Prevalence and impact of rhinitis, sleep disordered breathing and OSA in asthmatic patients

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Summary

Obstructive sleep apnea syndrome (OSAS) often coexists in patients with bronchial asthma. The reasons for this association are not clear enough and, particularly, the role of the commonest asthma comorbidity, rhinitis, in influencing patients symptoms, quality of life and prognosis, need to be further investigated.
The aim of this review is to define most of the pathogenetic aspects of the relationship among asthma, rhinitis and OSAS, and to evaluate the effect of these comorbidities on disease management and patient's life.

KEY WORDS: asthma; rhinitis; OSAS; comorbidity.

Introduction

International asthma guidelines state that sleep impairment is a criterion in defining disease severity (1). Furthermore, the presence and frequency of nocturnal symptoms is essential in establishing the level of asthma control. Some asthma features could influence Obstructive Sleep Apnea Syndrome (OSAS) development and severity; vice versa OSAS can influence asthma control achievement.
The aim of the present review is to analyse the potential relationship between asthma rhinitis and OSAS.
The most relevant symptom of rhinitis, both allergic and non-allergic, is the nasal congestion. This and the other rhinitis symptoms, such as rhinorrhoea, sneezing, itching nose and eyes, are usually present during the day as well as during the night, and can have a relevant impact on sleep quality. Indeed, the obstruction of upper airways is always involved in the pathogenesis of sleep disordered breathing (SDB), in particular Obstructive Sleep Apnea (OSA). Daytime sleepiness and fatigue, typical symptoms of OSAS, are often present in patients with rhinitis, so they can helpfully be used to investigate the presence of both diseases.
Furthermore, the treatment of both diseases is important not only to achieve the control of asthma, as suggested by guidelines, but also to improve the quality of sleep (2).

The keystone of OSAS physiopathology is the narrowing and collapsing of the airways which causes their obstruction during sleep.

OSAS is a respiratory disease characterized by episodes of complete or partial upper airways obstruction due to their collapse during sleep, necessitating recurrent awakenings to re-establish airway patency, associated with oxygen desaturation. It is a common disorder that has been reported to affect approximately 5% of the general population (3) and its prevalence increases with age. It has been estimated that more than 158 million adults suffer from sleep apnea in U.S., and only 1% of OSAS patients are receiving appropriate treatment for their disease (4). The keystone of OSAS physiopathology is the narrowing and collapsing of the airways which causes their obstruction during sleep. The site of this narrowing is usually localized in the pharynx (5). During the inspiration there is a reduction of pharyngeal pressure and of the tone of the pharyngeal dilatator muscles which predisposes to the posterior displacement of the soft palate and tongue during the night, causing the obstruction of the airways and making the patient snore. Upper airway size in OSAS patients is smaller than in healthy subjects: Computed Tomography (CT) scans and resistance measurements noticed bigger fat depositions in the lateral walls of the pharynx and structural differences of the facial bone, like as the retroposition of the maxilla and mandible which can predispose to airways collapsibility (6).
According to the patients and their bed partners, OSAS dominant symptoms are excessive sleepiness, snoring, restless sleep, fatigue, nocturia, nocturnal choking and awakenings that lead to sleep fragmentation and to cognitive impairment, with lacks of attention, concentration and memory (7).

Pathogenetic aspects

Recent studies have found several links in the pathogenesis of asthma, rhinitis and OSAS.
The link existing between upper and lower airways has been repeatedly observed in the past and has led to coin the concept of "united airways disease" (8). One poten-

Bronchial hyperreactivity (BHR) is a paramount feature of asthma, and may be considered a strong risk factor for the onset of asthma in patients with allergic rhinitis (AR), which in up to 80% of cases display BHR.

tial mechanism is the so-called nose-bronchial reflex, based on the release of mediators and cytokines by the respiratory mucosa or on the systemic impact of local inflammation via soluble mediators that involve the bone marrow (9-11). Bronchial hyperreactivity (BHR) is a paramount feature of asthma, and may be considered a strong risk factor for the onset of asthma in patients with allergic rhinitis (AR), which in up to 80% of cases display BHR. Another proof of this association is the response of AR to bronchodilation, which might depend on allergic inflammation that persists for a long time and tends to progress from the nose to the bronchi (12, 13). Recent data suggest that OSAS is an independent risk factor for asthma exacerbations (14).

It has been suggested that different mechanisms can lead to a worsening of asthma control in patients with concomitant OSAS: neuromechanical reflex bronchoconstriction due to increased vagal tone during apnea, gastroesophageal reflux, local and systemic inflammation and the indirect effect on dyspnea of OSAS-induced cardiac dysfunctions. Recent studies indicate also that OSAS patients show higher concentrations of VEGF (Vascular Endothelial Growth Factor), which may contribute to bronchial inflammation and hyper-responsiveness, and the cause and the effect could be found in apnea-induced hypoxia (15). Moreover, serum leptin concentrations are higher in OSAS and asthmatic people. It is a protein produced by adipose tissue and has a proinflammatory function because it contributes to stimulate the release of proinflammatory cytokines (16-20).

Allergic rhinitis and sleep

Several observational studies have documented a link between AR and sleep impairment.

Two European trials clearly demonstrated that allergic rhinitis adversely impacts sleep quality both in adults and in children/adolescents. The first study, conducted on a population of 476 subjects with AR, showed that in almost 40% of them rhinitis had a moderate or severe impact on sleep quality (21). The second one was conducted on a population of 221 children and adolescents suffering from AR, and showed that 79% of them had sleep quality severely impacted (22).

Leger et al. demonstrated that AR symptoms are associated with sleep complaints (23). Their purpose was to assess the consequences of rhinitis on sleep and to identify whether and how AR duration and severity are associated to sleep impairment. They evaluated a sample of more than 1000 patients who were asked to fill in validated questionnaires assessing quality of life and sleepiness score. Performing a case-control study on two populations, one composed by 502 controls and the other by 591 patients with AR, they found that difficulty in falling asleep, non-restorative sleep, snoring and nocturnal awakenings were referred by more than 40% of patients, while 63% reported a feeling of lack of sleep.

Nasal obstruction associated with congestion represents a risk factor for respiratory sleep disordered breathing, including snoring, increase of the number of microarousals, episodes of hypopnea and apnea.

Nasal obstruction associated with congestion represents a risk factor for respiratory sleep disordered breathing, including snoring (24), increase of the number of microarousals, episodes of hypopnea and apnea (25).

The hypothesis that rhinitis could lead to SDB, and OSAS in particular, may be explained by two physical principles. The Bernoulli principle states that the wider the beginning of the airway is, the less the risk for collapse is; the narrower the beginning is, the greater the risk for collapse is. The Venturi principle states that air must pass through a small tube faster than through a large tube, if the volume of air and time to pass through are equal. According to these physical principles, rhinitis, providing a narrowing of the initial airway, causes the flow to become turbulent. Furthermore, the upper airway behaves like a Starling resistor: the obstruction at the inlet (i.e. the nasal airway) produces collapsing forces that are manifest downstream in the collapsible segment, the pharynx (26).

Several mediators and pro-inflammatory cytokines released in allergic inflammation act in both allergic inflammatory response, mucosal edema and congestion and in altering sleep structure.

Obstructive apneas were found to be more frequent and longer in AR patients who have nasal obstruction than in those without obstruction, when sleep was measured by means of polysomnography (27). Furthermore, patients suffering from nasal congestion had a 1.8 times greater chance of moderate-to-severe sleep-disordered breathing than those without congestion (28). Compared with healthy control subjects, patients with AR had 10 times more microarousals from sleep in association with periodic breathing and hypopneic and hyperpneic episodes (29). To better define the potential interactions among nocturnal nasal obstruction, sleep and breathing disturbances in patients with OSA and chronic nasal congestion, Clarenbach et al. performed a randomized double-blind, placebo-controlled study on the effects of topical nasal decongestion xylometazoline. They found that the number of apnea/hypopneas (Apnea-Hypopnea Index - AHI) and oxygen desaturations was reduced (30).

Other symptoms, such as sneezing, itchy eyes, rhinorrhea, and nasal pruritus, may also contribute to sleep disturbances in patients with AR (31).

Other evidence showed that allergic rhinitis increases the production of multiple pro-inflammatory factors that affect sleep. Several mediators and pro-inflammatory cytokines released in allergic inflammation act in both allergic inflammatory response, mucosal edema and congestion and in altering sleep structure (32).

Patients with chronic nighttime rhinitis symptoms are two times more likely to snore than control subjects, and this is the reason why about 50% of rhinitis patients with nasal congestion have an odd ratio of 1.5 to snore than patients without nasal congestion (28). The logis-

tic regression model estimating the association of congestion with snoring, performed by Young et al., shows that individuals with chronic severe nasal congestion during the night have a 3.6-fold greater risk of habitual snoring at baseline and a 4.9-fold greater risk of habitual snoring at 5-year follow-up (24).
Although the correlation between snoring and apnea needs to be fully understood, nasal congestion is associated to sleep apnea. The greater the increase of nasal resistance is, the greater the increase in obstructive apnea is. This phenomenon seems strictly related to the cross sectional area of upper airways (33).

Asthma and OSAS: pathogenetical issues

OSAS and asthma are common, share similar nocturnal symptoms, and involve airway obstruction as the cornerstone of their pathophysiology (Figure 1). Asthmatics often rely on oral corticosteroids (OCS). Those requiring frequent bursts of OCS have a very high prevalence of OSA (34).

The interaction of OSAS and asthma could be reciprocal since asthma-related factors may also contribute to OSA deterioration.

In short, OSAS and asthma may have a bidirectional relationship in which each can exacerbate the other (35).
In 2009, Alharbi et al. performed a study to measure the prevalence of asthma in OSAS and to define the characteristics of patients with OSAS who suffer from asthma. They demonstrated a higher prevalence of asthma (35.1%) in patients with OSAS as compared to general population. OSAS patients with concomitant asthma have an higher BMI and AHI and a lower oxygen saturation compared to OSAS patients without asthma (36).
Julien et al. demonstrated a high prevalence of OSAS among patients with severe asthma, compared to patients with moderate asthma or without asthma (37). The interaction of OSAS and asthma could be reciprocal since asthma-related factors may also contribute to OSA deterioration (38).
Alkhalil et al. described the potential links between asthma and OSAS. The increased upper airways collapsibility and the nasal obstruction frequently accompanying asthma above described represent facilitating factors of OSAS development in these patients (14). On the other hand, asthma related factor such as neuroreceptorial mechanisms that induce an increased vagal tone with following bronchoconstriction, could worsen upper airways collapsibility. Asthma and OSAS patients often suffer also from gastroesophageal reflux disease (GERD). GERD has a higher prevalence in OSAS patients as compared to general population (39, 45) and represents an important trigger of nocturnal asthma exacerbation (39-45). Local airway and systemic inflammation may probably be involved in predisposing asthma patients to BHR leading to bronchial caliber instability and narrowing of bronchial diameter (46, 47). Airway obstruction can impact negatively cardiovascular conditions, for example hypertension and heart failure (HF), which often are present in untreated OSAS patients (48, 49). The increased concentration of serum leptin, typical of both OSAS and obese asthmatic patients, are still controversial and need to be deeply investigated (50, 51). The weight gain is typical of OSAS patients. One reason is sleep fragmentation which drives to a reduced production of growth hormone (GH) and consequentially to its reduced lipolytic action (53-55).

Local airway and systemic inflammation may probably be involved in predisposing asthma patients to BHR leading to bronchial caliber instability and narrowing of bronchial diameter.

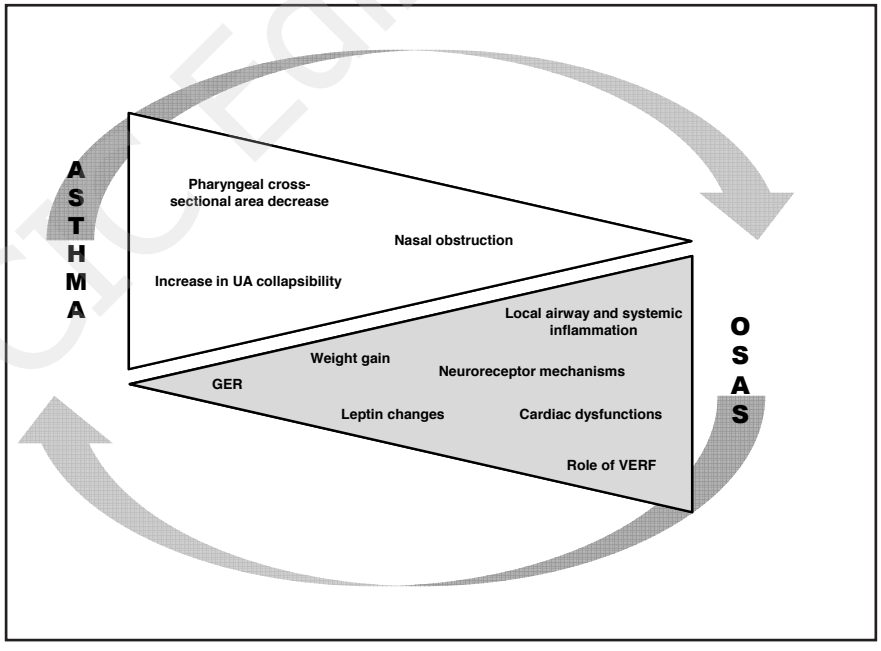

Figure 1 - Correlation between OSAS and bronchial asthma.

Asthma, OSAS, sleep and clinical features

In 2005 Juniper EF (56) administered the ACQ5 (Asthma Control Questionnaire) to 122 patients and found that the level of asthma control resulted to be inversely correlated to the presence of sleep disturbances. Patients with good control reported less frequent and less severe sleep disturbances compared to uncontrolled subjects. More interesting is the evidence that a significant percentage of subjects (11-20%) who achieved total control of asthma still reported sleep disturbances, that contribute to impair quality of life. There are two possible explanation of this evidence: ACQ is not able to correctly identify all factors that contribute to asthma control or, in controlled asthma patient, sleep can be disturbed by other concomitant causes.

OSAS is a potential contributor to overall asthma control on a much larger scale and independent of the other known contributors to asthma control.

Teodorescu et al. recently published on Chest an interesting observational study with the aim determine whether a high OSAS risk is associated to not well controlled asthma. In order to achieve this result, more than 470 patient filled in the sleep disorders questionnaire and the asthma control questionnaire (57). Mean age of studied population was 47 years a mean FEV1 was 93% of theoretical value. All patients were treated according to GINA guidelines and, above all, patients suffered from allergic rhinitis treated in 80% of cases with nasal corticosteroids while 62% with oral antihistamines.
The univariate association of not well-controlled asthma with high risk of OSAS showed that patients with high risk of OSAS had a 3.6 odd ratio to be not well controlled. As expected, other factors such as obesity, black race, nasal disorders, GERD and psychiatric diseases were associated with a greater risk of uncontrolled asthma; nevertheless multivariate step wise logistic regression models of uncontrolled patients showed that, also adjusted for the above-mentioned factors, high OSAS risk patients maintain a 2.87 odd ratio to be uncontrolled. In other words OSAS is a potential contributor to overall asthma control on a much larger scale and independent of the other known contributors to asthma control.
Similar results had been previously shown by ten Brink et al. who introduced OSAS among the 13 elements identified as risk factors of frequent exacerbations in difficult to treat asthma (58).
A study performed by Chan et al. demonstrated in nine patients with asthma and concurrent OSA that the initiation of continuous positive airway pressure (CPAP) therapy resulted in marked improvement in their asthma, with decreased symptoms, improved peak expiratory flow rate, reduced need for bronchodilator therapy, and resolution of their pattern of nocturnal worsening (59).
A more recent prospective study of 20 patients with severe OSAS and concurrent asthma demonstrated that CPAP therapy results in significant improvement in asthma quality of life (60).

Conclusions

To sum up, the data presented in this review support the evidence that rhinitis, asthma and OSAS frequently coexist. Although 40-80% of patients with asthma suffer also from rhinitis and almost 10-40% of patients with AR suffer from asthma (61), this comorbidity has not been deeply understood, even though it has been widely investigated in multiple studies.

Surely, asthma and OSAS correct diagnosis and therapy should previously consider the correct treatment of rhinitis.

As shown above, both AR and asthma may contribute to OSA, which, according to the pathogenetic aspects we have reported, can worsen the control of its concomitant comorbidities.
However, it remains difficult to draw firm conclusions regarding optimal management strategies in patients with OSAS-asthma overlap. Surely, asthma and OSAS correct diagnosis and therapy should previously consider the correct treatment of rhinitis.
A careful evaluation for exacerbating comorbidity, in addition to optimizing treatment of both OSAS and asthma remains crucial in this patients' population.

Competing interests

The authors declare that they have no competing interests.

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