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COMMENTARY

Is it severe asthma or asthma with severe comorbidities?

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Abstract: Severe asthma is defined as asthma that requires treatment with high-dose inhaled corticosteroids (ICSs) plus a second controller and/or systemic corticosteroids to prevent it from becoming uncontrolled or that remains uncontrolled despite this therapy. This definition has limitations: 1) it does not define any biological characteristic that distinguishes severe asthma from asthma in general and 2) it relies on the clinical interpretation of asthma symptoms that are not specific. Actually, wheezing, dyspnea, cough and chest tightness may be caused by the comorbidities (such as rhinosinusitis, obesity and vocal cord dysfunction [VCD]) which are associated with asthma. In clinical practice, clinicians are often prone to diagnose uncontrolled asthma and increase doses of ICSs without considering the comorbidities, resulting in poor control of symptoms. This commentary wishes the clinicians to focus on the comorbidities of asthma, particularly in patients with severe asthma, because the correct diagnosis of these comorbidities implies specific treatments that lead to a better asthma control.

Keywords: severe asthma, chronic rhinosinusitis, obesity, vocal cord dysfunction, dupilumab

The recent increase in therapeutic options for the treatment of severe asthma[1] has increased the importance of diagnosis and asthma phenotyping. According to International European Respiratory Society (ERS)/American Thoracic Society (ATS) task force, severe asthma is defined as asthma that requires treatment with high-dose ICSs plus a second controller and/or systemic corticosteroids to prevent it from becoming uncontrolled or that remains uncontrolled despite this therapy.[2] The criteria for uncontrolled asthma include: poor symptom control, frequent severe exacerbations or one serious exacerbation that requires hospitalization, intensive care unit (ICU) stay or mechanical ventilation in the previous year or airflow limitation. This definition has limitations: it does not define any biological characteristic that distinguishes severe asthma from asthma in general and it relies on the clinical interpretation of symptoms that should be attributed to asthma. However, asthma has no characteristic symptoms because wheezing, dyspnea, cough and chest tightness are the symptoms that are not specific, as these are caused by the comorbidities associated with asthma. Here, we use the term asthma comorbidity to refer to a condition that influences asthma severity, management or diagnosis, with consequent misattribution of shared symptoms. In pediatric patients, an association of asthma with cystic fibrosis (CF) may occur, by coincidence to the high prevalence of asthma in children, the so-called CF asthma.[3] The patient with CF is reported as having concomitant asthma if, in the treating physician's opinion, asthma contributes significantly to the patient's lung disease. The diagnosis of

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asthma is suggested by episodes of acute airway obstruction reversed by bronchodilators, a strong family history of asthma and/or evidence of atopy or laboratory evidence of allergy (ie, prick tests positive for common inhalant allergens). In the elderly, it is not uncommon to evaluate patients with persistent airflow limitation and smoking history, with some features usually associated with asthma, such as eosinophilic airway inflammation, the so-called asthma COPD overlap syndrome (ACOS), as defined by recent consensus criteria.[4] Clinicians should enquire about smoking habit of their difficult-to-treat asthma patients, as smoking is associated with reduced expression of histone deacetylase (HDAC2). HDAC2 appears to mediate the action of steroids to switch off activated inflammatory genes, but in smokers with asthma, HDAC2 activity and expression are reduced by oxidative stress through activation of phosphoinositide 3-kinase δ.[5] We will consider in more detail some comorbidities which, based upon the authors' experience, have a major impact on the management of asthmatic patients. In the clinical scenario of a patient who had previously received the diagnosis of asthma, whenever cough, dyspnea and wheezing are due to asthma comorbidities, such as rhinosinusitis, obesity and VCD, clinicians are prone to diagnose uncontrolled asthma and increase doses of ICSs, resulting in poor control of symptoms. This condition fulfills the criteria of severe asthma, and the correct diagnosis should be asthma with severe comorbidities.

The comorbidities may result in misdiagnosis, misinterpretation of symptoms, aggravation of one or more diseases. In contrast, the recognition of comorbidities facilitates more appropriate therapy or reduction of potentially risky therapies, such as systemic corticosteroids.

Specific treatments of comorbidities have been shown to improve asthma control. According to Ragab et al,[6] both medical and surgical treatments of chronic rhinosinusitis (CRS) were associated with subjective and objective improvements in asthma. Some new biological therapies targeting IL5 and IL4/IL13 may improve nasal polyps score and decrease asthma exacerbation rate.[1,7,8] The proportion of patients with symptoms of CRS has been reported to be as high as 74% in patients with severe steroid-dependent asthma, who showed a severe sino-nasal involvement as evaluated by computed tomography (CT) scan imaging.[9] Clinicians should consider the diagnosis of CRS based upon the presence of at least two of the four cardinal signs/symptoms (anterior and/or posterior nasal mucopurulent drainage, nasal obstruction/nasal blockage/congestion, facial pain, pressure and/or fullness and reduction or loss of sense of smell) in combination with objective evidence of mucosal inflammation.[10] Objective evidence of mucosal inflammation requires demonstration of one or more of the following findings, using nasal endoscopy and/or CT imaging: purulent mucus or edema in the middle meatus or ethmoid regions, polyps in the nasal cavity or the middle meatus, radiographic imaging demonstrating mucosal thickening or partial or complete opacification of the paranasal sinuses. In obese patients, the risk of misdiagnosing asthma and/or its severity is particularly high. Among 91 subjects (mean body mass index [BMI], 38 kg/m^2) with a diagnosis of asthma, taking a mean beclomethasone-equivalent dose of 1,273 mg/day, 36.3% had no bronchial hyperresponsiveness (possible misclassification of asthma diagnosis).[11] Therefore, clinicians should not accept asthma diagnosis based on symptoms alone particularly in obese subjects. The objective measurements of variable airflow obstruction or bronchial hyperresponsiveness are important to confirm the diagnosis of asthma in obese patients. If obese patients who are receiving asthma treatment are still reporting dyspnea and exercise intolerance, it is advised to check lung function and, if normal, to step down asthma therapy and recheck respiratory function. Otherwise, a misdiagnosis may lead to inappropriate treatment, with an increased risk of side effects and increased costs.[12] On the other hand, bariatric surgery not only improved small airway function, which could explain the improvement of asthma control and quality of life, but also induced a decrease in systemic and bronchial inflammation in morbidly obese patients with asthma.[13]

Prevalence of dysfunctional breathing, evaluated by Nijmegen questionnaire, in patients treated for asthma in primary care has been estimated to be 35% among women and 20% among men,[14] and reports of VCD mimicking severe asthma are not rare.[15,16] VCD is defined by the complete or partial adduction of the vocal folds with inspiration and/or expiration. This process seems to occur in response to irritation of the larynx or hypopharynx or secondary to emotional or physical stress.[17] The symptoms of VCD include high-pitched wheezing, usually more prominent with inspiration, hoarseness, dysphonia and cough.[18] Symptoms are often episodic with rapid resolution, with or without therapy. Patients may be misdiagnosed with asthma when VCD is responsible for their symptoms or have VCD and asthma simultaneously. The use of the flow volume loop may be helpful in recognizing VCD. The inspiratory loop typically exhibits decreased flow rate with variability in flow, resulting in a wavy, flattened curve instead of the typical smooth, oval appearance. A speech therapist or speech pathologist, knowledgeable about VCD, can be very helpful in treating this disorder.[19] Over half of the patients treated for asthma in the community who have

symptoms suggestive of dysfunctional breathing showed a clinically relevant improvement in quality of life following a brief physiotherapy intervention, and the improvement was maintained to be over 25% 6 months after the intervention.[20] In conclusion, we wish the clinicians to focus on the comorbidities of asthma, particularly in patients with severe asthma, because the correct diagnosis of these comorbidities implies specific treatments that lead to a better asthma control.

Disclosure

The authors report no conflicts of interest in this work.

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