Asthma and sleep-disordered breathing in children and adults

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AIMS: To review the ongoing clinical studies and recent publications that describe the interaction between asthma and sleep-related breathing disorders; to give an overview of the epidemiology of asthma and sleep-disordered breathing in adults and children; to discuss the shared risk factors and inflammatory pathophysiology of sleep-disordered breathing and asthma, and the evidence that suggests that upper-airway obstruction influences asthma severity and response to therapy; to discuss the evidence showing that treating sleep disorders, including insufficient sleep and sleep-disordered breathing, improves asthma outcomes; and to describe novel methods to measure asthma and sleep-related breathing disorders in the home-setting.

TARGET AUDIENCE: Allergologist, Allied health professional, Anaesthesiologist, Clinician, Fellow, General practitioner, Immunologist, Junior member, Nurse, Paediatrician, Physiologist, Pulmonologist, Researcher, Resident, Respiratory physician, Scientist, Sleep specialist/technologist, Student

AIMS

- State the epidemiology the bidirectional epidemiologic relationship between the asthma and sleep disordered breathing.
- Describe the proposed mechanisms linking asthma and sleep disordered breathing.
- Apply evidence to personalize management of paediatric and adult patients with both conditions.

SUMMARY

Epidemiology

Asthma and obstructive sleep disordered breathing (SDB) are both prevalent conditions in children and adults, with mounting evidence that a bidirectional relationship exists between the two disorders. They share risk factors for development, severity, and response to treatment. A number of pathophysiologic pathways have been implicated in the relationship between these two common disorders, many of which may have treatment implications.
Asthma

Estimates of the global prevalence of asthma ranges from 1 to 18% [1], with variation attributable to the difficulties defining asthma given its heterogeneity, variation in global health care resources, and true variation in susceptibility. Asthma is likely under-recognized in some populations, but may be over diagnosed and over treated in others. Risk factors are complex and vary with age and population studied, but include genetic background, pre-natal and early life infections and exposures, race, sex, diet, occupational exposures, indoor and outdoor pollution exposure, and co-morbid conditions (atopy, GERD, obesity).

SDB

Obstructive SDB prevalence is estimated to be 2-4% in adults [2,3] and 1-4% [4] in children using polysomnographic criteria along with clinical symptoms. Risk factors vary by age. In adults, obesity and male sex are the strongest risk factors for obstructive SDB [2]. While obesity is increasingly recognized as a risk factor for obstructive SDB in adolescents and children [5], this relationship may be stronger in adolescents and older children than younger children [6]. In young children, adenotonsillar hypertrophy is the strongest risk factor for obstructive SDB, and there are similar prevalence rates in boys and girls [7,8].

Any discussion about these two disorders must acknowledge that both asthma and obstructive SDB are heterogeneous conditions, complicating attempts to understand and study how they interact with each other. This heterogeneity makes this area ideal for discussion of personalized approaches to care, although there are clear gaps between the concept of disease phenotypes and translation in to precision medicine.

Epidemiologic interactions between Asthma and SDB

The interaction between obstructive SDB and chronic obstructive pulmonary disease (COPD) has been recognized as the “Overlap Syndrome” for some time, with greater morbidity and mortality observed in those with both conditions than either alone [9]. There is accumulating evidence that there are interactions between asthma and SDB as well.

Cross-sectional studies in adults [10-13] and children [5, 14-16] with asthma have consistently found an increased risk for obstructive SDB when compared with either control or reference populations, with most studies describing an approximate 2 fold increase. The relationship appears to be stronger in more severe or refractory asthma [17, 18], with co-morbid GERD [10], in women [10, 19], with use of inhaled corticosteroids [10], and with co-morbid obesity [5, 16]. One prospective study also found a dose dependent relationship between the duration of asthma and the development of incident OSA [20].

There are less consistent data about the prevalence of asthma in populations of adults with obstructive SDB, with reports ranging from no increase [21] to a 2 fold increase [22, 23] to a 7 fold increase in a single study [24]. Asthma prevalence was approximately 30% (3-4 fold higher than comparable populations without SDB) in a large retrospective study of children undergoing adenotonsillectomy for SDB [25] and in the only randomized controlled trial of adenotonsillectomy for childhood obstructive SDB [26].

Evidence that the Asthma-Obstructive SDB phenotype has treatment implications

Beyond evidence that each condition appears to increase the risk for finding the other, it is important to examine whether there is an interaction between the two conditions in a way that affects disease severity or response to treatment. In our cohort of children followed in a tertiary care asthma program, the
presence of obstructive SDB was associated with a 3.62 fold increase (95% CI 1.26-10.40) in the risk of being classified as severe asthma using a composite measure after treatment with guidelines based care during a one year prospective period independent of race, sex, and obesity. [27] In another cohort of several hundred adults in which OSA risk was defined using a validated questionnaire, high OSA risk was associated with a similar increased risk (OR 2.87, 95% CI 1.54-5.32) of poor asthma control after controlling for demographic factors, obesity, and GERD [28]. In the well characterized Severe Asthma Research Program cohort, participants with high OSA risk had more day and night symptoms, as well as higher neutrophil counts in induced sputum samples [29]. OSA was more common (OR 3.4, 95% CI 1.2-10.4) in those with an exacerbation prone phenotype in a difficult to treat asthma program [30]. The mechanisms discussed below may allow for the development of more personalized strategies in the future.

**Putative Mechanisms for Interactions**

Physiologic mechanisms that might link asthma and obstructive SBD include effects on the tracheal tug phenomenon [31], the interdependence of expiratory and inspiratory flow resistance [32], bronchoconstrictive effects of upper airway obstruction via vagal stimulation [33], increased resistance load on the lower airways [34], and exacerbation of normal physiologic reduction of functional residual capacity during sleep leading to increased resistance [35].

Shared local and systemic inflammation may explain the interaction between the two disorders, with evidence that obstructive SDB is associated with T cell [36] and neutrophil [37] inflammatory cell infiltration in the upper airway, and increased cysteine leukotriene receptor expression [38] and NF-κB expression [39]. Most studies investigating the relationship between obstructive SDB and systemic inflammation have found low grade chronic inflammation, with elevations in CRP, IL-6, NF-κB, and TNF-α. [39, 40] Oxidative stress due to intermittent hypoxemia has been linked to neutrophilic inflammation, induction of vascular growth factors, and may trigger bronchoconstriction via vagal stimulation [41-43].

Other than the effects on cysteinyi leukotriene expression, the neutrophilic and non-T_H2 type inflammation that characterizes the inflammatory and oxidative consequences of obstructive SDB are not likely to be as responsive to the inhaled corticosteroids typically used to treat asthma. While much of the focus in understanding the inflammatory relationship between SDB and asthma has focused on how SDB can worsen inflammation making asthma more severe or difficult to treat, chronic low-grade inflammation may also adversely affect the force generation properties of the upper airway muscles [44], linking asthma back to obstructive sleep disordered breathing in a bidirectional manner.

Shared comorbidities (rhinitis, obesity, GERD) may explain the link between obstructive SDB and asthma. Allergic or non-allergic rhinosinusitis may lead to upper airway obstruction as well as trigger lower airway inflammation and reactivity. The interaction between obesity and asthma has been well studied, although not always with consideration of how obstructive SDB may either confound or mediate observed relationships, possibly explaining some of the disparate findings in the literature.

Treatment effects may explain some of the observed associations. Some researchers have proposed that the relationship between more severe asthma and obstructive SDB is driven by use of high dose inhaled steroids or oral steroids. [10, 45] Proposed mechanisms include deposition of fat into the airways and steroid induced myopathy affecting upper airway muscles.

Sleep fragmentation has also been proposed to play a role in a bidirectional manner. Sleep apnea induced sleep fragmentation may impair cognitive functioning needed to manage asthma, or may have direct
impacts on airway resistance. Conversely, sleep fragmentation due to asthma may worsen upper airway collapsibility.

**Impact of treatment of obstructive SDB on asthma outcomes**

CPAP use in patients with asthma was first reported in 1988 by two groups. In a series of 15 subjects with uncontrolled asthma despite oral corticosteroids, treatment of mild to moderate OSA with CPAP over a 2-week period was associated with improved peak flow, reduced day and night symptoms, and reduced bronchodilator use. Symptoms worsened when CPAP use was stopped. In a second series of 10 adult and 5 adolescent males, use of CPAP was associated with a reduction in nocturnal asthma attacks. In another uncontrolled study of 43 adults with nocturnal asthma despite optimized medical management, treatment with CPAP in those found to have obstructive SDB resulted in improvement in nocturnal symptoms in the majority of those who were adherent to CPAP use. In a study of 33 participants with well controlled asthma and newly diagnosed obstructive SDB, CPAP use was associated with improved asthma and sleep related quality of life. In a large retrospective study, CPAP use abrogated an association with OSA and daytime asthma symptoms. Lung function was either not measured or found to be unchanged with CPAP treatment in these studies, but Bonay et al found that treatment with CPAP for one year resulted in improvement in lung function in those with obstructive lung disease but small yet statistically significant worsening in those without a history of obstructive lung disease. Others have shown improvement in chronic cough when CPAP is used, even in the absence of a formal asthma diagnosis.

Adenotonsillectomy is first line treatment for obstructive SDB in children who are surgical candidates. Similar to the evidence that CPAP treatment may improve asthma outcomes in adults, there are studies suggesting AT may be associated with improved asthma outcomes in children but no randomized clinical trials addressing this question. Kheirandish-Gozal et al reported on their practice in a difficult to treat asthma clinic, in which 43% of children who had a PSG were found to have obstructive SDB. Among those who underwent adenotonsillectomy, there was significant improvement in lung function, exacerbation rates, and use of quick relief medications. Findings from this study must be interpreted in light of significant attrition of eligible children. Researchers used data from a large US insurance database to study children with asthma who underwent adenotonsillectomy and compared them with matched cases who did not have the procedure. The children undergoing adenotonsillectomy had a significant reduction in acute exacerbation rates during one year of follow up post procedure, with no change in the control group. The database used for this study did not include higher risk patients with public insurance, somewhat limiting the generalizability of the findings. A retrospective database study in Belgium found using a similar case control design also found reduced respiratory medication use in children undergoing tonsillectomy compared with controls. In both of these studies, there appeared to be a larger effect size in younger children than older children and adolescents.

**Summary**

Asthma and obstructive SDB are prevalent conditions in both children and adults. While the heterogeneity of each disorder complicated efforts to study their interactions, there is mounting evidence that these disorders may influence each other in terms of risk of development, severity, and response to treatment. Putative pathways by which this bidirectional interaction occurs include physiologic changes, inflammatory and oxidative derangements, shared co-morbidities, and treatment effects. There is some uncontrolled evidence that treatment of obstructive SDB improves asthma outcomes. Further work may help direct personalized strategies that consider the phenotype of both upper and lower airway disease in making diagnostic and treatment decisions.
REFERENCES


FACULTY DISCLOSURES

Dr Kristie Ross has no relevant commercial disclosure to this presentation. I have grant funding from the National Institutes of Health to study the impact of adenotonsillecomy on children, including the impact on asthma outcomes.

EVALUATION

1. Which of the following is true about the epidemiologic evidence linking asthma and obstructive sleep disordered breathing?
   a. Most studies examining the rates of obstructive sleep disordered breathing in children and adults with asthma find there is an approximate 2 fold increase in risk compared to populations without asthma.
   b. There is a clear and consistent relationship between asthma severity and risk of obstructive SDB, such that most studies show children and adults with more severe asthma are at higher risk for obstructive SDB than those with less severe asthma.
   c. In the only randomized controlled study of children with obstructive SDB undergoing adenotonsillectomy, asthma rates were lower than would be predicted in a similar US population.
   d. A and B

2. Studies examining putative inflammatory mechanisms that link asthma and obstructive SDB have found
a. Consistent Th2 or type 2 inflammation (airway and systemic) in obstructive SDB, similar to classic asthma inflammation
b. Neutrophilic predominant inflammation thought to be due in part to oxidative stress in obstructive SDB, suggesting treatment with standard asthma therapies that target allergic inflammation may not be as effective
c. No evidence that there is chronic airway or systemic inflammation in obstructive SDB
d. No evidence that intermittent hypoxemia affects airway inflammation

3. Theoretical physiologic mechanisms that link asthma and obstructive SDB include all of the following EXCEPT:
   a. Tracheal tug phenomenon
   b. Increased respiratory load during attempts to open an occluded airway
   c. Obstructive events triggering vagal mediated bronchoconstriction
   d. Sleep fragmentation leading to bronchodilation

4. Adenotonsillectomy in children with obstructive SDB has been shown to:
   a. Reduce asthma exacerbations in a randomized controlled trial study design
   b. Be associated with reduced asthma exacerbations in a retrospective study using an insurance database
   c. Be associated with reduced respiratory medication use in a retrospective study using an insurance database
   d. B and C

5. CPAP use in those with asthma and obstructive SDB has been shown to:
   a. Consistently improve lung function across most studies
   b. Consistently worsen lung function by causing air trapping
   c. Improve some asthma related outcomes including quality of life and daytime and night-time symptoms in uncontrolled studies
   d. Improve asthma outcomes in randomized controlled trials