REVIEW ARTICLE

Bronchial asthma and obstructive sleep apnea hypopnea syndrome: Another overlap or mere coincidence

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***DOI No:*10.5958/0974-0155.2015.00001.7** *Indian J Sleep Med 2014; 9.4, 155-160*

Abstract

Both obstructive sleep apnea and bronchial asthma are diseases associated with systemic inflammation. The patho-physiology of both these diseases is interlinked and multiple links have been elucidated between their development. How, the development of one of these diseases leads to the worsening of the other one, is poorly understood. This overlap, deserves further research and guidelines need to be crystallized for the management of this condition, as delay in diagnosis and treatment is associated with an adverse outcome.

Keywords: Bronchialasthma, Obstructive sleep apnea hypopnea syndrome, Continuous positive airway pressure, Gastroesophageal reflux disease

Introduction

The realm of "one-airway, one-disease" is starting to look beyond the traditional combination of Allergic rhino sinusitis[ARS] and bronchial asthma (BA). The link between the upper and lower airway diseases has always been an area of active research and controversy. The association between obstructive sleep apnea/hypopnea syndrome (OSAHS) and chronic obstructive pulmonary disease (COPD) or fixed airway obstruction, the overlap syndrome,leading to hypercapnic respiratory failure and worse outcomes than either disease alone, is a well-known entity and is described well in literature. The link between BA characterized by airway hyperresponsiveness and OSAHS is less well described. It is known that both these diseases are a component of systemic inflammation and, often, therapy of OSAHS with positive airway pressure (PAP) devices improves asthma control in a suitable cohort of patients. The causal association between preexistent BA and OSAHS is not clearly understood. Here, we attempt to review the literaturetrying to elucidate the association of these two disease entities.

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Epidemiology

Previous studies such as the Tucson Epidemiological Study of Chronic Lung Diseases reported that patientswith obstructive lung diseasepresented more problems such as inducing and maintaining sleep and more daytime sleepiness than subjects without obstructive lung disease[1]. However, when separating subjects with asthma from those with chronic bronchitis, no significant association was found between subjects with asthma alone and difficulties such as inducing and maintaining sleep or daytime sleepiness[2]. Another group reportedthat subjects with asthma reported a less refreshing sleep than subjects without asthma. However, the authorsfound no statistically significant differences in the prevalence of daytime sleepinessbetween subjects with and without asthma[3].

Numerous, newer, better-designed studies have shown the link between BA and OSA, diagnosed either by polysomnography or by clinical features such as excessive daytime sleepiness. The study designs of these studies have been variable, ranging from community-based cross-sectional studies to clinic-based studies.

An elegantly designed cross-sectional study showed that, in patients with BA and airway hyperresponsiveness, the use of inhaled corticosteroid and asthma control along with GERD symptoms were associated with a higher excessive daytime somnolence and snoring independent of the classical risk factors such as obesity[4].

A large study (*n*=967) evaluated the association between habitual snoring and asthma. The study cohort was followed up for 14 years, and around 6% participants developed asthma during the follow-up period. The new-onset BA was a robust predictor for the development of habitual snoring [relative risk (RR), 2.8], irrespective of the baseline body weight and weight gain during the study period, where as pre-existent asthma was not[5].

The latest and the most convincing body of evidence linking the development of OSAHS to BA is an offshoot of the famous Wisconsin sleep cohort[6]. In this study, 22 of 81(27%) participants with asthma experienced incident OSA over their first observed 4-year follow-up interval compared with 75 of 466(16%)participants without asthma. Using all the 4-year intervals, participants with asthma experienced 45 cases of incident OSA during 167 4-year intervals (27%) and participants without asthma experienced 160 cases of incident OSA during 4-year intervals (17%); the corresponding adjusted RR was 1.39, controlling for sex, age, baseline, change in body mass index, and other factors. Asthma was also associated with the new-onset OSA with habitual sleepiness (RR, 2.72;*P* = 0.045). Asthma duration was related to both incident OSA(RR, 1.07 per 5-year increment in asthma duration;*P* = 0.01) and incident OSA with habitual sleepiness (RR, 1.18;*P* = 0.02). This study firmly points out that preexisting BA is associated with an increased risk of new-onset OSA.

The severity of asthma has been linked to the development of OSAHS[7,8]. It was shown that the prevalence of OSAHS went higher as the severity of asthma increased. In fact, the prevalence of OSAHS was as high as 50% in patients with severe asthma (Fig. 1).

Figure 1: Complex interactions between Asthma/ COPD OSA with factors of GERD, Obesity, Allergic Rhinos & Smoking playing additional role in overlapping diseases

Pathogenesis: the link between OSAHS and bronchial asthma

Does bronchial asthma lead to OSA?

The repertoire of BA including disease- or treatment-related factors leads to vulnerabilities of the upper airway, which may aid in the development of upper airway instability and consequent development of OSAHS. How exactly this happens is still a matter of speculation. However, several investigators have tried to find the missing link between the two conditions. Notable among these theories are discussed further.

Inflammation theory

Asthma is a state characterized by chronic airway inflammation. The systemic component of this airway inflammation is not as well recognized as it is in COPD. However, it has been postulated that the inflammatory process from the asthmatic process may spill over into the systemic circulation and weaken the respiratory musculature[8]. This in turn can destabilize the upper airway musculature, increasing the upper airway collapse. The systemic inflammation has also been linked to development of an unstable breathing control centre, which may further jeopardize the upper airway stability.

Pressure theory

BA is characterized by the active contraction of respiratory muscles during the expiratory phase along with the negative intraluminal inspiratory pressure, especially during acute attacks. Both these processes

augment the upper airway collapse. In addition, sleep in patients with BA is associated with a steeper decline in lung volumes vis-à-vis the normal population; this leads to a so-called, lower intensity of the "tracheal tug," which, in turn, may augment an upper airway collapse[9].

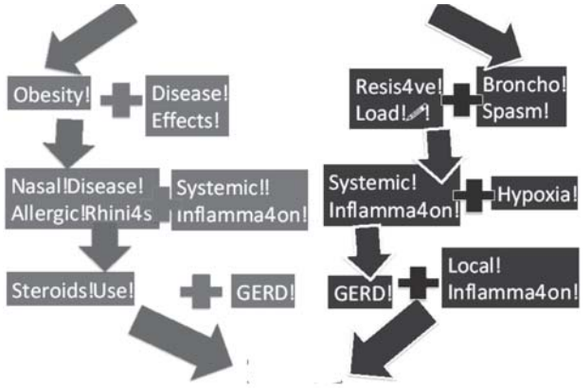

Figure 2: Bronchial Asthma/COPD

Drug theory

Glucocorticosteroids are the mainstay of controller therapy in BA. A major part of the inhaled corticosteroids is deposited in the upper airways, which may lead to a localized pharyngeal myopathy. This has been linked with the development of upper airway instability and the development of subsequent OSAHS[10].

Acid reflux theory

Persistent acid reflux is often an important cause of difficulty to treat asthma. This acid reflux may lead to pharyngeal muscle dysfunction by causing inflammatory myopathy and by inducing a localized pharyngeal spasm. This, in turn, leads to pharyngeal muscle weakening and promotes the development of OSAHS[11].

This study on this subject does not favor any one of these theories[11]. In a susceptible individual, an interplay of all these factors may act in concert to bring about the final disease phenotype. Further studies investigating the exact mechanisms underlying this association and the value of periodic OSA evaluation in patients with asthma are necessary.

Other side of the coin: possible mechanisms by which OSAS worsens asthma

Weight gain and obesity

Obesity is a major risk factor for asthma, especially for the development of difficult-to-treat asthma.Asthma is more prevalent in obese individuals, and obesity appears to contribute to severe asthma, because obese or overweight patients account for 75% of emergency department visits for asthma[12]. Morbidly obese subjects with asthma studied after weight loss show decreased severity and symptoms of asthma[13]. Obesity is commonly associated with OSA and is a traditional risk factor for the development and progression of features of OSA. This mutually contributive combination of obesity and OSA appears to increase airway hyperresponsiveness and worsen asthma control.

Local airway inflammation

OSAHS is linked with upper airway edema and chronic local inflammation. The obstructive events lead to the generation of high intraluminal pressures, which leads to repeated mechanical trauma and augmentation of local inflammation[14]. Studies have showna high concentration of inflammatory markers in the mucosa of patients with OSA. Inflammation of the upper airway may trigger downstream inflammation in the airways[15]. The role of vascular endothelial growth factor (VEGF) as a proinflammatory cytokine is being increasingly studied as a common link between OSA and BA. Of the repertoire of the inflammatory molecules being studied in this complex link, VEGF is appearing as a front runner, and further studies are required to pinpoint its exact role[16].

Gastroesophageal acid reflux

Often OSAHS and GERD have common risk factors such as obesity; however, patients with OSAHS exhibit a significantly higher GERD than do members of the average population even when one controls for alcohol intake and body mass index[17]. GERD is a well-known risk factor for the development of nocturnal asthma and is often implicated as a risk factor for difficult-to-treat asthma. Acid exposure of the mid esophagus can induce vagal reflexes, which in turn has been linked to the

development of an increased airway resistance[18]. GERD therapy with proton pump inhibitors and surgery has been reported to reduce asthma exacerbations, improve the quality of life, and decrease medication requirement in patients with asthma[19].

Neural receptors and mechanical effects

Patients with OSAS have a heightened vagal tone during sleep secondary to partial or complete airway obstruction occurring during apneas,which acts as a trigger for nocturnal asthma attacks in sleep apnics[20]. Therapy with anticholinergic agents leads to the improvement in forced expiratory flow and improved nocturnal asthma features. Neural receptors at the glottic inlets and in the laryngeal region have a powerful reflex bronchoconstrictive activity[21]. Stimulation of the larynx also increases activity in efferent parasympathetic nerve fibers going to the trachea and bronchi. Repeated stimulation of these neural receptors during snoring could stimulate neural reflex-induced bronchoconstriction. The more negative intrathoracic pressure developed during obstructive apneas intensifies the pulmonary capillary blood volume. This elevation was observed during sleep in subjects of asthma with nocturnal symptomsand may add to the negative effect of decreased lung volume in the development of nocturnal symptoms in sleep apnics[22]. Hypoxia secondary to OSA has been shown to simulate the carotid bodies, which may lead to reflex bronchoconstriction[23].

Leptin theory

Leptin is an adipokine that acts on the hypothalamus to induce satiety and increase metabolism. Serum leptin concentrations are increased in obese patients, suggesting leptin resistance in obesity. Leptin is a proinflammatory adipokine and has been linked to the development of asthma[24].

Obese male patients with OSAS exhibit leptin levels approximately 50% higher than those of similarly obese men without OSAS. Studies have demonstrated increased levels of serum leptin in patients with OSAS compared with those of nonapneic patients with similar levels of obesity[25]. The higher levels of the proinflammatory leptin have been linked to airway hyperresponsiveness in these patients.

Congestive heart failure

OSAS has been linked with many metabolic and cardiovascular consequences, which may complicate coexisting airway obstruction in patients with asthma. OSAS increases the risk of ischemic heart disease and congestive heart failure (CHF). CHF can cause airway obstruction, and studies indicate that bronchial narrowing in CHF is linked with hyperresponsiveness to cholinergic stimuli with subsequent constriction of airway smooth muscles[26]. Mechanisms proposed to be involved in the airway hyperresponsiveness associated with CHF, include downregulation of pulmonary β-receptors with suppressed adenylyl cyclase activity, which results in significant attenuation of cAMP-mediated airway relaxation[27]. Other implicated mechanisms include airway constriction secondary to pulmonary edema, nonspecific bronchial C-fiber activation, thickening of bronchial walls, changes in epithelial sodium and water transport, and increased endothelin levels[28]. OSA, through aggravating cardiac dysfunction, could further stimulate airway hyperresponsiveness in patients with asthma.

OLDOSA

It is a known fact that a dual interaction between asthma or COPD and OSA exists beyond random coexistence. On one hand, there is an increased prevalence of OSA in asthma/COPD and, hence, a distinct, broader clinical entity or "integrated" overlap syndrome, that is, OLDOSA (obstructive lung disease and obstructive sleep apnea) syndrome has been proposedby some researchers. These intricate that relationships may stem in part from a set of factors unique to these patients, related to disease severity, comorbidities, and corticosteroid medications, besides obesity and other traditional risk factors for OSA.

Implications

In daily clinical practice, one should (i) perform a targeted evaluation for OSA in every patient with obstructive lung disease (asthma, COPD, or small airway disease) by using a detailed history and/or standardized questionnaires (e.g., Epworth Sleepiness Scale and Berlin Questionnaire, albeit not validated in this setting) and sleep testing, when appropriate; it is likely that a *prebronchodilator*R (FEV1/forced vital capacity ratio)

below the lower limit of normal on the pulmonary function testing should prompt a more thorough clinical evaluation for sleep apnea; and (ii) obtain a focused clinical history and a functional assessment for possible OLD in all patients with established OSA, targeting smoking habits and intensity, episodic dyspnea, and nocturnal symptoms, which, understandably, may be difficult to attribute to one condition or another.

Conclusion

OSAS and asthma have certain common risk factors for development and are mutually detrimental to each other. We now know that OSAS is an independent risk factor for asthma exacerbations and that OSAS symptoms are more common in patients with asthma than in the general population. OSA and BA can worsen each other by a variety of mechanisms as outlined earlier. Many patients with difficult-to-treat asthma have shown an excellent response to CPAP therapy, when given for concomitant OSA. The exact link between the two conditions is still not clear, but a number of impressive theories try to explain this link.

We should understand the relationship between asthma and OSAS and screen our patients with OSA for asthma and vice versa early, so that early and timely interventions can decrease the combined morbidity.

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