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Asthma-COPD Overlap Syndrome: A work in Progress

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Asthma and Chronic Obstructive Pulmonary Disease (COPD) are the most common chronic airway diseases in clinical practice [1]. In the United States of America, approximately one in 12 adults has asthma, and one in 15 has COPD diagnosis [2,3]; by probability, coincidence of both diseases is expected at last in 0.5% of the general population [4].

Identifying the cause of respiratory symptoms in patients with "pure" entities (e.g., an 18-year-old female with asthma from childhood and nocturnal wheezing or a 70-year-old man with intense smoking and habitual sputum production) may be relatively straightforward; however, in daily practice it is frequent to find patients who present clinical characteristics of asthma and COPD at the same time. For this reason, since the year 2014, the guidelines of the global initiatives for asthma and COPD (GINA and GOLD, respectively) incorporate a dedicated appendix to asthma-COPD overlap syndrome (ACOS). Both initiatives define ACOS as the compound characterized by persistent airflow limitation and the presence of some clinical features commonly associated with asthma and others usually associated with COPD [5]. Unfortunately, the definition proposed by GINA and GOLD is not entirely accepted. In the literature exists at least 10 terms to refer the joint presence of asthma and COPD [6]; expressions such as overlap syndrome [7], combined asthma with COPD [4], mixed phenotype asthma COPD [8], COPD with asthma characteristics [9] and asthma with coexistence of COPD [10], are just some of the names proposed by various authors. Notwithstanding this definition ambiguity, ACOS seems to be a frequent entity, with an incidence between 6.5 to 61% of the population with asthma [10,11], and 14.6 to 56% in patients with COPD [7,12].

A less controversial aspect is the recognition of ACOS as a disease related to adverse outcomes. Patients with ACOS require hospitalization more frequently than patients with asthma or isolated COPD [13]. For the same level of lung function and despite a lower intensity in smoking, exacerbations in the ACOS patient tend to be more frequent than in patients with COPD, and more severe as compared to asthma [10,14]. The quality of life is worse compared to patients with COPD or asthma [14,15]. Finally, mortality also could be greater in patients with ACOS; at 18-year follow-up and after adjustment for baseline lung function, the risk of death was higher for ACOS (HR 1.45, 95% CI: 1.06-1.98), compared to COPD (HR 1.28, 95% CI: 1.13 -1.45) and asthma (HR 1.04, 95% CI: 0.85-1.27) [4].

The interest for the association between asthma and COPD is not a recent issue; in 1960, the professors Orie, Sluiter and de Vries of the University of Groningen in the Netherlands organized a multidisciplinary meeting for the study of the persistent respiratory symptoms unrelated to *Mycobacterium tuberculosis* infection. One of the central concepts derived from the called *International Symposium on Bronchitis* was the proposed by Orie to describe the relationship between asthma and chronic bronchitis. According to this theory, both diseases have a common origin and their clinical expression is determined by the interaction between endogenous (genetic, age, sex) and exogenous factors (allergens, tobacco, biomass, microorganisms). The idea caused great controversy and in 1969 was nicknamed "Dutch hypothesis" by Fletcher and Pride, who advocated the leading role of the respiratory infection as the etiological factor of chronic airway disease [16].

Currently, genomic studies do not support the common origin of asthma and COPD [17]. Although both entities share some clinical features, among them there are important differences at pathophysiological level; on the other hand, it is clear that the separatist vision that tries to isolate one disease from the other given the absence of a common origin (British hypothesis), also is not entirely adequate. Recently, the concept of "Th2 signature" has been of particular interest; it represents the sum expression of at last 100 genes in the airway. In patients with asthma, the Th2 signature is related to eosinophilic inflammation. In patients with COPD, high values in the composite score for the Th2 profile is linked to asthma-like inflammation, greater airflow obstruction, high values of reversibility, decrease in dynamic hyperinflation and symptomatic improvement after treatment with inhaled steroids [18]. The Th2 profile could be the link between both diseases; besides, it supports at least some genetic coincidence between patients with asthma or COPD, who in clinical practice could meet the diagnostic criteria of ACOS.

Nonetheless that the concept of ACOS is still far from being perfect, it is very useful; the correct identification of patients with ACOS avoids denying them the benefit of anti-inflammatory therapy. Once the physician has established the diagnosis of ACOS, the global initiatives advocate for starting treatment following asthma recommendations. The above is based on the possible increase in mortality resulting from bronchodilator monotherapy in patients with asthma, especially in the non-Caucasian population; namely, any suspected asthmatic component should lead to the prescription of inhaled steroids [19]. Given the absence of randomized trials for ACOS treatment, it is difficult to establish management guidelines based on solid evidence. In the expert's opinion, inhaled steroids should be offered to patients with asthma, even in those with irreversible airway obstruction, and in COPD patients with some of the asthma-like features such as reversibility of airflow obstruction, sputum eosinophilia, and bronchial hyperreactivity [19]. Finally, we do not know whether ACOS will lead to an excessive prescription of this kind of drugs.

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One of the interpretations of the Dutch hypothesis was that it tried to join two diseases into a single entity with a single treatment. Unfortunately, the most overlooked aspect is at once the most important; it consists of the strong recommendation of Orie and Sluiter to describe in detail the clinical characteristics of the patient rather than labeling him with a given disease [20]. Beyond the commonplace between asthma and COPD, this point is fundamental and constitutes the essence of this theory. With this concept, Orie took the first step towards phenotyping, as we know it today.

The ACOS concept reminds us that the genetic and the environmental context combines in unique ways in each patient, resulting in the development of alike but not necessarily identical pathophysiological pathways. The ACOS concept is the reminder of the need to understand each patient in his individuality rather than to categorize him as a carrier of a widespread disease. The discovery of the best way to care for ACOS patients is just beginning; it is a privilege to be a witness of this work in progress.

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