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Not every reversible airflow limitation is asthma

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To the Editor

Asthma is a chronic airway inflammatory disorder characterized by airway hyperresponsiveness and reversible airflow limitation.[1] Nevertheless, not every reversible airflow limitation is asthma. In this letter, we aim to describe the definition of reversible airflow limitation and the differences in airway diseases with reversible airflow limitation.

The definition of reversible airflow limitation

The bronchodilation (BD) test is the major method to distinguish reversible and nonreversible airflow limitation. A positive response in the BD test is defined as a postbronchodilator increase in forced expiratory volume in one second (FEV_1) >12% and 200 mL from baseline after inhaled salbutamol.[1] Reversible airflow limitation with a positive BD test can be observed in asthma and many other airway diseases.

Reversible airflow limitation is the key characteristic of asthma

Asthma is a chronic inflammatory disorder of the airways that involves multiple cell types and cellular elements and is characterized by recurrent episodes of wheezing, breathlessness, chest tightness, and coughing. The diagnostic criteria for asthma include a history of respiratory symptoms together with confirmation of variable expiratory airflow limitation.[1] Specifically, to confirm variable expiratory airflow limitation, objective measures should be taken to evaluate the expiratory airflow limitation and the excessive variability in lung function, including one or more of the following items: positive BD test, excessive variability in twice-daily peak expiratory airflow (PEF) over 2 weeks, significant increase in lung function after 4 weeks of anti-inflammatory treatment, positive exercise challenge test, and positive bronchial challenge test (usually only performed in adults).[1] In addition to asthma, many other airway diseases, including chronic obstructive pulmonary disease (COPD) and bronchiectasis, present with reversible airflow limitation with a positive BD test. Therefore, reversible airflow limitation alone should not be used to diagnose asthma.

The differential diagnosis between asthma and other diseases with reversible airflow limitation

COPD is a chronic airway inflammatory disease characterized by progressive decline in lung function and impaired quality of life. Irreversible airflow limitation is fundamental for the diagnosis of COPD, which is often measured by spirometry and defined as a FEV_1/forced vital capacity (FEV_1/FVC) ratio less than 70% after inhalation of a bronchodilator. Interestingly, a study involving 200 COPD patients reported that approximately 23% of patients showed a positive BD test (46 out of 200) and that these patients displayed better results in their lung function assessment, COPD Assessment Test (CAT), modified Medicine Research Council (mMRC) score and 6-minute walking distance test.[2] This suggests that COPD patients with reversible airflow limitation may be a clinical phenotype of COPD with unique clinical features. In agreement with this, our previous study examining 88 patients with stable COPD also observed a subpopulation of patients (20 out of 88, 22.7%) showing positive BD test results.[3] These studies suggest that reversible airflow limitation can be observed in a portion of COPD patients, thereby making it difficult to distinguish asthma from COPD using the BD test alone. Thus, for these patients, it is very important to focus on risk factors along with the responses to treatment trials to facilitate diagnosis. For example, early life exposures such as childhood infections, obesity, and allergy usually occur in adult-onset asthma, whereas environmental risk factors, such as adult tobacco smoking and biomass smoke, exposure to indoor air pollution, and occupational exposures, often cause COPD. Additionally, asthma symptoms can often be relieved by corticosteroid treatment, whereas long-acting inhaled antimuscarinic medications may be more useful for COPD patients.

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Table 1
Clinical differentiation of airway diseases with reversible airflow limitation.

Items	Asthma	COPD	Bronchiectasis	ABPA	EGPA	DPB	LAM
Morbidity	Common, approximately 1–18% of population	Common in smokers older than 40 years	Common	Rare, the prevalence of ABPA in asthma and cystic fibrosis is approximately 13% and 9%, respectively	Rare, 10.7 to 14.0 per million adults worldwide	Rare	Rare, 3 to 7 cases per million in women
Personal and family history	History of allergic rhinitis or eczema, or a family history of asthma or allergy	Smoking and occupational history	History of tuberculosis, or nontuberculosis infection, or cystic fibrosis, or primary ciliary dyskinesia, or rheumatoid arthritis	History of asthma	History of asthma, and/or nasosinusitis	History of chronic paranasal sinusitis	Use of oral estrogen during pregnancy or after delivery, history of pleural effusions and pneumothorax
Age of onset	Anytime throughout lifespan and often early in life (childhood)	Usually after the age of 40 years	Anytime throughout lifespan	25–55 years	7–74 years	40–50 years	Females of reproductive age
Physical examination	Often normal, the most frequent abnormality is expiratory wheezing (rhonchi) on auscultation	Barrel chest, accessory respiratory muscle use, prolonged expiration, wheezing	Localized moist crackles and wheezing on auscultation	In asthmatic patients with ABPA, wheezing, and/or rhonchi is present on auscultation. In cystic fibrosis patients with ABPA, crepitations are present on auscultation due to bronchiectasis	Expiratory wheezing on auscultation can be present in patients with asthma	Physical examination of the lungs reveals coarse crackles	Wheezing could be heard on physical examination in some patients
Chest high resolution CT scan	Usually normal but air trapping and increased bronchial wall thickness may be observed	Low attenuation areas denoting either air trapping or emphysematous change	Increased bronchial diameter as compared to that of the companion artery, “signet ring” or “string of pearls” appearance	Central bronchiectasis	Migratory infiltrates	Centrilobular nodular opacities are observed with bronchiectasis	Many small thin-walled cysts can be seen bilaterally in a diffuse distribution in the lungs
Lung function test	Variable expiratory airflow limitation, including positive BD test, positive bronchial challenge test, and positive exercise challenge test	A ratio of the forced expiratory volume in one second to forced vital capacity (FEV_1/FVC) less than 0.7	Obstructive ventilatory defect, residual volume increased	Obstructive ventilatory defect: most patients. Restrictive ventilatory defect and a reduced DLCO: part of patients	Airflow obstruction is present in 70% of patients	Obstructive ventilatory defect; vital capacity (VC) decreases and residual volume (RV) increases in advanced stages	Obstructive ventilatory defect and decreased DLCO
FeNO	>50 ppb	Usually normal	Usually normal	>50 ppb	>50 ppb	Usually normal	Usually normal
Peripheral blood eosinophils, cells/μL	Increased slightly	Usually normal	Usually normal	> 500	>1500	Usually normal	Usually normal
Serum total IgE, IU/mL	Usually increased slightly or normal	Usually normal	Usually normal	1000–10,000; elevated IgE levels against aspergillus fumigatus	100–300	Usually normal	Usually normal
Immunological biomarker	-	-	-	-	ANCA (+)	-	-
Response to therapy	Response well to corticosteroids, mostly inhaled corticosteroids	The most commonly used medication in COPD is bronchodilator, and corticosteroids can be used in cases with acute exacerbations	No response to corticosteroids; improving tracheobronchial clearance and controlling infection are vital	Respond well to systemic corticosteroids	Respond well to corticosteroids and immunosuppressants	No response to corticosteroids; macrolides antibiotics have beneficial effects	Limited benefits of systemic corticosteroids

ABPA: allergic bronchopulmonary aspergillosis; ANCA: antineutrophil cytoplasmic antibody; BD test: bronchodilation test; COPD: chronic obstructive pulmonary disease; CT: Computed tomography; DLCO: carbon monoxide diffusing capacity; DPB: diffuse panbronchiolitis; EGPA: eosinophilic granulomatosis with polyangiitis; FeNO: fractional exhaled nitric oxide; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; IgE: immunoglobulin E; LAM: lymphangioleiomyomatosis; ppb: part per billion.

Bronchiectasis is defined as an abnormal, permanent, and irreversible dilatation of the bronchia characterized by chronic cough, sputum production and recurrent airway infections, resulting in airflow limitation. High-resolution computed tomography (HRCT) is by far the best method to diagnose and assess the distribution of bronchiectasis. Similar to COPD patients, reversible airflow limitation can also be observed in some patients with bronchiectasis. A previous study demonstrated that 11.8–19.0% of patients with bronchiectasis had positive BD tests and further showed that there is no correlation between the BD test results and the etiologies of bronchiectasis, as patients with a positive BD test can have various etiologies, such as sequelae of tuberculosis, history of nontuberculosis infection, cystic fibrosis, primary ciliary dyskinesia and rheumatoid arthritis.[4]

Asthma often exhibits heterogeneous clinical characteristics, making it difficult to distinguish asthma from other airway disorders with reversible airflow limitation. As mentioned above, patient information other than symptoms, such as personal histories, especially history of diseases, tobacco smoking, and environmental exposure, and the responses to different treatments can be helpful to aid diagnosis. Moreover, some airway diseases with structural changes often have unique imaging features and thus can be distinguished from asthma by HRCT. For example, low attenuation areas denoting either air trapping or emphysematous changes can be observed in patients with COPD. The HRCT of bronchiectasis often exhibits increased bronchial diameter compared to that of the companion artery, “signet ring” or “string of pearls” appearance. However, most asthmatic patients have no imaging changes.[1] Furthermore, clinical and cellular biomarkers play a key role in facilitating the diagnosis of asthma, and some can predict or reflect the response to specific treatments. For example, blood eosinophil counts, sputum eosinophil percentages, and fractional exhaled nitric oxide (FeNO) are considered key biomarkers of airway inflammation in asthma and have been used frequently to improve the accuracy in diagnosing asthma and guide asthma interventions and treatment.[5] High levels of FeNO (≥50 part per billion [ppb]) and sputum eosinophils (≥2%) can be used to determine eosinophilic inflammation and support asthma diagnosis when objective evidence is needed.[5] Immunoglobulin E (IgE) is central to the pathophysiology of allergic asthma, and serum IgE serves as an important biomarker for asthma, which can be used to predict the response to anti-IgE therapy.[5] While these biomarkers are helpful to distinguish asthma from certain chronic airway inflammatory disorders, such as COPD and bronchiectasis, they are not specific to asthma.

Apart from the common respiratory diseases mentioned above, reversible airflow limitation has been found in some rare diseases, such as allergic bronchopulmonary aspergillosis (ABPA), eosinophilic granulomatosis with polyangiitis (EGPA), diffuse panbronchiolitis and lymphangioleiomyomatosis (LAM). Diseases with reversible airflow limitation and clinical differentiation are outlined in Table 1.

In conclusion, clinical features of asthma are often nonspecific, and reversible airflow limitation measured by BD test can be seen in other diseases. Therefore, not every reversible airflow limitation is asthma. Sometimes, it is difficult to distinguish asthma from many other chronic airway inflammatory disorders with reversible airflow limitation, such as COPD and bronchiectasis. As a result, a significant portion of individuals with asthma remain misdiagnosed and mistreated. In clinical practice, personal histories, especially history of diseases, tobacco smoking, and environmental exposure, should be carefully investigated, and long-term monitoring of treatment is needed. A combination of personal histories, inflammatory marker profiles and pulmonary function assessments will be helpful for improving asthma diagnosis.

Conflicts of interest

None.

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