A REVIEW ON ASTHMA-COPD OVERLAP SYNDROME

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ABSTRACT
One of the most common reasons for admitting in emergency department of hospitals is due to the exacerbation of obstructive pulmonary disease symptoms, which is mainly chest tightness and breathlessness. Individuals with chronic obstructive pulmonary disease (COPD) and asthma are an important but poorly characterised group. The genetic determinants of COPD and asthma overlap have not been studied. Overlap subjects reported a history of physician-diagnosed asthma before the age of 40 years. We compared clinical and radiographic features between COPD and overlap subjects. More females and African–Americans reported a history of asthma. Overlap subjects had more severe and more frequent respiratory exacerbations, less emphysema and greater airway wall thickness compared to subjects with COPD alone. Overlap subjects have more exacerbations, less emphysema and more airway disease for any degree of lung function impairment compared to COPD alone. We identified novel genetic variants associated with this syndrome. COPD and asthma overlap is an important syndrome and may require distinct clinical management.

KEYWORDS: COPD; AHR; Overlap.

INTRODUCTION
Asthma is the inflammatory disease of the airways which is reversible, characterized by dyspnœa, wheezing, chest tightness, bluish coloration of lips and face, increased pulse rate, sweating etc. Its prognosis is primarily related to levels of airflow obstruction and hyper responsiveness. Complication of asthma are lack of sleep, persistent cough, permanent change in lung functioning etc. [1] Chronic Obstructive Pulmonary Disease (COPD) is the
irreversible airway disease which progressively leads to permanent loss of lung functions and sometimes leads to mortality. Here the prognosis is the main goal and it is done primarily related to age initial level of airway obstruction. Secondarily, it is related to smoking, AHR and perhaps leads to reversible obstruction. Hence, asthma and COPD shares the presence of obstruction and AHR as risk factors. Their symptom overlaps to form pulmonary overlapping syndrome. American Thoracic Society (ATS), in their guidelines of 1995 defined asthma, chronic bronchitis, emphysema, COPD, airflow obstruction and identified 11 distinct syndromes. There was an overlap at 6 of these 11 syndromes. Overlap syndrome percentages are increased from mid to later life progressively. There are several areas of overlap between these disorders which results in the need of clinically defining this group of population with obstructive lung disease. It is important to distinguish their biological, clinical and diagnostic difference for the treatment implications, side effects of drugs, complication of therapy drug responses etc with advancing age. This study is more relevant in elder population as they have more relevant overlapping syndrome. The mixed COPD—asthma phenotype was defined as an airflow obstruction that is not completely reversible accompanied by symptoms or signs of an increased reversibility of the obstruction. Recent study from defined the clinical phenotype as “overlap phenotype COPD-asthma”. For this diagnosis were established two major and two minor criteria. Major criteria include very positive bronchodilator test (increase in FEV$_1$ ≥15% and ≥400 mL), eosinophilia in sputum and personal history of asthma. Minor criteria include high total IgE, personal history of atopy and positive bronchodilator test (increase in FEV$_1$ ≥12% and ≥200 mL) on 2 or more occasions. However, these criteria are neither specific nor sensitive. Airway eosinophilia is not exclusive to asthma and is present in COPD patients. The existing definition by Gibson and Simpson is “symptoms of increased variability of airflow and incompletely reversible airflow obstruction” but this is solely based on FEV$_1$ and bronchodilator response.

**Accepted differences in asthma and COPD**

Their differences are largely based on clinical findings. Widely asthma is manifested as intermittent, reversible airway obstruction but COPD is progressive and irreversible. Current guidelines proves that post bronchodilator therapy in asthma shows complete reversibility of obstruction but in COPD there is no reversibility or there is only partial reversibility. The younger patients are more to have asthma and older patients (above 60) have COPD. The major differences are seen the structural and inflammatory signatures of asthma and COPD -
the elevated IgE, induction of T_h2 cells, eosinophilic infiltration, reticular basement membrane thickening and smooth muscle hyperplasia are seen in asthma. But increased neutrophills, induction of T_h1 and T_h17 cells, TGF beta induced small airway fibrosis, goblets cell hyperplasia are typically found in COPD.\cite{8}

**Difficult to separate the overlap syndrome:** Clinically asthma and COPD has more similarities than dissimilarities. Their differentiation is very difficult because;
- Symptoms are part of disease continuation,
- Strong overlapping features
- To differentiate their treatment and prognosis there is no incentives
- Lack of standard guidelines to distinguish
- Physicians using inadequate and uncertain criteria to classify patients.

Recent reviews and clinical methods have failed to diagnose, manage and treat the pulmonary overlap syndrome of elder population. In pathologic comparison, there are no structural changes in asthma and COPD.\cite{9}

**Effect of smoking in overlapping syndrome**
Older or elder adults with significant smoking history will develop asthmatic features. Individuals having asthma has more probability to develop overlap syndrome. There is pathologic and functional overlap between asthma and COPD.\cite{10} Cigarette smoking leads to inflammation and remodeling. Smoking can influence the pattern of inflammation and steroid responsiveness as it promotes neutrophilic infiltration which leads to increased steroid resistance. In asthmatic smokers airways have more number of neutrophils. In COPD smokers eosinophilic count is more.\cite{11}

**Genetic linkage between two diseases**
Genetic studies and Genome Wide Association (GWA) studies failed to produce a link between asthma and COPD. The genes relating to the airway responsiveness are altered in subjects with asthma and COPD and this can provide small linkages. AHR increases with and age is an important factor in pulmonary overlap syndrome as there is change in the lung functions with advancing age. These aged genes have an important role in the development of overlap syndrome.\cite{12}
Frequency
A pathologic and functional overlap between them (overlap syndrome) is especially among the elderly. Results on the age distribution were found in general Italian population. They showed, through a screening questionnaire, that prevalence of asthma-COPD overlap was 1.6%, 2.1% and 4.5% in the 20-44, 45-64, 65-84 age groups, respectively.\[^{13}\]

Bronchial hyper-responsiveness (BHR)
BHR is the exaggerated response to a variety of stimuli which can cause bronchospasm and can be present in inflammatory airway diseases. Such stimuli are: pets, pollen, bugs in home, fungus, dust, strong odors, cold air, pollution, smoke, chemical fumes, exercise, anger, stress, etc. It is believed that the person that develops BHR to various stimuli will develop bronchodilator response after proper treatment, as well. This happens due to the fact that both bronchoconstrictor and bronchodilator response reflects the same underlying disease, and we can observe it in asthma and COPD.\[^{14}\]

How overlapping occurs
Having already analyzed all the potentially important common risk factors for overlapping asthma and COPD, such as increasing age, smoking, BHR, inflammation, remodeling and exacerbations, the big question is why does overlap happen. “Dutch hypothesis” tries to answer the question, stating that asthma and BHR predispose to COPD later in life and that asthma, COPD, chronic bronchitis, and emphysema are different expressions of a single airway disease.\[^{15}\] Furthermore, the presence of these expressions is influenced by host and environmental factors. Epidemiological studies, on the other hand, proved a correlation between respiratory illnesses during childhood and impaired adult lung function. Knowing that airway growth starts in utero, fetal or childhood exposures may contribute to adult asthma or COPD.\[^{16}\]

CONCLUSION
The definition of asthma and COPD is not enough to explain the pulmonary overlapping syndrome. Both have a diverse range of disease phenotype. COPD is a heterogeneous group of disease with different genetic background and anatomical sites of pathology same as asthma. Overlap syndrome is clinically relevant with 20% prevalence in population. Further researches are needed to assess the treatment of pulmonary overlapping syndrome. A current treatment guideline for overlapping disease is extrapolated from guidelines of asthma and COPD guidelines. Further research studies are needed in genetic studies, assessment of
ageing gene expression, inflammatory profiles, biomarkers and airway biopsies to assess immune cell theories and airway remodeling. Patients with overlap syndrome have worse lung functions, more respiratory symptoms and a low health related quality of life than either disease alone. Hence their intake of medicines is also higher. Inhaled corticosteroid therapy together with bronchodilator therapy is more effective for pulmonary overlapping syndrome. By this treatment there is a large improvement in FEV₁ can be seen younger patients, non-smokers, allergic patients, and with higher responsiveness. Asthma is usually seen in younger ones (mean age -40) and COPD in mean age of 65. The patients with overlap syndrome is seen in between these two age limits (mean age -50). The study concludes that majority of risk factors associated with COPD are modifiable. Smoking is the most important risk factor, so reduction in cigarette smoking and counseling can modify the lifestyle of COPD patients. Guidelines for rational prescribing practice for overlapping syndrome are put to improve the standard of prescribing pattern, mainly for antibiotics, as over and irrational prescribing can cause resistant strains of organisms. Most of the asthma and COPD exacerbation are due to bacterial and viral infections. Mainly Macrolide antibiotics (azithromycin) are used to treat overlap syndrome having both features of asthma and COPD this is because the macrolide antibiotics have immunomodulatory effects, on neutrophil migration and production of pro-inflammatory mediators and cytokines.

REFERENCES


