OSA in Patients with Severe Asthma-Alternative Overlap Syndrome

2.2

Ivan Čekerevac[1,2], Bojan Djokić[2]

1 Faculty of Medical Sciences Kragujevac

2 Clinic for pulmonology, University Clinical Center Kragujevac

Abstract

Bronchial asthma and obstructive sleep apnea (OSA) are common chronic diseases of the respiratory system. During the last decade, there has been a growing interest in the connection between these two disorders. Studies show that asthma patients are at increased risk for OSA, and the prevalence is on average around 70% in severe asthma patients. Rhinitis, gastroesophageal reflux disease and obesity are common comorbidities for both entities. OSA is an independent factor in the exacerbation of asthma and each condition in itself can contribute to the exacerbation of the other. Asthma, by its mechanical effect, has a direct impact on OSA, leading to greater collapse of the upper airway and worsening snoring and apnea symptoms in patients with OSA. On the other hand, OSA directly affects asthma through nerve reflexes, intermittent hypoxia, increases inflammation, increases the production of leptin and vascular endothelial growth factor as well as sleep fragmentation. Indirect effects in a bidirectional interaction are reflected in the prolonged effects of systemic corticosteroids, chronic diseases of the upper respiratory tract, tobacco use and increased body weight in asthmatics, which leads to worsening of OSA symptoms. It remains unclear whether OSA in asthmatics is merely a comorbidity or a specific new phenotype of asthma. In patients with asthma and OSA, CPAP treatment reduces asthma symptoms, improves morning expiratory flow, and improves quality of life parameters.

Keywords: severe asthma, OSA, alternative overlap syndrome

Bronchial asthma and obstructive sleep apnea (OSA) are frequent chronic diseases of the respiratory system. During the last decade, there has been a growing interest in the connection between these two disorders. For this reason, the term Alternative Overlap Syndrome (Asthma and OSA) was introduced in 2013, to distinguish it from the classic Overlap Syndrome (COPD and OSA). There is more and more evidence that OSA is associated with increased bronchial hypersensitivity[1] and inflammation[2] and thus may be an independent risk factor for exacerbation of bronchial asthma[3]. Studies show that asthma sufferers have an increased risk of OSA, and the prevalence is on average around 70% in severe asthma sufferers[4]. Many patients with asthma report poor sleep quality, daytime sleepiness and higher frequency of snoring during sleep than in the general population[5]. These symptoms are common in patients with OSA, indicating a connection between the two disorders[6]. Similar pathophysiological mechanisms are observed in both disorders, which are manifested by an increase in local and systemic inflammation, and common comorbidi-

https://doi.org/10.26493/978-961-293-297-8.47-51

ties such are gastroesophageal reflux, obesity, and rhinitis[7–9].

Asthma and OSA-alternative overlap syndrome

OSA is the most common breathing disorder during sleep, typically occurring in obese people[5]. Like asthma, OSA has its own phenotypes depending on the craniofacial morphology. Common risk factors for OSA include male gender, age, obesity, increased neck circumference (greater than 17 inches in men and 16 in women), craniofacial abnormalities (micrognathia, retrognathia), and the presence of cardiovascular comorbidities[4]. Certain studies point out that the presence of OSA in patients with asthma can be a separate phenotype of asthma[10,11]. The frequency of OSA in severe asthma and difficult-to-treat asthma ranges from 50 to 95%[4]. Such a large difference in frequency can be explained by the different methodology of the studies. In earlier studies, the methodology was based on self-reporting of snoring during sleep and periods of apnea[12,13]. Recent studies have included polysomnography in their methodology. After a four-year follow-up period, patients with asthma had a 40% higher risk of sleep apnea compared to patients without asthma[14]. In one retrospective study, asthma patients with frequent exacerbations, high doses of inhaled corticosteroids and frequent use of systemic corticosteroids had a more frequent diagnosis of OSA (15). Studies using polysomnography reported a higher incidence of sleep apnea (88 to 95%) compared to studies using a respiratory polygraphy (49% in severe asthmatics)[16]. The significant difference in frequency can be explained by the following: the respiratory polygraphy can underestimate the severity of OSA in patients with asthma; asthma can have an impact on the phenotypic expression of OSA by reducing the Aurosal index[14]. All this shows that more prospective research is necessary to evaluate the development of these two disorders.

Frequent comorbidities in asthma and OSA

Rhinitis: the prevalence of both allergic and non-allergic rhinitis in asthma sufferers is estimated at 80 to 90%, and rhinitis is a risk factor for the development of asthma[17,18]. Rhinitis causes chronic inflammation and nasal obstruction, which results in an increase in negative oropharyngeal pressure during inspiration and predisposes to airway collapse, increased apnea-hypopnea index (AHI) and OSA symptoms[19]. Chronic inflammation in the upper and lower respiratory tract can potentiate the development of OSA[20].

Gastroesophageal reflux disease (GERD): a common disorder found in about 58 to 65% of patients with OSA and as many as 80% of patients with asthma[7,21]. Persistent symptoms of GERD lead to inflammation of the upper respiratory tract, which can cause sleep fragmentation, snoring during sleep. Frequent microaspirations and direct injuries to the airways cause worsening of asthma by increasing the tendency to bronchial obstruction[4].

Obesity: Obesity is a risk factor for the development of OSA, but it is also an independent risk factor for asthma[4]. As a complex entity, it affects breathing through various mechanisms and physiological processes. Accumulation of fatty tissue in the upper parts of the respiratory tract leads to an increase in resistance and collapsibility, while in the region of the chest and abdomen it leads to restrictive disorders where functional residual capacity is reduced and ventilation is weakened[22]. OSA is more common in obese men, while asthma is more common in obese women, which suggests a potential influence of hormones[23].

Pathophysiological correlation between OSA and severe asthma – bidirectional interaction

OSA is an independent factor for the exacerbation of asthma and each condition in itself can have an effect on the worsening of

the other in alternative overlap syndrome. Asthma, with its mechanical effect, has a direct impact on OSA, leading to a reduction in lung volume by reducing the diameter of the airway, as well as by affecting the structure and function of the smooth muscles of the airway. All of this leads to greater collapse of the upper airway and worsens snoring and apnea symptoms in patients with OSA[4]. OSA also directly affects asthma through nerve reflexes, intermittent hypoxia, increases inflammation, increases the production of leptin and vascular endothelial growth factor as well as sleep fragmentation[4]. Intermittent hypoxia leads to systemic oxidative stress and the development of systemic inflammation, where an increase in tumor necrosis factor alpha (TNF-ά), interleukin-6(IL-6) and C reactive protein was observed in patients with

Indirect effects in a bidirectional interaction are reflected in prolonged effects of systemic corticosteroids, chronic diseases of the upper respiratory tract, use of tobacco and increased body weight in asthmatics, which leads to worsening of OSA symptoms[4]. GERD and cardiovascular comorbidities in patients with OSA affect the poor course of bronchial asthma. (Figure 1)

Clinical significance of alternative overlap syndrome

It remains unclear whether OSA in asthmatics is only a comorbidity or a specific new phenotype of asthma. On the one hand, allergic asthma is accompanied by a T2 inflammatory response and excessive production of interleukin 5 and interleukin 13, which lead to eosinophilia and hyperreactivity of airway

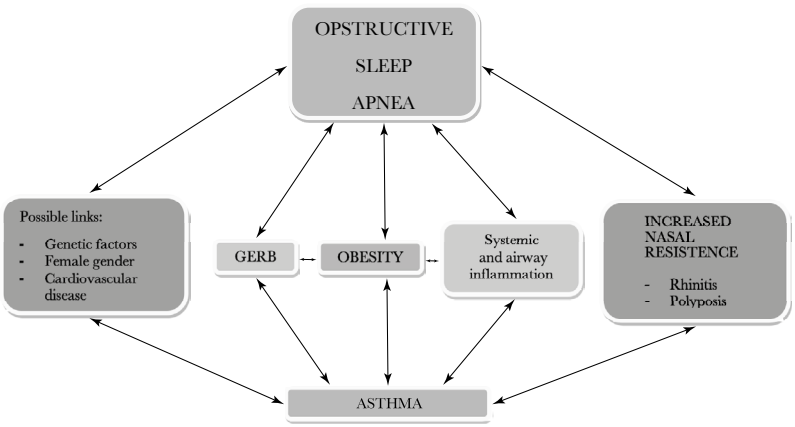

Figure 1. Obstructive sleep apnea and asthma: pathophysiologic links

AHI greater than 15[24]. Also, intermittent hypoxia can lead to stimulation of receptors of the carotid body and initiate reflex bronchoconstriction and participate in the occurrence of nocturnal symptoms associated with asthma[25]. Leptin, a hormonal protein produced by adipose tissue, has a proinflammatory effect and stimulates the release of IL-6 and TNF-ά from adipocytes[25].

smooth muscles and mucus hypersecretion, which are complicated by obesity and OSA. In contrast, obese patients who developed non-allergic asthma with late onset develop mechanical changes that lead to lung function disorders and favor the onset of obstructive apnea[5]. In these patients, the adipose tissue secretes several cytokines and adipokines that have direct effects on the airway epitheli-

um and can be a trigger for bronchial hyperactivity[26,27]. From the above, polysomnography is recommended for asthma patients with inadequate control of night symptoms despite proper treatment[28].

Mortality in patients with OSA and asthma is poorly researched. In one study, it was shown that patients with asthma and sleep disorders have a higher risk of mortality compared to asthma patients without sleep disorders[29]. In patients with asthma and OSA, CPAP treatment reduces asthma symptoms, improves morning expiratory flow, and improves quality of life parameters[30]. In one prospective study, it was shown that the proportion of adult patients with uncontrolled asthma dropped from 41.4 to 17.2% with CPAP treatment. It was also shown that the proportion of patients who had worsening asthma decreased from 35.4 to 17.2% after six months of CPAP machine use[7].

Conclusion

The association between OSA and severe asthma is based on coincident pathophysiological mechanisms, bidirectional interactions and the presence of similar comorbidities. Similar to asthma, OSA also promotes an inflammatory response through hypoxia and hypercapnia and sleep fragmentation leading to an irreversible increase in C reactive protein, tumor necrosis factor and other proinflammatory cytokines involved in airway collapse and hyperreactivity. Proinflammatory factors tend to decrease when these patients are treated with a CPAP device, which leads to improvement in asthma symptoms and a better quality of life.

References

1. Lin C-C, Lin C-Y. Obstructive sleep apnea syndrome and bronchial hyperreactivity. Lung. 1995;173(2):117-26.
2. Kheirandish-Gozal L, Gozal D. Obstructive sleep apnea and inflammation: proof of concept based on two illustrative cytokines. Int J Mol Sci. 2019 Jan 22;20(3):459. doi: 10.3390/ijms20030459.
3. ten Brinke A. Risk factors of frequent exacerbations in difficult-to-treat asthma. Eur Respirat J. 2005 Nov;26(5):812-8.
4. Pepito DL, Mohammed JM, Hardin KA. Obstructive Sleep Apnea and Asthma: More Than Chance?. Curr Pulmonol Rep. 2021 Mar 12;10(9):84-91.
5. Ragnoli B, Pochetti P, Raie A, et al. Interrelationship Between Obstructive Sleep Apnea Syndrome and Severe Asthma: From Endo-Phenotype to Clinical Aspects. Front Med (Lausanne). 2021 Jun 30:8:640636. doi: 10.3389/fmed.2021.640636.
6. Auckley D, Moallem M, Shaman Z, et al. Findings of a Berlin Questionnaire survey: comparison between patients seen in an asthma clinic versus internal medicine clinic. Sleep Med. 2008;9(5):494-9.
7. Serrano-Pariente J, Plaza V, Soriano JB, et al. CPASMA Trial Group. Asthma outcomes improve with continuous positive airway pressure for obstructive sleep apnea. Allergy. 2017;72(5):802-12.
8. Lafond C, Sériès F, Lemière C. Impact of CPAP on asthmatic patients with obstructive sleep apnoea. Eur. Respir. J. 2007;29(2):307-11.
9. Franklin KA, Lindberg E. Obstructive sleep apnea is a common disorder in the population-a review on the epidemiology of sleep apnea. J Thorac Dis. 2015 Aug;7(8):1311-22.
10. American Academy of Sleep Medicine. International classification of sleep disorders. 3rd ed. Darien, IL: American Academy of Sleep Medicine, 2014. 383 p.
11. Damianaki A, Vagiakis E, Sigala I, et al. The co-existence of obstructive sleep apnea and bronchial asthma: revelation of a new asthma phenotype? J Clin

Med. 2019;8(9):1476. doi: 10.3390/jcm8091476.
12. Larsson LG, Lindberg A, Franklin KA, et al. Symptoms related to obstructive sleep apnoea are common in subjects with asthma, chronic bronchitis and rhinitis in a general population. Respir Med. 2001 May;95(5):423-9.
13. Bhattacharyya N, Kepnes LJ. Ambulatory office visits and medical comorbidities associated with obstructive sleep apnea. Otolaryngol Head Neck Surg. 2012 Dec;147(6):1154-7.
14. Teodorescu M, Barnet JH, Hagen EW, et al. Association between asthma and risk of developing obstructive sleep apnea. JAMA. 2015 Jan 13;313(2):156-64.
15. Shen TC, Lin CL, Wei CC, et al. Risk of obstructive sleep apnea in adult patients with asthma: a population-based cohort study in Taiwan. PLoS One. 2015 Jun 11;10(6):e0128461. doi: 10.1371/journal.pone.0128461.
16. Prasad B, Nyenhuis SM, Imayama I, et al. Asthma and Obstructive Sleep Apnea Overlap: What Has the Evidence Taught Us? Am J Respir Crit Care Med. 2020 Jun 1;201(11):1345-57.
17. Togias A. Rhinitis and asthma: evidence for respiratory system integration. J Allergy Clin Immunol. 2003 Jun;111(6):1171-83;quiz 1184.
18. Leynaert B, Neukirch F, Demoly P, et al. Epidemiologic evidence for asthma and rhinitis comorbidity. J Allergy Clin Immunol. 2000 Nov;106(5 Suppl):S201-5.
19. Olsen KD, Kern EB. Nasal influences on snoring and obstructive sleep apnea. Mayo Clin Proc. 1990 Aug;65(8):1095-105.
20. Braunstahl GJ. Chronic rhinosinusitis, nasal polyposis and asthma: the united airways concept reconsidered? Clin Exp Allergy. 2011 Jun 14;41:1341-3.
21. Harding SM. Gastroesophageal reflux: a potential asthma trigger. Immunol Allergy Clin North Am. 2005 Feb;25(1):131-48.
22. Isono S. Obesity and obstructive sleep apnea: mechanisms for increased collapsibility of the passive pharyngeal airway. Respirology. 2012 Jan;17(1):32-42.
23. Chen Y, Dales R, Tang M, Krewski D. Obesity may increase the incidence of asthma in women but not in men: longitudinal observations from the Canadian National Population Health Surveys. Am J Epidemiol. 2002 Feb 1;155(3):191-7.
24. Cekerevac I, Jakovljevic V, Zivkovic V, et al. Impact of severity of obstructive sleep apnea (OSA) and body composition on redox status in OSA patients. Vojn. Pregl. 2018;75(11):1089-93.
25. Alkhalil M, Schulman E, Getsy J. Obstructive sleep apnea syndrome and asthma: what are the links? J Clin Sleep Med. 2009 Feb 15;5(1):71-8.
26. Sideleva O, Suratt BT, Black KE, et al. Obesity and asthma: an inflammatory disease of adipose tissue not the airway. Am J Respirat Crit Care Med. 2012;186(7):598-605.
27. Malerba M, Radaeli A, Olivini A, et al. Association of FEF25-75% impairment with bronchial hyperresponsiveness and airway inflammation in subjects with asthma-like symptoms. Respiration. 2016;91(3):206-14
28. Razak MRA, Chirakalwasan N. Obstructive sleep apnea and asthma. Asian Pacific J Allergy Immunol. 2016 Dec;34(4):265-71.
29. Han KT, Bae HC, Lee SG, et al. Are sleep disorders associated with increased mortality in asthma patients? BMC Pulm. Med. 2016 Nov 17;16(1):154. doi: 10.1186/s12890-016-0313-2.
30. Alkhalil M, Schulman ES, Getsy J. Obstructive sleep apnea syndrome and asthma: the role of continuous positive airway pressure treatment. Ann Allergy Asthma Immunol. 2008 Oct;101(4):350-7.