Common Manifestation of Airway Diseases: Chronic Obstructive Pulmonary Disease and Asthma Bronchiale

Abstract
The differentiation of chronic obstructive pulmonary disease (COPD) and asthma bronchiale is often difficult. The airway inflammation is basically different in two disease, but because of wide variety of phenotypes there is significant overlap (5-40%) manifestation, in these cases we can speak about common manifestation. Pharmacotherapy has major effect on quality of life. There is not a mistake if we consider the common manifestation as asthma bronchiale, and the basic therapy is inhaled corticosteroids and use anticholinergic or beta-mimetic bronchodilators as add on therapy. Proper therapy choice can help improve the quality of life and reduce the frequent and severe exacerbations.

Introduction
Clinical symptoms can hardly differentiate COPD and asthma bronchiale [1-8]. Significant smoking anamnesis can support COPD origin, but some asthmatic patients are smoker, also [1-9]. Most of the asthmatic patients have paroxismatic dyspnoic wheezing in the early morning or after exercise [1-9]. In COPD, the dyspnoea is progressive and it is manifested during exercise at first. Hey fever with obstructive pulmonary disease support the definition of allergic asthma bronchiale, but there is a significant portion of COPD patients with hey fever as co-morbidity [10]. Asthma bronchiale and COPD together show similar clinical feature as asthma bronchiale [1-8]. Lung function is crucial for differentiation. In asthma bronchiale most of the cases have reversible airway obstruction, lung function goes to normal values [10]. The airway obstruction in COPD is irreverisible or partly reversible [9].

Definitions
According to GINA 2017 definition, asthma bronchiale is a chronic inflammatory airway disease, in etiology take part different inflammatory cells and particulums [11]. Inflammation related to bronchial hyperreactivity (BHR) results recurrent wheezing, episods of dyspnoea, chest tightness and coughing [11]. Symptoms come mostly at night or in the early morning, it is worsening during exercise, and related to different degree of airway obstruction, which can be reversible with or without pharmacotherapy. According to GOLD 2017 guideline COPD is a preventable and treatable disease with extrapulmonary manifestations, which individually worsen the condition [12]. The characteristic of the disease is airflow limitation, which is not fully reversible [12]. In general, the functional condition is progressive, and it is related to chronic inflammatory process of the lung. Etiological factors are inhalation of injurable material such as particulums and gases. Exacerbations and co-morbidities individually worsen the degree of the disease [12].

Based on airway conditions there is two contradictory hypothesis of the common manifestation of the two disease. According to dutch hypothesis asthma bronchiale chronic bronchitis and emphysema are a common genetical disease with different manifestations, in pathogenesis airway hyperreactivity is the main factor [3-8]. According to british hypothesis chronic bronchitis, emphysema and asthma bronchiale are three different disease with three different manifestations, three different origin and three different prognosis. Reversibility can help to differentiation [3-9]. In the opposite part, international guidelines are dealing with asthma bronchiale and COPD common manifestation. According to GINA 2017, inhalatory exposition of injurable materials (mainly smoking) can cause a mixed inflammatory typical process of asthma bronchiale and COPD in patients with asthma bronchiale. In general, asthma bronchiale and COPD can differentiate, but in some patients with asthma bronchiale can manifest irreversible airway obstruction, and in theses cases the differentiation of the two diseases might be difficult (4,11). According to GOLD 2017, the differentiation of chronic asthma bronchiale and COPD is not possible based on currently available radiological imaging and lung function tests. In these cases COPD and asthma bronchiale might be each other co-morbidities [4-12]. The definition of COPD and asthma bronchiale in terms of common clinical manifestation is characteristics by variable airway obstruction, which is not fully reversible [13].

Obstructive lung diseases
Obstructive lung diseases are the following: emphysema, COPD, reversible chronic bronchitis, asthma bronchiale, variable airway obstruction, COPD with asthmatic clinical feature, irreversible, atopic emphysema [14,15]. asthma bronchiale can devide different clinical entities, recent data support that a T_{H2} cell type and an non-T_{H1} pathophysiological pathway are present, also [16].

Epidemiological data
Based on US data, 15,8% of obstructive lung diseases has COPD+asthma bronchiale together in California (17). 15-30% of the obstructive patients has overlap in Europe. 24% of the severe asthmatic patients have COPD+asthma bronchiale from the same
Airway reversibility

The definition of reversible airway obstruction is more than 12% or at least 200 ml increment from basic FEV1, after short-acting bronchodilator usage [4,11,12]. Significant reversibility and normalisation of lung function support asthma bronchiale diagnosis [11]. COPD+asthma bronchiale common manifestation show acut or significant reversibility in lung function and eosinophilia in sputum [20].

Airway resistance

Interleukin-6 as an inflammatory marker has role in the control of pathophysiological process in terms of airway resistance increment [13]. The increment of airway resistance show the histological change (asthma bronchiale remodelling), but airway resistance is basically high in COPD lead to flow limitation [9]. Airway resistance is significantly different compared to the two diseases [14]. In asthma bronchiale compared to COPD, airway resistance is lower in stable condition and in exacerbation, also [14].

Chest hyperinflation

The chance of developing chronic resting and dynamic hyperinflation is high because of anatomical abnormalities, like alveolar wall disruption, airtrapping or expiratory flow limitation in COPD. Acut hyperinflation can develop in asthma bronchiale also, but the degree is much less and it can significantly reduce after the asthmatic attack [11].

Eosinophilic sputum

There are data about counting of eosinophilic cells in the sputum in international literature, but it is not part of the daily routine in Hungary. Diagnosing of both diseases we need to focus clinical feature and lung function data [4-9].

Inflammatory cells in the airways

There is inflammation in small- and big airway in asthma bronchiale. The count of T-cells, major basic proteins and mastocytes in small (<2mm) and big (>2mm) airway is not significantly different, however there is more activated eosinophils in small airways [14-18]. Dominant neutrophilic inflammation takes part in COPD and the main characteristics are obstruction or closing of terminal bronchiolus [21]. Favourable therapeutic effect can develop based on the influence of distal airways [21-25]. Sufficient lung deposition leads to proper therapeutic effect in small airways [21].

Separated clinical entity

In spanish COPD guideline, the COPD and asthma bronchiale common airway manifestation is a separated entity with the following criteria [3-27] (Figure 1):

I. Major criteria:

a. asthma bronchiale in anamnesis
b. Significant reversibility: FEV1 ≥15% and ≥400 ml
c. Eosinophilic sputum

II. Minor criteria:

a. Positive bronchodilator test (at least 2x: FEV1 ≥12% and ≥200 ml)
b. Atopy in anamnesis
c. Increased IgE

III. Overlap is present, if COPD is present +:

IV. 2 major criteria or

V. 1 major and 2 minor criteria

COPD: chronic obstructive pulmonary disease.
### Table 1: Demographic data and co-morbidities in the common manifestation of COPD and asthma bronchiale (Modified based on [19]).

| Disease                        | Asthma (Severe)                      | Asthma + COPD                          | COPD               |
|--------------------------------|--------------------------------------|----------------------------------------|--------------------|
| Demographic Data               |                                      |                                        |                    |
| >40 years                      | >40 years, 50-65 years                | >65 years                              |                    |
| Female > Male                  | smoker or ex-smoker                  | smoker or ex-smoker                    |                    |
| ex-smoker or <5 py smoking history | >10 py smoking history              | >10 py smoking history                  |                    |
| obesity                        | atopy                                | atopy is absent                         |                    |
| typic atopy                    | Rhinosinusitis                       | GERD                                   |                    |
| rhinosinusitis                 | GERD                                 | daily albuterol usage                   |                    |
| GERD                           | significantly reduced exercise tolerance | significantly reduced exercise tolerance |                    |
| Frequent albuterol usage       | main problem: very frequent exacerbations> COPD alone | oxygen-dependent                          |                    |
| Limited exercise tolerance     |                                       |                                        |                    |
| prenisolon-dependency          |                                       |                                        |                    |
| main problem: frequent exacerbations |                                      |                                        |                    |

COPD: Chronic Obstructive Pulmonary Disease; GERD: Gastroesophageal Reflux Disease.

### Table 2: Functional variables, clinical features in COPD, asthma bronchiale and common manifestation of the two disease (Modification based on [30]).

| Disease                        | Asthma bronchiale                      | Asthma bronchiale+COPD                  | COPD               |
|--------------------------------|----------------------------------------|----------------------------------------|--------------------|
| From moderate to severe intermittent or chronic airway obstruction | From moderate to severe intermittent or chronic airway obstruction | From moderate to severe chronic airway obstruction (GOLD II-IV) |                    |
| FEV1/FVC<0.70                  | FEV1/FVC<0.70                          | DLCO<80%pred                           |                    |
| FEV1,<68%pred, >or<65%pred after albuterol usage | FEV1,<68%pred, or<65%pred after albuterol usage | FeNO>25 ppb                           |                    |
| SARP cluster 3, 4 or 5         | DLCO normal or low                     | Static or dynamic hyperinflation        |                    |
| DLCO normal                    | DLCO normal or low                     | Static or dynamic hyperinflation        |                    |
| >3% eosinophilic sputum        | Static hyperinflation                  | Not frequent awakeness at night         |                    |
| >3 exacerbation/year           | >3-5 exacerbation/year                 | frequent awakeness, >4/week             |                    |

COPD: Chronic Obstructive Pulmonary Disease, FEV1: Forced Expiratory Volume in the First Second, FVC: Forced Vital Capacity; DLCO: Diffusion Capacity; FeNO: Exhaled Fractioned Nitrogen-Monoxide.

### Table 3: Pathophysiologic background of COPD, asthma bronchiale and common manifestation of the two disease (Modification based on [32]).

| Disease                        | Asthma (mean)                        | Asthma+COPD (mean)                     | COPD               |
|--------------------------------|--------------------------------------|----------------------------------------|--------------------|
| Pathophysiologic background    |                                      |                                        |                    |
| airway inflammation: eosinophil>neutrophil | airway inflammation: eosinophil + neutrophil, CD4+, CD8+ T-lymphocytes | emphysema, alveolar destruction |                    |
| mastocytes                     | alveolar macrophages, smooth muscle hyperplasia + emphysema | airway inflammation: neutrophil>eosinophil |                    |
| CD4+ T-lymphocytes             | peribronchiolar fibrosis              | alveolar macrophages                    |                    |
| smooth muscle hyperplasia and hypertrophy | IgE, IL-4, IL-5, IL-13, IL-8, IL-6, TNF-alfa, eotaxin, proteases | mastocytes? |                    |
| no emphysema                   |                                       |                                        |                    |
| IgE, IL-4, IL-5, IL-13, eotaxin |                                       |                                        |                    |

COPD: Chronic Obstructive Pulmonary Disease; IgE: Immunglobulin-E; IL: Interleukine; TNF: Tumor Necrosis Faktor.
Table 4: Pharmacotherapy of COPD, asthma bronchiale and common manifestation of the two disease.

| Disease                        | Asthma          | Asthma+COPD       | COPD                  |
|-------------------------------|-----------------|-------------------|-----------------------|
| First-choice pharmacotherapy  | ICS, ICS+LABA   | ICS+LAMA+LABA, smoking cessation, pulmonary rehabilitation | bronchodilator-LAMA or LABA or both smoking cessation pulmonary rehabilitation |
| Add on therapy                | LABA, LAMA, LTRA, teofilin, omaluzumab, prednisolone | LABA, LAMA, LTRA, or roflumilast or teofilin, omaluzumab, prednisolone | ICS Or Roflumilast, Teofilin |
| Optional therapy              | Anti IL-5, Anti IL-13 ICS+LABA 1x/Day Azitromycin Vaccines broncial thermoplasty | therapy of asthma bronchiale and COPD according to FeNO values and endotypes | LAMA+LABA 1x/Day, Carboxy, Azitromycin anti IL-8, p39 protein kinase inhibitors hemophybus influenza vaccine endobronchial valves lung transplantation |

ICS: Inhaliative Corticosteroid; LABA: Long-Acting Beta-Agonist Bronchodilator; LAMA: Long-Acting Anticholinergic Bronchodilator; LTRA: Leukotrien Antagonist; IL: Interleukine; FeNO: Exhaled Fractioned Nitrogen-Monoxide.

Table 5: Spanish guideline, pharmacotherapy of COPD, asthma bronchiale and common manifestation of the two disease [modified based on [28]].

| Phenotypes | Stages |
|------------|--------|
| A          | I      | II     | III    | IV      |
| Non-exacerbator with emphysema or chronic bronchitis | LAMA or LABA | LAMA or LABA | LAMA+LABA | LAMA+LABA+teofilin |
| B          | LABA+ICS | LABA+ICS | LAMA+LABA+ICS | LAMA+LABA+ICS (if needed teofilin or PDE4 inhibitor) |
| Mixed COPD-asthma bronchiale | LABA or LABA | (LABA or LAMA)+ICS | LAMA+LABA+ICS | LAMA+LABA+ICS (if needed teofilin) |
| C          | LAMA or LABA | LAMA or LABA | LAMA+LABA+ICS | LAMA+LABA+ICS (if needed teofilin) |
| Exacerbator type with emphysema | LAMA or LABA | LAMA or LABA | LAMA+LABA+ICS | LAMA+LABA+ICS (if needed teofilin) |
| D          | LAMA or LABA | LAMA or LABA | LAMA+LABA+ICS (if needed PDE4 inhibitor) | LAMA + LABA + (ICS or PDE4 inhibitor) |
| Exacerbator type with chronic bronchitis | LAMA or LABA | LAMA+LABA+ICS (if needed PDE4 inhibitor) | LAMA + LABA + (ICS or PDE4 inhibitor) |
| COPD: Chronic Obstructive Pulmonary Disease; LAMA: Long-Acting Anticholinergic Bronchodilator; LABA: Long-Acting Beta-Agonist Bronchodilator; SAMA: Short-Acting Anticholinergic Bronchodilator; SABA: Short-Acting Beta-Agonist Bronchodilator; ICS: Inhalative Corticosteroid; PDE4 Inhibitor: Phosphodiesterase4 Inhibitor. |

Case Report

43 years female patient, who had symptoms of hey fever for 10 years and 3 times/week awoke in the early morning before using bronchodilators for 5 years. She was a passive smoker and she had 15 py (pack year=pack/day x smoking years) smoking history. In stable condition lung funtion was the following after 2 years (10 py smoking history). Using LAMA+LABA+ICS therapy was recommened for reduction of dyspnoea and increase of daily activity. Smoking cessation was suggested to the patient. Hospital and therapeutic cost. These type of patients come to medical office more often, so it causes significantly more health and financial cost. The cost of COPD+asthma bronchiale common manifestation is true:

a. Smoking asthmatic patient
b. Uncontrolled patients with asthma bronchiale on fix combination (ICS+LABA) therapy

c. Airway obstruction shows only small reversibility or fixed.

Case Report

46 years male patient with asthma bronchiale, who smoked 10 cigerretes/day for 20 years (10 py smoking history). Using ICS+LABA combination he had not significant early morning paroxism, but he had a progressive exertional dyspnoea. He had reduced daily activity, also. Lung function parameters ( reversibility test): FEV; 1,53L(43%pred)-1,65L(47%pred), FVC: 2,54L (72%pred)-2,68L (76%pred), FEV/FVC: 59-61%. Outcomes: An anticholinergic add-on therapy seemed to achieve the reduction in lung function worsening. Complex pulmonary rehabilitation (basically chest physiotherapy+training programs) was recommened for reduction of dyspnoea and increase of daily activity. Smoking cessation was suggested to the patient. Hospital and therapeutic cost. These type of patients come to medical office more often, so it causes significantly more health and financial cost. The cost of COPD+asthma bronchiale common manifestation is true:

a. The treatment cost of asthma bronchiale+COPD common manifestation’s patient is significantly larger
b. Severe exacerbation is often, which is very expensive [34-36].

Conclusion

According to an American study, the cost of yearly treatment if only asthma is manifested is 2.307 USD, if COPD is 4.879 USD, but 14.924 USD if the two disease is common manifested. In summary, asthma bronchiale and COPD can be manifested not just separately, the ratio of common manifestation is 15-30% in the obstructive group. Inflammatory response, lung function, value of exhaled, fractioned nitrogen-monoxide can be typical in these patients. If the two disease are common manifested add on anticholinergic therapy lead to better quality of life if asthmatic patients has COPD and in patients with COPD add on ICS therapy lead to better quality of life and reduction in exacerbation rate if asthma is manifested also. Acceptable quality of life, reduction in the rate of hospitalisations and exacerbations can be achieved with proper pharmacotherapy control. Smoking cessation and pulmonary rehabilitation are necessary for the complex treatment of these patients, also.

Acknowledgement

None.

Conflict of Interest

The authors declare that they have no conflict of interest.

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