



Allergy and sleep-disordered breathing

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Purpose of review

An inconsistent link between sleep-disordered breathing (SDB) and allergic rhinitis has been reported in the literature for decades. This review attempts to highlight some of the recent epidemiological studies purporting and refuting this connection, discuss possible mechanisms for this relationship and discuss how treatment of allergic rhinitis can help ameliorate SDB.

Recent findings

Recently, a large systematic review that included 18 studies and 27 000 individuals of the association between allergic rhinitis and SDB in children was published supporting a correlation between SDB and allergic rhinitis.

Summary

Although the evidence generally supports a connection between SDB and allergic rhinitis, this connection is not definitive and the mechanism linking these two diseases remains poorly understood. In addition to epidemiological studies, several small studies have demonstrated an improvement in SDB upon treatment of allergic rhinitis; however, large studies using objective measures to quantify SDB and allergic rhinitis are needed.

Keywords

allergic rhinitis, obstructive sleep apnea, sleep disordered breathing

INTRODUCTION

Sleep-disordered breathing (SDB) ranges from simple snoring to obstructive sleep apnea (OSA). It affects at least 2–4% of the pediatric and adult population and is associated with increased rates of daytime sleepiness, attention deficit disorder, hypertension, cerebral vascular events and myocardial infarctions [1[¶]]. Allergic rhinitis occurs in 10–20% of children in the United States and has been identified as a potential risk factor for SDB [2[¶]]. In addition, the treatment of allergic rhinitis may lead to improvement of both allergic rhinitis and SDB [3]. This review will highlight our current understanding of the relationship between SDB and allergic rhinitis.

SLEEP-DISORDERED BREATHING

SDB is a continuum of disorders ranging from simple snoring caused by intermittent airway collapse to complete obstruction resulting in OSA [4,5^{¶¶}]. SDB affects children and adults with startlingly high rates. In children, the prevalence of SDB is estimated to be 10–20% whereas the prevalence of OSA is estimated to be 2% [6]. In adult population studies, the prevalence of SDB and

OSA are frequently estimated to be 20 and 3%, respectively [7].

In contrast to adults with SDB who commonly exhibit fatigue and excessive daytime sleepiness, children more frequently exhibit hyperactivity, inattentive behavior, and poor school performance [8]. In addition to behavioral symptoms seen in children, adults with SDB have elevated rates of cardiovascular disease, hypertension, stroke, and myocardial infarction [7,9]. Although the mechanism between SDB and vascular disease is often

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KEY POINTS

- Allergic rhinitis is associated with sleep disordered breathing (SDB).
- Allergic rhinitis may cause a predilection towards SDB by increasing airway resistance, perturbing the nasal-ventilator reflex, increasing systemic inflammation or an unidentified mechanism.
- Treatment of allergic rhinitis improves objective and subjective symptoms of SDB.

attributed to increased systemic inflammation, this remains an area of active investigation [10].

Although SDB is a multifactorial disease, the basic physics behind the condition are simple. As the diameter of the upper airway decreases, airflow resistance increases; at a certain point resistance becomes too high and breathing temporarily ceases. Increased resistance can occur secondary to craniofacial abnormalities such as micrognathia or maxillary hypoplasia, neurologic disorders or genetic factors [11–13]. Additionally, narrowing of the airway can be caused by hypertrophy of lymphoid tissue in Waldeyer's ring (tonsil, adenoid and lingual tonsil) [14] or inflammation of nasal mucosa [15].

ALLERGIC RHINITIS INFLAMMATION

Allergic rhinitis is estimated to affect up to 40% of the population and cost 2 to 5 billion dollars annually in medical care and lost productivity in the United States [16²²,17]. Upon initial exposure to allergens such as dust mites, pollens, pet dander, molds or cockroach residues, genetically predisposed individuals undergo sensitization to specific allergens. In this process, CD4⁺ T cells are presented with processed antigen and initiate a systemic cytokine release resulting in an IgE production. In subsequent encounters with the allergen, IgE bound mast cells and basophils rapidly degranulate releasing histamine and increasing production of leukotrienes and prostaglandins. Locally these molecules cause vasodilatation of the mucosal blood supply, increased secretion of mucus, and increased capillary permeability [18] resulting in pruritis, rhinorrhea and nasal congestion. Although these effects are hallmarks of allergic rhinitis, a broader systemic inflammatory response is also initiated. The inflammatory mediators, specifically histamine and cytokines, released during allergic reactions can directly affect the central nervous system and contribute to disturbed sleep and fatigue [19,20] as well as arthralgias and myalgias [21].

ALLERGIC RHINITIS RESISTANCE

During the natural course of sleep, normal patients increase the amount of time they spend nasal breathing [22]. Nasal breathing reduces the resistance as compared to oral breathing by 2.5 times [23]. This increase in fractional time spent nasal breathing is altered in patients with allergic rhinitis. Triggered by allergens, patients with allergic rhinitis have increased mucosal edema and mucus secretion that results in complaints of congestion. The persistent congestion is further exacerbated by natural circadian rhythms that increase mucosal secretion during typical sleep times and the preferred supine sleep position [24,25]. Although the feeling of congestion is the most significant cause of morbidity for patients [26,27], this can be quantified by measuring nasal airflow, airway conductance and nasal cavity volume [28].

In a survey of patients with allergic rhinitis, 49% of children and 51% of adults reported being awoken because of congestion and 49% of children and 48% of adults reported difficulty falling asleep because of congestion. Only 17% of the surveyed patients reported that nasal congestion did not interfere with sleep [29]. Another study looked at a cohort of seven patients with seasonal allergic rhinitis who underwent polysomnography when symptomatic and again when asymptomatic and found that apenic events per hour decreased from 1.7 to 0.7 ($P < 0.005$) [30]. The discomfort associated with allergic rhinitis and the increased resistance of the airway as a result of congestion are practical explanations for the associated disruption of sleep and increased fatigue that patients with allergic rhinitis experience; however, the underlying mechanism is likely more complicated.

ALLERGIC RHINITIS NASAL-VENTILATOR REFLEX

In addition to increasing airway resistance, nasal obstruction perturbs the nasal-ventilator reflex. It has been shown that nasal breathing compared to oral breathing increases ventilation [31,32]. Interestingly, this phenomenon can be abolished by obstruction of the nares or application of topical anesthetics to the nasal mucosa and the loss of the reflex led to an increase in central and obstructive apenic episodes [32]. These historic studies implicate a yet unidentified mechanoreceptor and provide a possible link between SDB and allergic rhinitis and raise interesting questions regarding the use of nasal continuous positive airway pressure as compared to standard masks.

TREATMENT OF ALLERGIC RHINITIS INFLUENCES SLEEP-DISORDERED BREATHING

In addition to mechanistic explanations of the relationship between SDB and allergic rhinitis, their association is further supported by the observation that treatment of allergic rhinitis can improve symptoms of SDB. In a randomized, double-blind, placebo-controlled study, 40 children with allergic rhinitis and asthma received either nebulized beclomethasone dipropionate or placebo for 4 weeks. Compared with baseline and placebo, improvement was observed in local inflammation as assessed by exhaled nitric oxide and systemic inflammation as assessed by interleukin-5 urinary excretion [33[■]]. In addition, symptomatic relief of nasal obstruction, rhinorrhea, breathing difficulty and sleep disturbance were also reported in the treatment group in this study [33[■]]. A similar, placebo-controlled blinded study was conducted in an adult cohort by Gurevich *et al.* [3] that demonstrated a similar improvement in nasal congestion, daytime somnolence, and daytime fatigue, and improving sleep quality after treatment with intranasal budesonide. Although these two studies demonstrate symptomatic improvement of allergic rhinitis and SDB using validated instruments, they do not objectively assess improvement using the diagnostic gold standard for SDB and OSA, namely polysomnography.

In a randomized, double blind, placebo controlled, crossover study with 4-week treatment with either fluticasone or placebo 24 patients with rhinitis and suspected OSA underwent polysomnography at baseline, after 4-week treatment with placebo and after 4-week treatment with fluticasone [34]. This study demonstrated an improvement in nasal airway resistance after treatment with fluticasone compared to placebo ($P < 0.01$). Additionally the apnea hypopnea index decreased from 20 events per hour to 11.9 events per hour in the fluticasone-treated patients compared with placebo-treated patients ($P < 0.05$) [34].

SLEEP-DISORDERED BREATHING AND ALLERGIC RHINITIS

Recent epidemiological studies both support and refute the hypothesis that SDB and allergic rhinitis are interconnected in adult and pediatric populations [2[■],35–38].

Adults

In an adult study of 112 patients, who were diagnosed with OSA by polysomnography, 33% of patients were diagnosed with allergic rhinitis based

on allergic skin testing or multiple allergic simultaneous test [38]. Although there was a high prevalence of allergic rhinitis in this population, it is within the frequently cited rates of allergic rhinitis in the general population of 10–40% [39]. Without a control group, they were unable to draw conclusion regarding the relationship between allergic rhinitis and OSA. In their cohort, patients with allergic rhinitis and OSA experienced more fatigue, daytime sleepiness and stress than patients with OSA alone; however, these symptoms are frequently reported by patients with allergic rhinitis regardless of OSA [20]. Their study did demonstrate that patients with allergic rhinitis and OSA compared with OSA alone had similar severities of OSA as assessed by apnea hypopnea index, respiratory effort-related arousal, total sleep time [38].

In a study by Canova *et al.* [40], 72 patients with previously diagnosed OSA treated with continuous positive airway pressure had formal allergy skin testing and were compared with a control cohort of patients with COPD. Although COPD patients are not the ideal control group for comparisons, their OSA cohort was significantly more likely to have positive skin testing for perennial allergens. Unfortunately, neither of these studies utilized a normal control group.

Pediatrics

In a large multicenter study that looked at adenotonsillectomy outcomes for treatment of OSA in over 500 children, over 39.5% of children were identified as having allergic rhinitis [35]; however, this prevalence is within estimates of allergic rhinitis in the general population [39] and the absence of a control group prevented determining if this allergic rhinitis was increased in this population. Of note, this large, multicenter study did not identify allergic rhinitis as a factor influencing response to adenotonsillectomy for treatment of SDB [35]. Although patients with allergic rhinitis ($P = 0.04$) and OSA ($P = 0.01$) may benefit from topical nasal steroids [3] standard treatment for childhood SDB (i.e. adenotonsillectomy) also appears to reduce the severity of SDB in children with coexistent allergic rhinitis. In a recent study by Ishman *et al.* [2[■]], 21 patients with positive environmental allergy testing completed the Obstructive Sleep Apnea-18 and the Pediatric Sleep Questionnaire. The results of the allergy group were compared with a 113-child control group. Formal diagnosis with polysomnography was not conducted, but they did find a significant increase in predicted SDB based on these standardized metrics. In a large study ($n = 1144$) of German third graders designed to estimate the

population prevalence of OSA, no association ($P=0.065$) was identified between OSA and previously diagnosed allergic rhinitis [36]. In this study, the majority of patients who screened positive for OSA and a small subset of the non-OSA control group underwent home polysomnography to diagnose OSA. Currently, the American Association of Sleep Medicine recommends against use of portable monitoring over standard polysomnography for the diagnosis of OSA because of concerns that SDB will be significantly underestimated, as there is no EEG to determine the presence of arousals in most home studies [5[■]]. Additionally, no formal evaluation of patients' allergy status was performed other than family reports of previous diagnosis. In a retrospective study of 302 Thai children with symptoms of chronic rhinitis, skin prick testing was performed to characterize their symptoms as either allergic rhinitis or nonallergic rhinitis (NAR) [37]. In the retrospective chart review, snoring was more common in NAR ($P<0.01$). It should be noted that although snoring is sensitive for identifying patients with OSA the specificity of snoring is low [41[■]]. Recently, a qualitative systemic review of the last 25 years was published examining the evidence of the association between allergic rhinitis and SDB in children. The authors identified 18 articles with 27 015 patients that met their inclusion criteria [42[■]]. In this review, two-thirds of the articles demonstrated statistically significant association between allergic rhinitis and SDB whereas one-sixth of their articles found no statistically significant correlation. It should be noted that the majority (61%) of the articles did not utilize formal polysomnography for the diagnosis of OSA and allergy testing was not frequently utilized (39%) to diagnose allergic rhinitis [42[■]].

CONCLUSION

Based on the epidemiology and treatment data, there appears to be a correlation between allergic rhinitis and SDB; however, the precise relationship between these two distinct entities remains to be more fully elucidated. Future research studies need to assess using quantitative measurements of allergy and SDB using polysomnography to further define this connection.

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Conflicts of interest

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- of special interest
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