Abstract

Asthma and chronic obstructive pulmonary disease (COPD) represent a substantial proportion of primary care practice. In adults, differentiating asthma from COPD can be difficult but it is important because of the marked differences in treatment, disease progression, and outcomes between these two conditions. The symptoms present in both conditions are non-specific and overlapping. Under-diagnosis and misdiagnosis of COPD and over diagnosis of asthma are commonly reported. The diagnosis of obstructive respiratory diseases has been considered a challenge for many years. An increasing understanding of the clinical heterogeneity of asthma and chronic obstructive pulmonary disease, together with the inadequacy awareness of the current definitions, has led to attempts in developing a new taxonomy for airways diseases. Defining the various phenotypes is a research priority with great clinical relevance because of the potential to inform on the risk factors, underlying pathophysiological processes, natural history, monitoring and most important, the treatment. This is mainly because of the overlap between asthma and COPD and the difficult diagnosis of COPD in the early stages. In this context it will be very important to make the monitoring of disease progression by lung function and other domains in relation to initial clinical or physiological characteristics and especially according to phenotypes.

Keywords: Asthma; Pulmonary disease, chronic obstructive; Phenotype; Diagnosis.

Introduction

Obstructive lung diseases clearly have a large impact on health care worldwide. Chronic obstructive pulmonary disease (COPD) affects at least 16 million Americans, and asthma is gradually increasing in frequency. In fact, the burden of these conditions may well be underestimated as it has been demonstrated that many patients remain underdiagnosed, perhaps in part due to the COPD latency in smokers.
COPD is the third leading cause of mortality in the USA, and it is estimated that medical costs due to COPD exceed $15 billion annually. Mortality due to COPD is increasing, and it has been estimated that it will become the third largest cause of mortality worldwide by 2020.

Features of COPD and asthma overlap, often rendering a firm diagnosis difficult to achieve for the clinical practitioner. There are hypotheses suggesting that both asthma and COPD may indeed share common origins, with differences in phenotype presentation being related to disease evolution or interaction between endogenous and exogenous factors. Others suggest that the 2 conditions are clinically and pathophysiologically distinct. Review of studies aimed at understanding the genetic factors involved in these diseases suggest that there are at least some shared chromosomal loci involved in genetic susceptibility and gene-environment interaction in both diseases. Studies of the underlying inflammation demonstrate a difference in the preponderance of inflammatory cells and mediators in each disease, yet many shared characteristics in the inflammatory process are evident between the 2 conditions.

The traditional approach has been to present this phenotypic overlap in a Venn diagram, however, this results in approximately 15 phenotypes, whose pathogenesis or response to treatment have not been clearly defined. More recent work has used cluster analysis to characterize different types of airway disorders. Cluster analysis is a collection of methods for defining groups of individuals based on measured characteristics, then grouping them into clusters based on their similarities and differences. The groupings are constructed such that the degree of association is strong between members of different clusters. If different treatment strategies provide different outcomes for these groups, it will provide confirmation of the clinical value of cluster analysis.

Bronchial asthma

Asthma is a syndrome characterized by airflow obstruction, that varies markedly both spontaneously and with treatment. Asthmatics exhibit a particular type of inflammation in the airways that renders them more responsive than non-asthmatics to a wide range of triggers, leading to excessive narrowing with consequent reduced airflow, and symptomatic wheezing and dyspnea. Narrowing of the airways is usually reversible, but in some patients with chronic asthma there may be an element of irreversible airway obstruction.

The onset of asthma usually occurs during childhood, and risk factors include prior atopic reactions and a family history of atopy or asthma. The initial clinical presentation varies, most often with intermittent symptoms but sometimes with constant wheezing, cough, or shortness of breath. Wheezing on expiration is the classic symptom, but some patients present primarily with cough, especially at night. Symptoms typically occur after exposure to allergens, and triggers include viral upper respiratory infections, pollen, dust mites, animal dander, environmental irritants (most commonly tobacco smoke), cold air, and in some patients, physical exertion.

The characteristic symptoms of asthma are wheezing, dyspnea, and coughing, which are variable, both spontaneously and with therapy. Symptoms may be worse at night and patients typically wake in the early morning hours. Patients may report difficulty in filling their lungs with air. There is increased mucus production in some patients, with typically tenacious mucus that is difficult to expectorate. There may be increased ventilation and use of accessory ventilation muscles. Typical physical examinations are inspiratory, expiratory, rhonchi, and throughout the chest, and there may be hyperinsufflation. Some patients, particularly children, may present with a predominant nonproductive cough (cough-variant asthma).

The recent development of targeted asthma therapy has raised renewed interest in asthma phenotypes. However, there is no standardized method or agreed-upon classification system.
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to define asthma phenotypes. Focus has recently shifted to classification of asthma based in immunopathology, specifically the cellular make-up of the inflammatory response.\textsuperscript{10}

**COPD**

COPD is defined as a disease state characterized by airflow limitation that is not fully reversible. COPD includes emphysema, an anatomically defined condition characterized by destruction and enlargement of the lung alveoli; chronic bronchitis, a clinically defined condition with chronic cough and phlegm; and small airways disease, a condition in which small bronchioles are narrowed. COPD is present only if chronic airflow obstruction occurs; chronic bronchitis without chronic airflow obstruction is not classified as COPD.\textsuperscript{11}

In the early stages of COPD, patients usually exhibit an entirely normal physical examination. In patients with more severe disease, the physical examination is notable for a prolonged expiratory phase and may include expiratory wheezing. In addition, signs of hyperinsufflation including a barrel chest and enlarged lung volumes with poor diaphragmatic excursion may be apparent. Patients with severe airflow obstruction may also exhibit use of accessory muscles of respiration, sitting in a characteristic tripod position to facilitate the actions of the sternocleidomastoid, scalene, and intercostal muscles. Patients may develop cyanosis.\textsuperscript{11} Advanced disease may be accompanied by systemic wasting with significant weight loss, bitemporal wasting, and diffuse loss of subcutaneous adipose tissue. This syndrome has been associated with both inadequate oral intake and elevated levels of inflammatory cytokines, such as TNF-α.\textsuperscript{11}

COPD is essentially unknown in children and is rare in young adults without a α1-antitrypsin deficiency history. However, after 40 years of age, the COPD prevalence increases substantially with aging and the prevalence of patient-reported asthma declines slightly.\textsuperscript{12} In general, the COPD risk increases with pack-years of smoking, or less often, with ongoing occupational exposure to inhaled toxins or irritants.\textsuperscript{13} While daily symptoms are present in people with asthma, the COPD symptoms are more likely to be constant and progressive, reflecting the fact that airway obstruction in COPD is not due to the reversible airway constriction and inflammation responsible for asthma, but rather to structural changes and mechanical derangements with abnormal elastic recoil.\textsuperscript{14}

**Differential diagnosis:**

In patients who present with symptoms of airflow obstruction, differentiating COPD from asthma may not always be straightforward. With classic symptoms, good medical histories, and supporting objective data, this distinction can often be made by the clinician with reasonable certainty. However, many patients exhibiting signs and symptoms of dyspnea, cough, sputum production, and wheezing often do not fit the classic description of asthma or COPD. The common scenario for asthma is a patient who is young, atopic, a nonsmoker with variable airflow obstruction, hyperinflated, and wheezing often do not fit the classic description of asthma or COPD. The common scenario for COPD is a middle-age or elderly patient who is a lifelong smoker with chronic, productive cough, progressive dyspnea, and evidence of more fixed obstruction, parenchymal injury, and diffusion impairment. It has been widely acknowledged that there is significant overlap in the phenotypic expression of these 2 conditions, which can be difficult for the primary care physician who is faced with different treatment paradigms targeted to each condition.\textsuperscript{1}

Hyperventilation, which is defined as elevated functional residual capacity in relation to total lung capacity, is usually evident at rest when associated with COPD, and worsened with exertion or exacerbation, whereas asthma typically has been associated with hyperinflation during acute attacks.\textsuperscript{1} Classically, diffusing capacity for carbon monoxide is decreased in patients with COPD and usually normal or increased in asthmatics.\textsuperscript{1} It has been widely held
that decreased elastic recoil is a hallmark of COPD, particularly emphysema, while asthma is associated with normal elastic recoil.\textsuperscript{1}

Hardin’s trial\textsuperscript{15} was one of the first large studies to describe chest computed tomography (CT) findings in subjects with both COPD and asthma. These subjects demonstrated more gas-trapping on expiratory CT scans compared to subjects with COPD alone. This is consistent with CT imaging studies demonstrating an increase in gas trapping among subjects with asthma, and may reflect an increase in small airway disease in this group. There was no difference in emphysema or airway wall thickness between COPD subjects with and without asthma. Moderate COPD can present great variability with regard to the degree of associated emphysema, and when individuals with moderate COPD were studied, there was no difference between these individuals and those with both COPD and asthma. These results suggest that airway inflammation may reduce pulmonary function more so than parenchymal destruction, in patients with both COPD and asthma.\textsuperscript{15}

**Phenotypes**

In recent years it has become possible to characterize the phenotype of COPD patients with reference to other reported clinical cases of patients with COPD.\textsuperscript{16} The term “phenotype” as applied to COPD refers to those attributes of the disease that alone or combined describe the differences among patients with COPD with regard to parameters that have clinical significance; symptoms, exacerbations, response to treatment, evolution of the disease, and death.\textsuperscript{17} There are 3 phenotypes that are associated with prognostic factors and with different responses to the available treatments:\textsuperscript{16}

1. Exacerbating
2. Asthma-COPD mixed
3. Hyperinsufflated emphysema.

Some studies have described other possible phenotypes, but these are of little clinical importance. A “fast decliner” refers to a patient that suffers a decrease in pulmonary lung function, as measured by forced expiratory volume in 1 second (FEV\textsubscript{1}), faster than other patients.\textsuperscript{18} The practical problem is that it is impossible to detect this phenotype without rigorous monitoring of lung function for a period of at least 2 years. Notably, there is also no treatment that is specifically recommended for this type of patient. Another is the chronic bronchitis phenotype, defined as the presence of cough and expectoration at least by 3 months by 2 consecutive years.\textsuperscript{4} This phenotype can be associated with airway disease that is evident via TCAR.\textsuperscript{19} However, chronic bronchitis can occur concomitantly with the 3 above mentioned COPD phenotypes; exacerbating, asthma-COPD mixed, and hyperinsufflated emphysema; thus, it is arguably most appropriately described as a modifying factor of any of the 3 main phenotypes.\textsuperscript{16} The “systemic COPD” phenotype has been described in patients that present with obesity, cardiovascular disease, diabetes, or systemic inflammation.\textsuperscript{20} It is true that these patients have a distinct prognosis, but the author considers that we cannot deem systemic COPD to be a specific phenotype, because it does not fulfill the definition above, as the systemic manifestations or comorbidities do not of themselves constitute the manifestation of COPD. Comorbidities are very important, but should be considered as a part of a phenotype, rather than the defining factor.\textsuperscript{16} Finally, a special phenotype is characterized by emphysema caused by deficiency of α-1-antitrypsin, which presents as emphysema with a basal predominance appearing early in life. The incidence of it is higher in smokers, and it has a genetic basis.\textsuperscript{21} It has a low incidence however, and thus the author prefers to consider it as being outside the scope of a general classification system.

**Exacerbating phenotype**

This is defined as COPD that exhibits two or more exacerbations in a one year period. These exacerbations should be separated by a period
of at least 4 weeks since the end of the treatment for the first exacerbation, or 6 weeks since the beginning of it in cases where the patient wasn’t treated; this is to differentiate the new event from the previous event, or from treatment failure of the previous event. Hypersecretion is associated with increased airway inflammation and with a higher risk of respiratory infection, and this could explain its association with the appearance of repeated exacerbations. Viral infection, gastroesophageal reflux, and the presence of cardiovascular diseases have also been associated with more frequent exacerbations in these patients. In cases where the exacerbating phenotype was established, treatment of bronchial infection or bronchiectasis with antibiotics, in conjunction with an anti-inflammatory, can be useful for these patients.

Mixed asthma-COPD phenotype

This COPD phenotype is defined as the presence of a non-completely reversible obstruction to airway flux accompanied by signs or symptoms of increased reversibility of airway obstruction. In the spectrum of bronchial obstruction to airflow, there are asthmatic smokers, asthmatics that develop non-completely reversible obstruction to airflow, and non-smokers that develop chronic obstruction to airflow. The asthmatic smokers exhibit characteristics that are similar to COPD, with a decreased response to corticosteroids and decreased frequency of eosinophilic inflammation, and they have a higher probability of exhibiting neutrophilia in the airways.

There are epidemiological studies of COPD incidence showing that young asthmatics that develop COPD have a disease with characteristics that differ from those of non-asthmatics that develop COPD. In the former, allergic rhinitis, bronchial hyperresponsiveness, the presence of wheezes, and increased concentrations of plasmatic IgE are more frequent and indicate that there is a mixed asthma-COPD phenotype. More than 40% of COPD patients have a history that is compatible with asthma, and this double diagnosis increases with age. There is increasing evidence that patients that have asthma and COPD exhibit faster disease progression than those that have only one of these conditions. Airway hyperresponsiveness and a diagnosis of asthma have been associated with more decline in FEV₁ both in smokers and nonsmokers, and asthma has been recognized as a risk factor for COPD. The presence of bronchial hyperresponsiveness in patients with COPD has been associated with an increase in disease exacerbations, and mortality. The coexistence of asthma and COPD is associated with the presence of comorbidities and an increase in the utilization of health care. Despite these known interactions between COPD and asthma, the clinical aspects of patients with this combination of conditions have not been well described, and in fact the double diagnosis of COPD and asthma is frequently an exclusion criteria for participation in studies into each separate disease.

Soriano et al. have estimated that approximately 23% of COPD patients that are between 50 years and 59 years of age could have a mixed asthma-COPD phenotype, and this percentage may increase to 52% in those aged between 70 years and 79 years. Other studies have evaluated the prevalence of mixed (identified by eosinophilia in the sputum) in patients with COPD in 38%, associated straightly with the therapeutic response to corticosteroids. Using the bronchodilator test as reference, 31.5% of the patients identified as having COPD in the epidemiological EPI-SCAN study yielded a positive test. Based in these results, we can conclude that between 20% and 40% of COPD patients may be of the mixed asthma-COPD phenotype. Patients with the mixed phenotype that present certain characteristics including sputum or peripheral eosinophilia, history of asthma and atopy in childhood or youth, frequent exacerbations, very positive bronchodilator test, or wheezing are prone to present response to inhaled corticosteroids, despite their lung function. On the other hand, patients with COPD in the absence of the above characteristics tend
to show a discrete response to association of inhaled corticosteroids and long duration bronchodilation. The diagnosis of mixed phenotype implies the presence of a history of asthma or atopy, reversible bronchodilator test, marked eosinophilia (peripheral or in the respiratory secretions), increased IgE, positive cutaneous tests to respiratory allergens, and increased concentrations of exhaled nitric oxide.

Generally, later age of onset favors diagnosis of COPD. Complete reversibility of airway flow limitation with the use of bronchodilators suggests asthma. Hyperinsufflation at rest is more likely in COPD. Abnormal diffusion capacity is associated with COPD, whereas diffusion capacity is usually normal or increased in patients with asthma. Reduced elastic recoil is a characteristic of COPD, especially in patients that have abnormal enlargement of airspaces with destruction of the airspace walls, as is present in emphysema. Lastly, a history of atopy favors the diagnosis of asthma, especially if it is present in young patients.

COPD is frequently difficult to differentiate from asthma, which can lead to inappropriate treatments, affecting the outcome. In a prospective study of patients with a history compatible with COPD, Tinkelman et al. have studied patients with a previous clinical diagnosis, and compared their spirometric results. The study enrolled patients aged 40 years or older with a previous diagnosis or treatment-history consistent with COPD. Previous diagnoses of chronic bronchitis, emphysema, or asthma were reported by the patients. These individuals underwent pre- and post-bronchodilator spirometric assessment. A diagnosis of COPD was made if there was a relationship between post bronchodilator FEV₁ and the FVC was <70%. Spirometric testing was completed by 597 patients, of which 235 (39.4%) were diagnosed as having COPD. Among the patients with a diagnosis of COPD based on these spirometric tests, 121 (51.5%) reported a previous diagnosis of asthma, without concomitant COPD being diagnosed. Eighty-nine (37.9%) patients reported a previous diagnosis of bronchitis or emphysema, and 25 (10.6%) didn’t report any previous diagnosis. Despite the consensus with regard to recommendations, diagnostic confusion between asthma and COPD is common.

The diseases differ in asthmatic non-smokers with bronchial hyperresponsiveness as compared with smokers with COPD without bronchial hyperresponsiveness. Smoking affects the bronchial inflammation pattern and corticosteroid responsiveness. Asthmatic smokers have more neutrophils than eosinophils in their airways, similar to COPD patients. Smoking promotes neutrophilic inflammation in both asthma and COPD, resulting in increased resistance to corticosteroid treatment. As the severity of the disease increases, the inflammatory pattern becomes similar to that of COPD, and corticosteroid resistance increases. Similarly, increased eosinophils are evident in the mucosa during acute exacerbations of discrete COPD, as is commonly found in asthma.

This similarity in the inflammatory responses can be a physiopathologic relationship to clinical phenotype in the asthma/COPD superposition syndrome. Despite the definitions of asthma and COPD published by the International Respiratory Society, there remains considerable clinical and pathological overlap between these 2 diseases, which challenges such limited definitions.

The superposition syndrome is more prevalent in older patients. Generally, lung function deteriorates as the patient ages. Older asthmatics exhibit more nonreversible obstruction than younger asthmatics, and they have more severe symptoms. Their disease can present as chronic obstruction to airflow, mimicking COPD. Bronchial hyperresponsiveness increases as the patient ages; it is 3 times more prevalent in old adults compared to young patients. Age is a very important variable when evaluating COPD because of the known alterations in lung function that occur in older patients, and the possible role of genetic influence, especially in COPD. Thus, comparisons of the effects of age on asthma and
COPD must be studied in patient cohorts with similar ages, including inhaled expositions and disease severity. Increased age can be a powerful diagnostic factor, influencing the borderline that separates asthma from COPD, thus contributing to manifestations of the superposition syndrome.30

Hyperinsufflated emphysema phenotype

This phenotype defines the patients with COPD that present with dyspnea and intolerance to exercise as the predominant symptoms, and that exhibit signs of frequent hyperinsufflation. Patients with this phenotype present with reduced corporal mass index.16 Clinically, this COPD phenotype is determined based on hyperinsufflation data, evidence of emphysema via TCAR, and decreased diffusion as measured by DLCO/VA adjusted for hemoglobin.16 There is an independent familial aggregation of emphysema of this phenotype, indicating a genetic influence. Identifying this phenotype is of clinical importance, as the degrees of dyspnea, exercise tolerance, and hyperinsufflation are independent predictors of obstruction severity. COPD is a heterogeneous entity, and the peculiarities of the treatment of this disease have only recently been considered. Recent advances in pharmacological and nonpharmacological therapies have showed that clinical responses may differ according to the characteristics of the picture. The concept of phenotype as applied to COPD has led to the definition of several kinds of patients with significant improvements in prognosis and therapy. This advance is important for the development of diagnostic individualization and more appropriate therapy.

Conclusion

Herein, we reviewed the clinical differential diagnosis of asthma and COPD. This is sometimes difficult in primary care practice, even when an accurate history is available, and a thorough clinical examination is conducted. Spirometry is very important and in classical cases the diagnosis can be straightforward. Accurate diagnosis is important due to marked differences in treatment, disease progression, and outcomes between the two conditions. In asthma and COPD, particularly the latter, different phenotypes have been proposed that may benefit from therapies that are specific to those phenotypes. Several trials have studied these phenotypes and certainly these studies will yield a better understanding of these diseases. This will enhance the development of individualized therapies designed for specific phenotypes.

References


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