Asthma and Chronic Obstructive Pulmonary Disease: Natural History, Phenotypes, and Biomarkers

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Abstract

Purpose of the review—In the clinical setting, patients who present with a combination of asthma and chronic obstructive pulmonary disease (COPD) related traits are not uncommon. This review discusses recent advances in the characterization of the natural course, phenotypes, and molecular markers of cases with co-existing asthma and COPD and in the understanding of the nature of the link between these two conditions.

Recent findings—Recent epidemiological evidence indicates that asthma accounts for a substantial proportion of cases of irreversible airflow limitation in the general population and that, in addition to the critical role of environmental exposures in adult age, alterations of developmental processes in childhood may also predispose subjects with asthma to COPD later in life. Findings from clinical and experimental studies emphasize the existence of remarkable heterogeneity within the group of subjects with co-existing asthma and COPD in terms of natural history of lung function, risk factors for disease progression, lung structural changes, and immunological profiles.

Summary—The phenotypic complexity of cases with co-existing asthma and COPD challenges a rigid categorization of patients into existing diagnostic labels and suggests the importance of integrating clinical, functional, morphologic, immunological, and molecular assessments to tailor and optimize prevention and treatment.

Keywords

asthma; chronic obstructive pulmonary disease; chronic bronchitis; emphysema

Introduction

Asthma and COPD are considered distinct obstructive lung diseases, with different diagnostic and management strategies(1–3). Yet, in the clinical setting patients who present with a combination of asthma- and COPD-related phenotypes are not uncommon. Understanding the natural history, risk factors, and molecular pathways involved in these cases of overlapping disease may have critical implications not only for their prevention and treatment, but also for a better comprehension of the links between these conditions. Nearly fifty years ago, Orie and colleagues(4) proposed in what would be later dubbed the “Dutch hypothesis” that asthma and COPD should be considered different expressions of one disease entity. Since then, much debate has taken place in the scientific community and multiple studies have over time emphasized the similarities between these “phenotypes” or the differences between these “diseases”. Although the nature of the link between asthma and COPD has not been
conclusively resolved, these studies have produced considerable advance in our knowledge as they have progressively applied more homogeneous clinical definitions and more refined functional, morphologic, immunological, and in recent times genomic and proteomic assessments. This review discusses the significant progress made on this subject in the last few years, with a particular focus on studies that were published since January 2008.

Definitions

Much of the difficulty in distinguishing asthma, chronic bronchitis, emphysema, and COPD originates from the fact that their working definitions are not mutually exclusive and are differentially based on clinical, functional, and anatomic criteria. For example, the Global Initiative for Asthma (GINA) has proposed an operational definition of asthma based on the presence of airway inflammation, respiratory symptoms, reversible airflow limitation, and bronchial hyperresponsiveness(1). In contrast, the two traditional main sub-phenotypes of COPD are defined either clinically (chronic bronchitis: cough and phlegm production for three months in at least two consecutive years)(5) or anatomically (emphysema: permanent enlargement of the airspaces distal to the terminal bronchioles)(5). Furthermore, the most widely used definition of COPD, which was established by the Global Initiative for Chronic Obstructive Lung Disease (GOLD), emphasizes the importance of the functional assessment of usually progressive, non-fully reversible airflow limitation(2,3), measured as a ratio between forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) after bronchodilator below 0.7.

The unifying definition of COPD by the GOLD guidelines has been largely adopted by the research community and has enhanced substantially comparability across different studies on COPD in the last ten years. In this context, two methodological issues need to be briefly discussed here, as they can affect the extent of the phenotypic overlap between asthma and COPD. First, because the FEV1/FVC ratio declines with age, using the fixed cut-off of 0.7 for all ages – despite its practical advantages – will underestimate the prevalence of the disease in young adults and overestimate it in older subjects(6–8). Similarly, it may under-diagnose the disease among women because females on average have higher FEV1/FVC ratios than males. The ATS/ERS guidelines on lung function(9) have proposed the alternative use of lower limits of normal (LLN) to define airflow limitation, which should remove age- and sex-related effects. Several recent multi-center studies have provided findings in support of this approach(6–8).

In one of them(6•), among 20-to-44-years-old participants in the European Community Respiratory Health Survey less than 50% of subjects with airflow obstruction by LLN met the GOLD criteria for COPD, suggesting that, by using the GOLD definition, the majority of cases of airflow limitation would be missed in a young population. Because asthma is frequent among young adults and women, defining airflow limitation based on LLN instead of the fixed 0.7 cut-off might result in a larger number of asthma cases being identified as having co-existing COPD.

However, these observations should be interpreted with caution in light of a second methodological issue: the GOLD criteria are based on lung function after bronchodilator, whereas the majority of epidemiological studies on this subject did not include reversibility testing and, therefore, used only pre-bronchodilator lung function. This is not a secondary issue. Data from the Burden of Obstructive Lung Disease study showed that administration of 200 μg of albuterol reduced COPD estimates by 25% in the general population(7•) and this bronchodilator effect may be stronger in young as compared with older adults(10). Given the key role of reversible airflow limitation in asthma, one would expect that using post-bronchodilator lung function will resolve airflow limitation preferentially among asthmatics and will, in turn, reduce the proportion of COPD cases associated with asthma. However, to what extent this is the case remains to be determined(11).
Epidemiology

That asthma, chronic bronchitis, emphysema, and COPD are frequently reported (in different combinations) by the same subjects has been long known and effectively illustrated in epidemiological studies using the proportional Venn diagram (12–14). In one of these studies (14*) (Figure 1), using phenotypic data that also included post-bronchodilator lung function and chest CT scans the authors found that more than one third of subjects with COPD had never smoked and that asthma accounted for more than 50% of COPD cases both among smokers and never smokers. The hypothesis that asthma may have a key, or at least contributing, role in the development of a substantial proportion of COPD cases in the general population is consistent with previous prospective studies that found active asthma to increase the risk of acquiring a subsequent label of COPD by 8 to 12 times (15,16).

In this context, it is noteworthy that the co-existence of asthma and COPD appears to identify cases with particularly elevated severity (12), mortality risk (17), and economic burden (18, 19). In a large Medicaid database, cases with co-existing diagnoses of asthma and COPD had an average annual medical cost that was six times higher than that of asthma cases and three times higher than that of COPD cases (18). The increased disease severity shown by subjects with multiple obstructive lung diseases is also suggested by a recent cluster analysis on a group of 175 well-characterized subjects with current respiratory symptoms and/or airflow obstruction (20**). One of the five clusters that were identified included subjects with co-existing signs of asthma (reversibility and atopy), chronic bronchitis (sputum production), and emphysema (reduced DLCO, hyperinflation, and macroscopic emphysema on CT scanning). This cluster had the most severe disease based on degree of airflow limitation, hospital admissions, and prescribed treatment. However, it only accounted for 10% of participants and was mainly composed of heavy smokers, suggesting that this cluster might capture only a subgroup of particularly susceptible cases in which the effects of asthma and smoking operate synergistically. This is only one of the many observations (reviewed in the next sections) that support the existence of significant phenotypic heterogeneity not only among patients labeled with the single entities of asthma or COPD (21,22) (23*), but also within the group of patients with co-existing asthma and COPD.

Natural History

In light of the above observations, understanding the natural history of cases that develop COPD as a sequela of (or in association with co-existing) asthma represents a research priority. In terms of lung function, in principle there are at least three mechanisms through which any subject (with or without asthma) can develop impaired levels in adulthood: an incomplete growth of lung function in childhood, an early start of its decline after the plateau phase, or an acceleration of lung function decline in adult age (or any combination of these mechanisms). A recent report from the Tucson Epidemiological Study of Airway Obstructive Disease (TESAOD) (24) has addressed the question of which of these mechanisms is mainly at work in asthmatics vs. non-asthmatics who develop persistent airflow limitation (as a hallmark of COPD). Results indicated that, whereas subjects without asthma develop COPD mainly as a consequence of an accelerated decline of lung function usually associated with cigarette smoking, among subjects who develop COPD following persistent childhood asthma the bulk of lung function impairment is already established by young adulthood (Figure 2). These findings are consistent with other long-term longitudinal studies (25–28) that have shown strong tracking of lung deficits associated with childhood asthma into adolescence and up to mid-adult life. Taken together, these observations are compatible with a scenario in which the interplay between genetic predisposition and environmental exposures (including viral infections and key signals for immune maturation) in childhood may impact key developmental processes and in turn predispose susceptible asthmatics to development of COPD many years later (29–
31). Indeed, some of these genetic and environmental influences might already take place in utero (29••), as being in the lowest quartile of airway function shortly after birth was found to be associated with a mean 5% deficit in FEV1/FVC throughout the period from age 11 years up to age 22 (32).

The above considerations should not underplay by any means the influence of environmental exposures in adult life on risk and natural course of these conditions, first and foremost cigarette smoking and occupational hazards, whose removal is still the single most important preventive intervention in COPD. Nor should they be interpreted as evidence that asthma is in no case associated with an accelerated decline of lung function. In fact, some epidemiological studies have found a faster FEV1 decline among adults with asthma as compared with subjects with no asthma (33,34) and also in the above mentioned TESAOD study (24) the subgroup of subjects with adult-onset asthma developed persistent airflow limitation by means of both moderate FEV1 deficits in young adulthood and accelerated FEV1 decline thereafter. Clinical studies have shown that, in patients with asthma, this accelerated decline of lung function is related to bronchial CD8+ cell infiltrates (35), airway neutrophilic inflammation (36), and the frequency of acute exacerbations (37) (38•).

Thus, the natural history of lung function through which subjects with asthma develop COPD may be different depending on the age at onset of disease and the sub-type of asthma.

**Lung Structural Changes**

By now, it should be clear why biomarkers – in their broad sense of objectively measured characteristics that can be used as an indicator of pathogenic processes or responses to therapeutic interventions (39) – represent one of the most active areas of research in obstructive lung disease.

Among such objective characteristics is the assessment of airway remodeling, which may be responsible for part of the phenotypic overlap between asthma and COPD. However, the lung structural changes that take place in these conditions are considerably different (40) (41•). For example, alveolar parenchyma destructive alterations (the hallmark of emphysema) are mostly found in COPD. In contrast, increased airway smooth muscle mass, a key determinant of bronchial hyperresponsiveness, is mainly related to asthma and among asthmatics it is remarkably associated with severity of disease and the presence of airflow limitation (42) (43••), even early in childhood (44••). Similarly, the degree (42,45) and composition (46) of thickening of the airway reticular basement membrane appear able to differentiate asthma from COPD, although the relation of this feature of airway remodeling to asthma severity remains somewhat controversial (42,43,45). Interestingly, even among asthmatics with COPD-like neutrophilic inflammation, high resolution CT (HRCT) scan emphysema score was lower but the bronchial wall thickening greater than in patients with traditional COPD (47•).

Thus, the development of persistent airway obstruction in subgroups of asthmatics might be characterized by the degree of specific asthma-related features of airway remodeling. However, to what extent the assessment of the type and degree of lung structural changes can be used to guide classification and treatment of patients in the clinical setting remains unclear. This is a rapidly evolving area of research, which most likely will benefit from advances in less invasive technological tools, such as quantitative HRCT scanning (48).

**Immunological Profiles**

Important differences also exist in the immunological cells and mediators that are involved in asthma and COPD (49) (50••). Asthma is characterized by eosinophilic inflammation that is largely responsive to steroids, a predominance of CD4+ cells, release of Th-2 like mediators
such as IL-4, IL-5, IL-13 – and a main location of the pathological process in the proximal airways. In contrast, in COPD neutrophils, macrophages, and CD8+ cells play a major role and are responsible for much of the airway inflammation and lung damage, especially in the small airways, with release of pro-inflammatory cytokines and chemokines, such as IL-6, IL-8, IL-1β, TNF-α.

These differences become less clear when cases of severe asthma are compared with COPD. Findings from several studies support the hypothesis that severe asthma has an immunological profile that resembles to some extent that found in COPD, with a predominance of neutrophilic inflammation(47,50–54), larger involvement of CD8+ T cells(35), and higher IL-8 mRNA levels in sputum(55). However, an alternative and equally extensive body of evidence indicates that the degree of traditional asthma-related phenotypes – such as eosinophilic inflammation, atopic sensitization, and serum IgE levels – can play a direct role in the development of persistent airflow limitation(24,56–59).

Thus, it appears that subjects with asthma can develop severe disease, non-fully reversible airflow limitation, and COPD both in association with particularly severe degrees of asthma-related lung structural changes and eosinophilic inflammation; and in combination with the co-occurrence of COPD-related inflammatory patterns. The former pathway may be mainly at work among cases with asthma onset in childhood and the latter among cases with adult-onset asthma or overlying exposure to cigarette smoking. Consistent with the existence of multiple pathways, both levels of airway neutrophils and atopic sensitization were independent predictors of air trapping in the Severe Asthma Research Program(60•) and increases in both blood eosinophils and blood neutrophils were associated with decreases in FEV1 values and risk of COPD-like symptoms, respectively, in the French EGEA study(61•).

To illustrate even further the dynamic nature of the relation between these conditions, the co-occurrence of asthma-like phenotypes in patients with COPD is also possible. For example, eosinophilic airway inflammation is found in a sub-group of patients with COPD, among whom it is associated with increased levels of the Th-2 like cytokine IL-5, some degree of reversibility of airflow limitation, increased exhaled nitric oxide, and a better response to pharmacological treatment with steroids(22,62–65), all features that resemble asthma-like phenotypes.

In Search of Genetic and Molecular Biomarkers

The above observations point towards the complexity of the phenotypic heterogeneity of cases with co-existing asthma and COPD and reinforce the importance of searching for new genetic and molecular biomarkers to identify homogeneous subgroups of patients in terms of etiologic mechanisms and response to treatment. Although to date most studies on molecular biomarkers of asthma and COPD – reviewed elsewhere(66–70) – have focused on one disease at a time, some of their findings have important implications on our understanding of molecular pathways involved in cases with co-existing diseases.

For example, several genes originally identified for asthma have been subsequently found to be also associated with COPD-like phenotypes(71) and may be involved in the link between these two diseases. The case of a disintegrin and metalloprotease 33 (ADAM33) is illustrative. First identified as an asthma and bronchial hyperresponsiveness gene via positional cloning (72), ADAM33 has been later associated with decline of lung function and COPD susceptibility in the general population(73,74). The possible involvement of this gene in cases of progression of asthma into COPD-like phenotypes is also supported by the observations that genetic variation in ADAM33 predicts accelerated decline of lung function among asthmatics(75) and that bronchoalveolar lavage levels of its soluble form – which has been shown to have potential tissue remodeling properties(76) – are strongly correlated with severity of asthma, as measured by levels of FEV1 % predicted(77).
The existence of shared molecular markers in subgroups of patients with asthma and COPD is also suggested by studies measuring concentrations of molecules in serum/plasma. For example, differentiation of asthma from COPD using serum inflammatory markers has proved challenging(78,79) and serum levels of C-reactive protein (CRP), which are known to be elevated in patients with COPD(69), have been also found to be increased among patients with non-atopic asthma(80,81). These findings could underline the existence of shared inflammatory pathways or simply reflect the “unspecific” nature of inflammatory markers, such as CRP, that may be elevated in response to multiple conditions and/or environmental exposures. To overcome such limitation, a related line of research is focusing on identifying molecules in blood that are produced mostly in the lungs and thus may be specifically linked to pulmonary disease(82) or that are specifically associated with well-known pathogenic processes involved in asthma or COPD(83•). This approach might also be more effective in discriminating between the two diseases(83).

The public health and clinical impact of biomarker research in asthma and COPD to date has been also limited by the cross-sectional nature of most molecular studies, which has precluded resolution of whether concentrations of the biomarker in biofluids are elevated as a cause or a consequence of the disease. Most likely, the use of prospective study designs and the integration of information from both biomarker concentrations in fluids and variation in their encoding genes(84) (85••) (86•) will be important elements to resolve directionality in biomarker ↔ disease associations and minimize residual confounding and bias in future studies. Also, the increasing use of large multiplex biomarker panels(43), genomics(87–89) and proteomics (90,91) techniques will facilitate exploration of new molecular pathways, with the goals of capturing interactive effects between multiple genes, molecules, and environmental exposures and identifying novel biomarkers that may be specifically linked to cases with asthma, cases with COPD, or cases at risk for the combination of these conditions.

Conclusion

In conclusion, findings from recent studies emphasize the frequency and clinical impact of the overlap between asthma and COPD and the considerable phenotypic heterogeneity of cases with co-existing diseases. This complexity challenges a rigid categorization of patients into existing diagnostic labels of either asthma or COPD and suggests the importance of multiple clinical, functional, morphologic, immunological, and molecular assessments that can be used to tailor and optimize treatment and prevention of subjects with (or at risk of) these diseases. Moving towards such an integrated approach will certainly require time, but the phenotypic characterization and the exploration of the genetic and molecular components of these diseases are now progressing to an unprecedented pace, with the promise of generating soon more effective preventive and diagnostic profiles.

Acknowledgments

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In a random population sample of 25 to 75 years old subjects, the authors of this report found that individuals with airflow limitation and/or respiratory symptoms could be grouped into five main clusters. Results provide important insights on how different asthma- and COPD-related phenotypes are distributed in the general population.


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Figure 1. Proportional Venn diagram depicting the overlap of asthma, chronic bronchitis, emphysema, and COPD in the Wellington Respiratory Survey [reproduced with permission from ref(14)]

Data refer to 469 participants (age 25 to 75 years) with completed information. The rectangle represents the entire study population; the clear circles within each area represent the proportion of subjects with COPD (post-bronchodilator FEV1/FVC ratio < 0.7); and the isolated clear circle represents participants with COPD who did not meet criteria for any additional phenotype of asthma, chronic bronchitis, or emphysema.
Figure 2. Natural history of lung function among participants in the TESAOD Study
[reproduced with permission from ref(24)]

The natural history of lung function of participants who developed persistent airflow limitation (i.e., an FEV1/FVC ratio consistently lower than 0.7 in multiple surveys) was studied over the span of adult life, according to whether or not they had a physician-confirmed diagnosis of asthma. Results are shown for the groups of subjects with 1) no asthma and persistent airflow limitation; 2) asthma onset > 25 years and persistent airflow limitation; 3) asthma onset ≤ 25 years and persistent airflow limitation. The line on top represents predicted values for subjects with no asthma and no airflow limitation. Depicted values represent predicted FEV1 values for a 175-cm tall male from the best fitting random coefficients model.