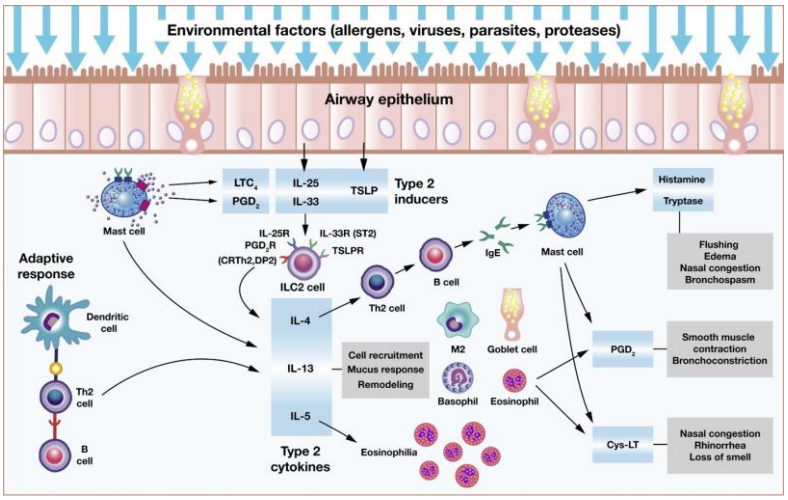

Figure 3. Pathogenesis of nasal polyps and bronchial asthma (20).

ACOS – Asthma and COPD Overlap Syndrome

ACOS is defined as an obstructive lung condition with clinical and inflammatory features of asthma and COPD. There are several hypotheses about the etiopathogenesis of this clinical entity. According to the Dutch theory, asthmatics exposed to inhalants that cause COPD can develop ACOS, and COPD patients can develop asthma-like symptoms when sensitized to allergens. According to the British hypothesis, asthma and COPD are separate diseases from ACOS; the development of ACOS is related to pulmonary injury of early origin (prenatal or pediatric) combined with genetic and epigenetic factors (21).

GOLD and GINA have published a joint document where they suggest a diagnostic approach to ACOS, but it does not present actual criteria. According to them, the characteristics that support the diagnosis of ACOS are older than 40 years but reporting symptoms in childhood or later, the presence of respiratory symptoms, including dyspnea on exertion, airflow limitation that is not fully reversible, diagnosis of asthma and/or inhalant exposure, comorbidities affecting clinical and functional deterioration, COPD-like findings on X-ray, sputum eosinophilia, with or without neutrophils. Meanwhile, according to the Spanish Thoracic Society, the diagnosis of ACOS is confirmed by confirming the following 2 major criteria, or by fulfilling 1 major criterion and 2 minor criteria (Table 1) (22).

Table 1. Minor and major diagnostic criteria for ACOS.

Major	Minor
1. Bronchodilator test significantly positive (increased FEV1% > 15% and >400 ml)	1. High total IgE
2. Eosinophilia in sputum	2. Personal history of atopy
3. Personal history of asthma	3. Positive bronchodilator test (increase in FEV1 by at least 12% or 200 ml)

Discussion

Asthmatic patients often have co-morbidities that may directly or indirectly affect the level of therapeutic asthma control. For example, they may be responsible for the development or further evolution of a different asthma phenotype (as in the case of obesity, smoking, aspirin hypersensitivity and allergic bronchopulmonary aspergillosis), may be part of the same pathophysiological process (such as allergic rhinitis), may act as confounding factors in the diagnosis or therapeutic approach (obesity and obstructive sleep apnea) and/or may be associated with a specific factor or condition that may modulate the clinical presentation of asthma or affect efficacy/compliance with treatment (GERD, respiratory infections, smoking and psychopathologies such as stress and depression).

In this literature review, we briefly discussed some of those health conditions that coexist with severe bronchial asthma, which cannot be ignored when discussing a more comprehensive management of this pathology. In recent years, Fitzpatrick's (2020) definition, which qualifies asthma as a spectrum of co-existing disorders, is becoming more acceptable; considering it as a single disease is a reductionist point of view, which constitutes the main barrier against advances towards personalized treatment. (23)

Conclusion. Bronchial asthma coexists with many other health conditions, such as obesity, cardiovascular diseases, chronic rhinosinusitis with nasal polyps, autoimmune diseases etc., which are often overlooked. In order to have a more comprehensive management of this pathology, a diagnostic and therapeutic approach of the contributing factors and comorbidities, should be taken.

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