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 call 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 paroxysmatic dysnopic wheezing in the early morning or after exercise [1-9]. In COPD, the dyspnoea is progressive and it is manifested during exercise at first. Hay fever with obstructive pulmonary disease support the definition of allergic asthma bronchiale, but there is a significant portion of COPD patients with hay 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 irreversible 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 individuale 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-morbidites 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 clinical 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 devides different clinical entities, recent data support that a T_{h2} cell type and an non-T_{h2} 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 parients have COPD+asthma bronchiale from the same...
Californian database [18]. According to a clinical study, common manifestation of COPD+asthma bronchiale has 42.7% frequent exacerbation rate, and within this group 32.8% of these patients has severe exacerbation [19].

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 acute 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 bronchioles [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

![Figure 1: Spanish guideline, COPD+asthma bronchiale bronchiale common phenotype [28].](image)

COPD: chronic obstructive pulmonary disease.

Recently published study compared to asthma bronchiale, COPD and asthma bronchiale +COPD common airway manifestation in terms of demographic data (Table 1), lung function, pathophysiologic variables (Table 2), characteristic inflammatory cell types (Table 3) and therapeutic option (Tables 4 & 5) [28,29]. As a therapeutic guide if we can not decide whether the patient has asthma bronchiale or COPD we can treat the patient as asthmatic because leaving inhalative steroid in asthma bronchiale is dangerous. In COPD, we need to treat small airways, deliver pharmacotherapy to small airways [30-32]. Beta-receptor density is higher in small airways, and anticholinergic receptor density is higher in big airways [30-33]. ICS+LABA combination can use the common, sinergistic effect of glucocorticoid and beta-adrenergic receptor [30,31]. Cover all part of the surface of the airway is important, we need to achieve all therapeutic target [32]. The following criteria can be used for COPD+asthma bronchiale common manifestation if a patient with COPD comes to the medical office:

i. Airway obstruction is variable, but not fully reversible in COPD
ii. Positive bronchodilator test
iii. Bronchial hyperreactivity
iv. Asthma bronchiale in anamnesis
v. Atopy in anamnesis
vi. Frequent exacerbations
vii. Smoking anamnesis
Table 1: Demographic data and co-morbidities in the common manifestation of COPD and asthma bronchiale (Modified based on [19]).

<table>
<thead>
<tr>
<th>Disease</th>
<th>Asthma (Severe)</th>
<th>Asthma + COPD</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic Data</td>
<td>&gt;40 years</td>
<td>&gt;40 years, 50-65 years</td>
<td>&gt;65 years</td>
</tr>
<tr>
<td></td>
<td>Female &gt; Male</td>
<td>smoker or ex-smoker</td>
<td>smoker or ex-smoker</td>
</tr>
<tr>
<td></td>
<td>ex-smoker or &lt;5 py smoking history</td>
<td>&gt;10 py smoking history</td>
<td>&gt;10 py smoking history</td>
</tr>
<tr>
<td></td>
<td>obesity</td>
<td>atopy</td>
<td>atopy is absent</td>
</tr>
<tr>
<td></td>
<td>typic atopy</td>
<td>Rhinosinusitis</td>
<td>GERD</td>
</tr>
<tr>
<td></td>
<td>rhinosinusitis</td>
<td>GERD</td>
<td>daily albuterol usage</td>
</tr>
<tr>
<td></td>
<td>GERD</td>
<td>significantly reduced exercise tolerance</td>
<td>significantly reduced exercise tolerance</td>
</tr>
<tr>
<td></td>
<td>Frequent albuterol usage</td>
<td>main problem: very frequent exacerbations &gt; COPD alone</td>
<td>oxygen-dependent</td>
</tr>
<tr>
<td></td>
<td>Limited exercise tolerance between worse conditions</td>
<td>main problem: exacerbations, reduced exercise tolerance</td>
<td></td>
</tr>
<tr>
<td></td>
<td>prednisolon-dependency</td>
<td>main problem: exacerbations</td>
<td></td>
</tr>
<tr>
<td></td>
<td>main problem: frequent exacerbations</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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]).

<table>
<thead>
<tr>
<th>Disease</th>
<th>Asthma bronchiale</th>
<th>Asthma bronchiale+COPD</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>From moderate to severe intermittent or chronic airway obstruction</td>
<td>From moderate to severe intermittent or chronic airway obstruction</td>
<td>From moderate to severe chronic airway obstruction (GOLD II-IV)</td>
<td></td>
</tr>
<tr>
<td>FEV&lt; sub&gt;1&lt;/sub&gt;/FVC&lt;0.70</td>
<td>FEV&lt; sub&gt;1&lt;/sub&gt;/FVC&lt;0.70</td>
<td>DLCO&lt;80%pred</td>
<td></td>
</tr>
<tr>
<td>FEV&lt; sub&gt;1&lt;/sub&gt;,68%pred, &gt; or &lt;65 %pred after albuterol usage</td>
<td>FEV&lt; sub&gt;1&lt;/sub&gt;,68%pred, or &lt;65 %pred after albuterol usage</td>
<td>FeNO&gt;25 ppb</td>
<td></td>
</tr>
<tr>
<td>SARP cluster 3,4 or 5</td>
<td>DLC0 normal or low</td>
<td>Static or dynamic hyperinflation</td>
<td></td>
</tr>
<tr>
<td>DLC0 normal</td>
<td>FeNO&gt;25-50 ppb</td>
<td>Static hyperinflation</td>
<td></td>
</tr>
<tr>
<td>&gt;3% eosinophilic sputum</td>
<td>Static hyperinflation</td>
<td>Not frequent awakeness at night</td>
<td></td>
</tr>
<tr>
<td>&gt;3 exacerbation/year</td>
<td>&gt;3-5 exacerbation/year</td>
<td>frequent awakeness, &gt;4/week</td>
<td></td>
</tr>
</tbody>
</table>

COPD: Chronic Obstructive Pulmonary Disease; FEV< sub>1</sub>: Forced Expiratory Volume in the First Second, FVC: Forced Vital Capacity; DL<sub>C0</sub>: 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]).

<table>
<thead>
<tr>
<th>Disease</th>
<th>Asthma</th>
<th>Asthma+COPD</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathphysiologic background</td>
<td>airway inflammation: eosinophil&gt;neutrophil</td>
<td>airway inflammation: eosinophil + neutrophil, CD4+, CD8+ T-lymifocytes</td>
<td>emphysema, alveolar destruction</td>
</tr>
<tr>
<td></td>
<td>mastocytes</td>
<td>alveolar macrophages, smooth muscle hyperplasia+emphysema</td>
<td>airway inflammation: neutrophil&gt;eosinophil</td>
</tr>
<tr>
<td></td>
<td>CD4+ T-lymphocytes</td>
<td>peribronchial fibrosis</td>
<td>CD4+, CD8+ T-lymphocytes</td>
</tr>
<tr>
<td></td>
<td>smooth muscle hyperplasy and hypertrophy</td>
<td>IgE, IL-4, IL-5, IL-13, IL-8, IL-6, TNF-alfa, eotaxin, proteases</td>
<td>mastocytes?</td>
</tr>
<tr>
<td></td>
<td>no emphysema</td>
<td>peribronchial fibrosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IgE, IL-4, IL-5, IL-13, eotaxin</td>
<td>IL-6, IL-8, TNF-alfa, proteases</td>
<td></td>
</tr>
</tbody>
</table>

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.

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

ICS: Inhalative 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]].

<table>
<thead>
<tr>
<th>Fenotypes</th>
<th>Stages</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Non-exacerbator with emphysema or chronic bronchitis</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>LAMA or LABA or SABA or SAMA</td>
</tr>
<tr>
<td>B Mixed COPD-asthma bronchiale</td>
<td>LABA+ICS</td>
</tr>
<tr>
<td>C Exacerbator type with emphysema</td>
<td>LAMA or LABA (LABA or LAMA + ICS or PDE4 inhibitor)</td>
</tr>
<tr>
<td></td>
<td>(LABA or LAMA + ICS or PDE4 inhibitor)</td>
</tr>
<tr>
<td></td>
<td>LAMA or LABA</td>
</tr>
<tr>
<td>D Exacerbator type with chronic bronchitis</td>
<td>LAMA or LABA</td>
</tr>
</tbody>
</table>


Case Report

43 years female patient, who had symptoms of hay 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 function was the following after 10 years and 3 times/week awoke in the early morning before smoking cessation program for this patient, also. If the following values and endotypes she 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: 65-68%. The patient had frequent clinical worsening with wheezing and she often need to have medical service. Outcomes: As an additional treatment ICS was chosen, and the exacerbations was disappeared, quality of life and lung function improved significantly, but lung function was fixed at a mild obstruction level. We offered a smoking cessation program for this patient, also. If the following patient with asthma bronchiale comes to medical office we need to think about asthma bronchiale+COPD common manifestation, and to use anticholinergic bronchodilator as add-on therapy:

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.

References

11. http://ginasthma.org/


