Małgorzata Krajnik[1], Krzysztof Kuziemski[2], Iwona Damps-Konstanska[2], Beata Wajda[2], Lucyna Gorska[2], Karol Kempinski[2], Krzysztof Specjalski[2], Ewa Jassem[2]

[1]Chair of Palliative Care, Nicolaus Copernicus University, Collegium Medicum in Bydgoszcz, Poland

[2]Department of Allergology, Medical University of Gdansk, Poland

Difficult-to-treat asthma — an uncontrolled disease. Is there any relation to the experience from palliative medicine?

Abstract

Background and aim. Difficult-to-treat asthma is characterized by uncontrolled symptoms occurring in spite of intensive treatment (corticosteroids and long-acting β2-agonists) for at least 6 months and is connected with severe obturation in the bronchotracheal tree. It still creates an important global medical and economical problem. The aim of the study was to evaluate the occurrence of persistent symptoms, exacerbating factors and co-morbidities in patients with difficult-to-treat asthma. It was also a challenging idea to apply palliative medicine to help patients with this type of asthma.

Material and methods. Twenty-seven patients (21 women and 6 men, ages ranging from 23 to 60) diagnosed with difficult-to-treat asthma were included in the study. Data were collected from the internet database of severe, difficult-to-treat asthma, introduced to the Department of Allergology in 2005. All patients' spirometries and additional factors were assessed.

Results. The median predicted value of FEV_1 was 55% (range: 34–104%) while 18 patients had FEV_1 lower than the 60% predicted value. All patients suffered from dyspnoea, chronic cough and wheezing and had additional factors escalating the symptoms of asthma. The most important factor which leads to exacerbation was long-term stress and rhinitis. Twelve (45%) patients from this group have poor tolerance of exercise. In spite of intensive treatment, 17 (65%) patients constantly overused short-acting beta-agonists (SABA) and all had long-term treatment with oral steroids. In most cases, co-morbidities were recognized: obesity and hypertension.

Conclusions. This study showed that the role of additional factors and co-morbidities plays a significant part in the course of asthma. It seems to be necessary to introduce a unified system of registering and managing patients with severe and difficult-to-treat asthma. That palliative care is very important for selected patients with chronic uncontrolled cough or dyspnoea should be a subject for newly planned clinical trials.

Key words: asthma, cough, palliative medicine

Address for correspondence: Ewa Jassem
Department of Allergology, Medical University of Gdansk, Poland
e-mail: ejassem@amg.gda.pl

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Introduction

"Asthma is an inflammatory disorder of the airways, which involves several inflammatory cells and multiple mediators that result in characteristic pathophysiological changes. In ways which are still not well understood, the pattern of inflammation is strongly associated with airway hyperresponsiveness and asthma symptoms" [1].

The latest version of the GINA guidelines (November 2007) introduced several changes to those already existing [1], such as the new classification of asthma based on the control of symptoms and the definition of difficult-to-treat asthma. According to this description, difficult-to-treat asthma is characterized by uncontrolled symptoms occurring in spite of intensive (stage IV) treatment for at least 6 months. Usually, respiratory function measured by spirometry shows severe obturation of the airways (FEV_1 < 60% of predicted value).

The severe stage of asthma is an important medical and economical problem. Frequent exacerbations associated with this type of asthma and persistent symptoms requiring constant management generate significant costs, as high as 1–2% of the total medical budget in western European countries [1].

In 1994, *European Network for Understanding of Severe Asthma* (ENFUMOSA) was introduced to work on severe and difficult-to-treat asthma [2]. The results of researches undertaken by the group showed that the risk factors for severe asthma include gender. Females with higher body mass index (BMI) and hypertension were especially at risk. Other factors determining the course of the disease in women were chronic sinusitis, the perimenopausal period, aspirin intolerance and physical activity. In men, physical activity, stress and aspirin intolerance exacerbated asthma [2]. Resistance to steroids was also underlined as a factor contributing to the severity of the disease [3]. By contrast, true steroid resistance caused by the polymorphic variant of the gene coding for the glicocorticosteroid receptor is a rare entity. Much more frequently, asthma is "simply" a steroid-dependent disease, requiring the use of systemic (oral) treatment. Recently, anti-IgE treatment has been introduced in a group with severe asthma [4]. This new agent enables improvement to the quality of life.

The aim of the study was to assess the occurrence of persistent symptoms, factors exacerbating the course of the disease and co-morbidities in patients with severe, difficult-to-treat asthma. We also considered the idea that there is a need to implement some experience from palliative medicine into the management of this group of patients.

Material and methods

The study group comprised 27 patients with severe, difficult-to-treat asthma, treated at the Allergology Department, Medical University, Gdansk between 2005–2007. There were 21 women and six men, aged from 23 to 60; median age: 35 years. Median FEV_1 was 55% of the predicted value (range: 34–104%), and 18 patients had FEV_1 lower than the 60% predicted value. The mean time from diagnosis to the time of the assessment was 21.6 years, range: from 7 to 50 years. At the time of the assessment bronchial obstruction reversibility was present in 10 patients. Data were collected from the database of severe, difficult-to-treat asthma, introduced to the Department of Allergology in 2005. The Local Ethic Committee has approved the study (NKEBN/369/ /2005).

Results

All patients suffered from dyspnoea, chronic cough and wheezing. Twelve (45%) underline poor tolerance of exercise (Table 1). In spite of intensive treatment, 17 (65%) patients constantly overused short-acting beta-agonists (SABA) and all had long-term treatment with oral steroids.

All patients had additional factors escalating their symptoms and exacerbating the course of the disease (Table 2): stress and allergic rhinitis being the most common. They also had a number of co-morbidities (Table 3), the most prevalent being obesity and hypertension.

Discussion

Whether palliative medicine has any connection with the treatment of asthma remains open. Currently, the answer to this question is usually "No". However, the clinical course of severe and difficult-to-treat asthma resembles the course of severe chronic obstructive pulmonary disease (COPD). The need for palliative care for the latter has been discussed for the last decade. Some authorities indicate that chronic severe pulmonary symptoms significantly decrease the quality of life of patients with COPD, having a strong impact on all its aspects [5]. Furthermore, it has been stressed that patients with severe COPD require the same terminal care and support as patients with advanced malignancies [6–8].

Table 1. Patients' (n = 27) characteristic and chronic symptoms occurrence

Characteristic	Number
Gender	
Men	6
Women	21
Age	
Mean	46.8
Range	23–60
Years from diagnosis	
Median	21.6
Range	7–50
FEV_1	
Median	55%
Range	34–104%
Bronchial obstruction reversibility (at the time of assessment)	10
Eosiniphilia	1
Total IgE	
Median	
Range	10–757
Positive SPT	6
Permanent use of oral steroids	27
SABA overuse	Mean = 4 puffs/day (17 patients used ≥ 2 × day
Chronic dyspnoea	26
Chronic cough	26
Poor tolerance of exercise	12
Wheezing	26
Gender	
Men	6
Women	21
Age	
Mean	
Range	23–60

FEV_1 — one second forced expiratory volume; SPT — skin prick testing; SABA — short-acting beta-agonists

Table 2. Factors escalating symptoms of asthma

Factor	Number
Cigarette smoking	10
Chest X-ray abnormalities	2
Allergic rhinitis	20
Chronic sinusitis	4
GERD	17
Stress	25
Vocal cords dysfunction	5
Aspirin (NSAIDs) intolerance	10
Co-existing COPD	0

GERD — gastroesophageal reflux disease; NSAIDs — non-steroidal anti-inflammatory drugs; COPD — chronic obstructive pulmonary disease

Table 3. Co-morbidities

Co-morbidity	Number
Overweight/obesity	15
Hypertension	11
Cardiac disease	5
Venous thrombosis	0
Osteopenia/osteoporosis	3
Diabetes	2

Our small study including patients with severe and difficult-to-treat asthma showed that, in spite of intensive treatment, persistent disturbing pulmonary symptoms are common in this group of patients. Thus, if asthmatic patients suffer for a long time from dyspnoea and cough resistant to the recommended and widely accepted treatment modalities, some propositions from palliative medicine might be taken into consideration. One of them is the administration of nebulized opioids. Systematic analysis of randomized controlled clinical trials has not proved the efficacy of inhaled opioids in controlling dyspnoea or exercise tolerance in patients with COPD or idiopathic pulmonary fibrosis [9]. However, predominantly low-level clinical evidence supports inhaled opioids for the palliation of dyspnoea in patients with advanced cancer and cystic fibrosis [10–12]. The fundamental and still unanswered question is whether opioids act locally in the respiratory tract. We recently performed an immunohistochemical visualization of opioid receptors in the human airways and revealed their presence in the tracheal and bronchial epithelium and in sensory unmyelinated nerves containing peptides [13]. Previous functional studies showed that in vitro opioids, by inhibiting proinflammatory neurotransmitters released from sensory nerves, reverse the constriction of isolated bronchi and diminish mucus production [14––21]. All these data support the idea that opioids, by local action, may decrease the dyspnoea and cough related to neurogenic inflammation, thus suggesting their potential benefit for asthma. However, asthma creates some specific problems. One of them is connected with the fear of the bronchospasm due to the histamine release by morphine. It has been suggested that only higher doses of morphine may evoke such a reaction on the mast cells of the respiratory airways [20]. Otulana and coworkers investigated the safety and pharmacokinetics of inhaled morphine in 20 subjects with moderate-to-severe asthma [22]. Morphine was well-tolerated and caused no clinically significant bronchoconstriction in most patients. Four subjects who experienced a

significant drop in FEV_1 recovered after a dose of albuterol [22]. However, while the problem of potential bronchoconstriction after opioids is unclarified, nebulized morphine is not recommended for asthmatic patients at present. To avoid this potential risk, other opioids have been tried, such as very low doses of nebulized fentanyl citrate or morphine-6-glucuronide [23, 24].

Nebulized opioids seem to be a very promising treatment option in carefully selected cases, such as a patient with a 16-year history of asthma who suffered severe coughing, bronchospasms and greatly reduced exercise tolerance [25]. His cough failed to respond to all standard asthma therapy and even to nebulized lidocaine. He was commenced on nebulized morphine with a dramatic reduction in cough and successfully treated for 2.5 years. However, our small study also showed that the role of additional factors and co-morbidities having an influence on the course of asthma should be taken into account.

In summary, it seems necessary to introduce a unified system of registering and managing patients with severe and difficult-to-treat asthma, as was done for patients with chronic heart diseases. Implementation of palliative care for carefully selected patients with chronic uncontrolled cough or dyspnoea should be a subject for newly planned clinical trials.

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