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Coexistence of asthma and obstructive sleep apnea

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ABSTRACT

Obstructive sleep apnea (OSA) and asthma are common respiratory diseases that can coexist in the same patient. Epidemiological and pathophysiological data suggest an independent association between the two diseases. Over the past few decades, a wealth of data has emerged on the prevalence of asthma and OSA. The prevalence ranges from 38% to as high as 70%.

Key words: asthma; obstructive sleep apnea; respiratory diseases

Introduction

Over the past decade, there has been increasing interest in the relationship between asthma and obstructive sleep apnea (OSA). Both asthma and OSA are highly prevalent airway diseases [1]. Obstructive sleep apnea is characterized by episodes of complete or partial airway collapse accompanied by decreased oxygen saturation or awakening from sleep [2]. This disorder results in fragmented, unrestorative sleep and other symptoms such as loud, disruptive snoring, apnea during sleep and excessive daytime sleepiness, morning headaches, depression, difficulty concentrating and memory loss [3]. OSA has a significant impact on cardiovascular health,

mental illness, quality of life and driving safety. Asthma is a chronic lung disease that affects people of all ages, and is caused by inflammation and muscle tension around the airways, making it difficult to breathe. Symptoms of asthma can include coughing, wheezing, shortness of breath and tightness in the chest. These symptoms can be mild or severe and can come and go over time [4]. Asthma is usually characterized by chronic inflammation, airway hyper responsiveness (AHR) and reversible expiratory flow limitation [5].

Both obstructive sleep apnea and asthma are common diseases, and their incidence has recently shown a gradual increase. OSA and asthma are mutually detrimental. As recent data suggest, OSA can worsen asthma symptoms and vice versa. This may be due to simple coexistence, shared risk factors, or separate interactive mechanisms between these upper airway pathologies [6]. The co-occurrence of asthma and OSA has been called “alternative overlap syndrome” [7].

Asthma

Asthma is one of the most common respiratory diseases, usually associated with chronic airway inflammation. It usually manifests as wheezing, shortness of breath, a feeling of tightness in the chest, and coughing, which is variable in frequency as well as severity [8]. The chronic inflammatory process in the airways leads to bronchospasm, vasodilation, airway swelling and activation of sensory nerve endings. In the course of asthma, there is activation of inflammatory cells, including mast cells and dendritic cells, as well as lymphocytes and eosinophils. The predominant lymphocytes in allergic asthma are helper T cells (Th2), and in non-allergic asthma are innate lymphoid cells [9].

It is estimated that nearly 390 million people worldwide suffer from asthma, and this number is expected to reach 400 million by 2025. According to the National Health Service, there were 2.2 million asthma patients in Poland in 2019 [10].

The diagnosis of asthma begins with a history of respiratory symptoms. These symptoms often worsen at night and in the early morning. They can be triggered by viral infections, exposure to allergens, exercise, strong odors, cigarette smoke, exhaust fumes and even laughter. In a patient with a history suggestive of asthma, a spirometry test is performed. The diagnosis of asthma is supported by an increase in first-second expiratory volume (FEV1) of more than 200 ml and 12% over the FEV1 value before the administration of a bronchodilator on spirometry. Spirometry testing should be performed before treatment is initiated [11].

Asthma is divided by allergic and non-allergic etiology. Allergic usually begins in childhood, often co-occurs with other atopic diseases, positive family history of atopic diseases. Non-

allergic, on the other hand, usually occurs in adults, the course is progressive, and skin tests for allergy are negative. Another division is the division of the type of asthma by phenotype, with late onset, with established bronchial obstruction and coexisting obesity. Depending on the type of airway inflammation, eosinophilic asthma, neutrophilic asthma and poor-cell asthma are distinguished. In clinical practice, asthma is divided according to the degree of control.

The disease often progresses episodically and tends to resolve, but in many cases symptoms recur in adulthood. Asthma is characterized by exacerbations that develop quickly (within minutes or hours) or gradually (over many hours or days) and can be life-threatening if left untreated. Long-term uncontrolled asthma leads to progressive irreversible bronchial obstruction [12]. Table 1 outlines treatments to control chronic asthma in adults.

Table 1. Control treatment of chronic asthma in adults (based on GINA 2022, modified) [12].

Step 1	
ad hoc intake of a combination preparation containing formoterol and a low dose of ICS	**I**
taking a low-dose ICS every time the patient takes an emergency SABA	**II**
ineffective [a] ↓	
Step 2	
Ad hoc intake of a combination preparation containing formoterol and a low dose of ICS	**I**
Low-dose GCS	**II**
- LTRA or - taking ICS in a low dose every time the patient takes ad hoc SABA - the addition of specific allergen sublingual immunotherapy may be considered[c]	**III**
ineffective [a] ↓ proper control [b] ↑	
Step 3	
regular and ad hoc intake of a combination preparation containing formoterol and a low dose of ICS	**I**
low-dose GCS + LABA	**II**

- medium-dose GCS - you may consider including LTRA - you may consider including sublingual specific allergen immunotherapy [c]	**III**
ineffective [a] ↓ proper control [b]↑	
Step 4	
regular use of a preparation containing formoterol and a medium dose of ICS + ad hoc intake of a preparation containing formoterol and a low dose of ICS	**I**
medium-dose and high-dose ICS + LABA	**II**
- inclusion of either LAMA[d] or LTRA - high-dose ICS	**III**
ineffective [a] ↓ proper control [b]↑	
Step 5	
- inclusion of LAMA[d] - Asthma phenotype assessment and biological treatment - you may consider high-dose ICS + LABA[e]	**I**
- inclusion of either azithromycin or LTRA - low-dose oral GCS (balance of benefits and risks should be assessed)	**II**

[a] Lack of symptom control, asthma exacerbations are present, or risk factors for exacerbations and/or persistent obstruction are present, check that the patient is adhering to medical instructions and taking medications correctly before increasing the intensity of treatment.

[b] In patients whose asthma has been well controlled for ≥3 months and whose risk of exacerbations is low, evaluate the indications for reducing the intensity of treatment.

[c] In patients allergic to house dust mites, with coexisting allergic rhinitis and FEV_1>70% wn.

[d] Use tiotropium with a soft mist inhaler (SMI).

[e] Formoterol-containing formulation in patients who use adjuvant formoterol and low-dose ICS.

I – first choice treatment

II – alternative treatment

III – other control treatment options

GCS – glucocorticosteroid

ICS – inhaled glucocorticosteroid

LABA – long-acting β2-agonist (inhaled)

LTRA – leukotriene receptor antagonist

SABA – short-acting β2-agonist (inhaled)

Obstructive sleep apnea

Obstructive sleep apnea is a common condition that can be associated with serious adverse consequences. The affliction is characterized by recurrent episodes of partial or complete obstruction of the upper airway during sleep, a shallowing of airflow or complete cessation of airflow (apnea), despite continuous inspiratory efforts. Failure to provide adequate alveolar ventilation results in oxygen desaturation, and when this disorder is prolonged, the partial concentration of carbon dioxide increases [13]. OSA is defined by the occurrence of breathing pauses of at least 10 seconds during sleep. The severity of OSA symptoms is measured by the apnea/hypopnea index (AHI), which defines the sum of all apneas and shortness of breath occurring during an hour of sleep. The AHI is divided into: mild (AHI 5-15), moderate (AHI 16-30) and severe (AHI > 30) [8]. OSA affects nearly 1 billion people worldwide (AHI>5), with 425 million people aged 30-69 suffering from moderate or severe obstructive sleep apnea (AHI >15) [14, 15].

Patients with obstructive sleep apnea experience symptoms both during the day and at night. At night, awakenings with a feeling of shortness of breath are very common, but also loud snoring, the need to urinate several times, clammy sweats in the upper half of the body, and impaired libido. During the day, there is excessive sleepiness, irritability, restlessness, impaired memory and impaired concentration. These symptoms significantly impair quality of life and impede daily functioning [8].

The main factor that causes OSA is obesity, but a short neck, a crooked nasal septum, enlarged tonsils, medications and stimulants that reduce muscle tone also contribute to OSA. Increasing body weight by 10%, increases the risk sixfold, and when the neck circumference exceeds 48cm, by as much as 20 times. That's why it's so important to take care of healthy eating and proper body weight, which will significantly reduce our risk of the disease [8].

Asthma and obstructive sleep apnea

Recent studies have shown that there is an association between bronchial asthma and OSA, and that there is a bidirectional relationship in which one disorder adversely affects the other [16]. It has been suggested that neuromechanical reflex bronchoconstriction, gastroesophageal reflux, local and systemic inflammation, and the indirect effect of OSA-induced cardiac dysfunction on dyspnea are mechanisms leading to worsened asthma control in patients with coexisting OSA [17].

Asthma and obstructive sleep apnea share similar mechanisms affecting the respiratory system and similar risk factors. Failure to properly recognize both of these diseases occurring simultaneously can create problems in treatment. Asthma can exacerbate sleep apnea, while sleep apnea can make the diagnosis of asthma difficult under certain circumstances [18]. Both asthma and obstructive sleep apnea (OSA) syndrome are common diseases, and their co-occurrence can be associated with serious consequences. The prevalence of OSA syndrome among asthma patients is higher than in the general population. Especially in asthmatic patients with nocturnal symptoms persisting despite treatment [19]. Increasing evidence seems to indicate that, like asthma, OSA promotes an inflammatory response through hypoxia, hypercapnia and sleep fragmentation, resulting in a reversible increase in C-reactive protein (CRP). Production of TNF-α, a pro-inflammatory cytokine, is elevated in patients with OSA and plays an important role in airway collapse and reopening. Both pro-inflammatory factors tend to decrease after C-PAP treatment, thereby improving asthma symptoms and quality of life [20].

Twenty-seven percent of bronchial asthma patients developed obstructive sleep apnea within the first four years, compared to 16 percent of those without known asthma. People struggling with bronchial asthma are about 40% more likely to develop obstructive sleep apnea compared to healthy individuals. In addition, the longer the subjects had asthma, the stronger the association with the occurrence of obstructive sleep apnea, and they were more likely to complain of greater daytime sleepiness than healthy subjects [6]. Asthma, as well as obstructive sleep apnea, is manifested by the occurrence of dyspnea as a result of airway narrowing. This narrowing is associated with inflammation, which can be triggered by various environmental or genetic factors [18]. In addition to common risk factors such as obesity, gastroesophageal reflux disease and allergic rhinitis, emerging evidence suggests that the two diseases may complicate each other's clinical course. On the one hand, OSA modifies asthmatic airway inflammation and is associated with poor asthma control. On the other hand, asthma and its medications increase upper airway collapse, contributing to the development and severity of OSA. The nocturnal respiratory symptoms of OSA and asthma are often similar, and hospital polysomnography is often necessary for correct diagnosis, especially in children. It is unclear whether OSA in asthmatic patients is merely a comorbid condition or a specific “subphenotype” of asthma. On the one hand, patients with allergic asthma are often characterized by T2-dependent inflammation and overproduction of IL-5, resulting in airway eosinophilia, and IL-13, leading to airway smooth muscle hyperreactivity and excessive mucus secretion, resulting

in the development of obesity and OSA [21]. On the other hand, however, in obese patients with later onset non-allergic asthma, mechanical changes affecting lung function may promote the development of obstructive apnea. In these patients, adipose tissue secretes several cytokines and adipokines that can directly affect the airway epithelium and induce bronchial hyper responsiveness [22]. The relationship between OSA, obesity and asthma may be even more complex and may involve other factors, including mechanical, dietary and genetic factors. A plausible explanation for this relationship comes from the "integrated airways" hypothesis, according to which the inflammatory process within a continuous upper airway obstruction causes fluctuations in chest pressure, frequent agitation and occasional hypoxia, all of which contribute to an inflammatory environment, increasing the risk of comorbidities [23].

In asthmatic patients, it is therefore advisable to look for OSA syndrome, especially in patients with symptoms of sleep-disordered ventilation [19]. A treatment method for patients with OSA syndrome is continuous positive airway pressure (CPAP) administered through a nasal or full-face mask, which leads to the elimination of obstructive sleep apnea and shortness of breath during sleep. CPAP treatment can also have a positive effect on the course of asthma [24].

The impact of obesity on the development of asthma and obstructive sleep apnea

Asthma is a heterogeneous disease, complicated by multiple comorbidities and known risk factors. Comorbidities such as obesity, gastroesophageal reflux and obstructive sleep apnea contribute to disease severity. Emerging literature suggests that there is a common pathophysiology that drives the development and control of the effects of these diseases [25]. One factor that increases the risk of both asthma and obstructive sleep apnea is obesity. Obesity disrupts the anatomy of the upper airways and contributes to compromised airway mechanics, which in turn promotes the development of apnea. Obesity affects chronic inflammation by increasing cytokines and adipocytokines. Excessive body weight also reduces airway diameter. The pro-inflammatory effects of obesity are not the only factor that contributes to the development of asthma. The effects of obesity on the mechanics of the respiratory system carry with them the effects of decreased respiratory volume, which can lead to an increase in respiratory muscle tone and hyper responsiveness; fat tissue accumulated in the abdominal cavity also causes an increase in pressure [19]. In obese patients with asthma, after weight loss, improvements in asthma symptoms and reduced need for medication have been observed [1]. Interestingly, a study by Ioan et al. (2022) showed that for school-aged children, the risk of moderate to severe obstructive sleep apnea was increased in obese, male children. Prevalent

asthma was associated with a lower risk of moderate/severe OSA in children. Both diseases share common pathophysiophysiological mechanisms, including decreased β-receptor density and diurnal changes in secreted cytokines and hormones, so early treatment of asthma symptoms may prevent the development of OSA.

SUMMARY

Obstructive sleep apnea (OSA) and asthma are very common chronic respiratory diseases. In addition to their frequent coexistence due to their high prevalence and shared risk factors, these disorders are characterized by a mutual interaction in which each disease affects the severity of the other. Airway and systemic inflammation, neuroimmune interactions and the effects of asthma-controlling drugs (corticosteroids) are factors that predispose patients with asthma to OSA. Conversely, undiagnosed or inadequately treated OSA adversely affects asthma control, in part through the effects of intermittent hypoxia on airway inflammation and tissue remodeling [6]. Although there are strong epidemiological links between OSA and asthma, the mechanism of this association is complex and not well understood, and the relationship between these diseases is likely bidirectional. However, there is a lack of knowledge about the common molecular pathways between these diseases. A better understanding of the mechanisms by which asthma and obstructive sleep apnea interact with each other will provide insight into targeted therapeutic approaches for patients suffering from these conditions.

DISCLOSURE

Author's contribution

Conceptualization: Hubert Olszewski, Alicja Andrzejak, Mateusz Szarek, Kacper Stolarek; methodology: Alicja Andrzejak, Hubert Olszewski, Marcin Walter.; software: Hubert, Olszewski, Mateusz Szarek, Kacper Stolarek, Alicja Andrzejak; formal analysis: Alicja Andrzejak, Marcin Walter , Kacper Stolarek.; investigation: Hubert Olszewski, Mateusz Szarek, Kacper Stolarek, Alicja Andrzejak; resources: Mateusz Szarek, Alicja Andrzejak, Marcin Walter, Kacper Stolarek; data curation: Hubert Olszewski, Alicja Andrzejak, Mateusz Szarek; writing - rough preparation: Alicja Andrzejak, Hubert Olszewski, Mateusz Szarek writing - review and editing: Marcin Walter, Hubert Olszewski, Alicja Andrzejak, Kacper Stolarek; visualization: Hubert Olszewski, Alicja Andrzejak, Mateusz Szarek, Marcin Walter;

supervision: Alicja Andrzejak, Hubert Olszewski, Kacper Stolarek, Mateusz Szarek.; project administration: Alicja Andrzejak, Hubert Olszewski, Marcin Walter

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