

Interactions of Obstructive Sleep-Disordered Breathing With Recurrent Wheezing or Asthma and Their Effects on Sleep Quality

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Summary. Snoring is the most characteristic symptom of obstructive sleep-disordered breathing (SDB) and recurrent wheezing is the most common clinical manifestation of asthma. The purpose of the present review is to outline the impact of SDB and recurrent wheezing/asthma on sleep quality and to summarize the epidemiologic and pathophysiologic evidence supporting an association between the two disorders. Enlarged tonsils and adenoid or obesity predispose to obstructive sleep apneas and hypopneas which are accompanied by arousals, restless sleep, and frequently daytime sleepiness, inattention, hyperactivity, and academic difficulties. Subjects with history of wheezing are also at risk for sleep disturbance and daytime cognitive dysfunction. Asthmatic children have more frequent snoring, apneas, and hypopneas during sleep than non-asthmatic subjects and tonsillar hypertrophy mediates at least in part this epidemiologic association. In addition, preliminary evidence indicates that treatment of sleep apnea with adenotonsillectomy results in improved control of coexisting asthma. Elevated concentrations of leukotrienes and oxidative stress markers have been detected in the exhaled breath condensate of children with asthma and probably contribute to bronchoconstriction. Moreover, sleep apneic children have increased expression of leukotrienes and leukotriene receptors in adenotonsillar tissue. Viral respiratory infections may induce inflammation and oxidative stress in the asthmatic airway enhancing not only bronchospasm, but also biosynthesis of leukotrienes within pharyngeal lymphoid tissues, which promote adenotonsillar enlargement and sleep apnea. In conclusion, taking under consideration the epidemiologic association between obstructive SDB and asthma, when one of the two disorders is diagnosed, the possibility of the other disease being present should be entertained. **Pediatr Pulmonol.**

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Obstructive sleep-disordered breathing (SDB) and asthma are inflammatory diseases of the upper and lower airway tract, respectively, with daytime and nocturnal symptoms.^{1,2} One or both of the disorders may affect quality of life,^{3–5} behavior and cognition,^{4,6} respiratory function,² and possibly cardiovascular health.⁷ Coexisting obstructive SDB and asthma in the same individual can potentially have a cumulative effect on morbidity and for this reason, the two disorders should be recognized and treated early. The aims of the present review were: (i) to outline the impact of obstructive SDB and recurrent wheezing/asthma on sleep quality in childhood; (ii) to summarize evidence indicating that upper and lower airway obstruction are not uncommonly found in the same individual; and (iii) to review

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pathogenetic mechanisms which are shared by the two disorders.

PATHOPHYSIOLOGY OF OBSTRUCTIVE SDB

The term “obstructive SDB” describes a spectrum of abnormal breathing patterns during sleep characterized by snoring and increased respiratory effort.⁸ Depending on the severity of upper airway obstruction, these breathing patterns may range from primary snoring to upper airway resistance syndrome, obstructive hypoventilation, and obstructive sleep apnea (OSA). American Thoracic Society has defined OSA as a disorder of breathing during sleep resulting from intermittent partial and/or complete upper airway obstruction (hypopnea or obstructive apnea, respectively), which impairs normal ventilation and sleep pattern.⁹

It should be noted that patency of the upper airway is the result of a fine balance between upper airway resistance, pharyngeal collapsibility, tone of the pharyngeal dilator muscles, and negative intraluminal pressure generated by the inspiratory muscles.⁸ This balance of mechanical forces can be impaired by abnormalities such as: (i) adenotonsillar hypertrophy or allergic rhinitis; (ii) obesity; (iii) craniofacial anomalies; (iv) abnormal neuromotor tone and/or abnormal control of breathing.

Enlarged tonsils and adenoid or obesity are common abnormalities that can increase resistance to airflow and the tendency of the pharyngeal airway to collapse during inspiration (pharyngeal collapsibility).^{10,11} Increased upper airway resistance leads to more negative than usual inspiratory intrapharyngeal pressure and reflex activation of the pharyngeal dilator muscles.¹² The subsequent neuromuscular activation increases stiffness of the collapsible pharyngeal wall and maintains pharyngeal lumen patency despite the increased upper airway resistance.¹³ However, abrupt, intermittent reductions in activation of the pharyngeal dilator muscles during sleep cause sudden airway collapse and hypopneic or apneic events.¹⁴ The resulting excessive respiratory effort and hypercapnia related to pharyngeal obstruction trigger recognizable EEG arousals, increased sympathetic tone, reactivation of the pharyngeal dilator muscles and ultimately restoration of the pharyngeal airway patency.¹⁵

EFFECTS OF OBSTRUCTIVE SDB ON SLEEP QUALITY

EEG arousals as well as intermittent hypoxia contribute to the increased neurocognitive morbidity associated with obstructive SDB.^{16–19} Respiratory-related EEG arousals and insufficient sleep duration affect adversely the prefrontal cortex leading to increased prevalence of inattention, behavioral problems (hyperactivity, impulsivity, aggression), and cognitive dysfunction in

children with SDB.¹⁷ Repetitive arousals up-regulate synthesis of proinflammatory mediators which are involved in the pathogenesis of daytime sleepiness.^{20–23} Furthermore, intermittent hypoxia and hypercarbia have a negative effect on the hippocampus and prefrontal cortex functions, most likely via processes of oxidative stress and systemic inflammation.^{24–26}

Children have reduced cortical arousals and a pattern of obstructive hypopneas rather than true apneic events which predominates in comparison to adults.²⁷ Therefore, additional research is necessary to elucidate the pathogenetic links between obstructive SDB, sleep disruption, and neurobehavioral deficits in childhood.

PATHOGENESIS OF RECURRENT WHEEZING/ASTHMA

Childhood asthma is a chronic inflammatory disease of the lower respiratory tract with episodic and at least partially reversible lower airway obstruction and with bronchial hyperreactivity.² Recurrent wheezing is the most characteristic symptom of asthma.²⁸ Data from the Tucson (Arizona) birth cohort show that by the age of 3 years one-third of all children experience at least one episode of wheezing which is usually viral-induced (early-onset wheezers).^{29,30} While 60% of them will cease having symptoms by the age of 6 years (transient early wheezers), the others will continue wheezing during school age and eventually will be given a diagnosis of asthma.^{29,30} A subgroup of children with recurrent wheezing after the age of 3 years (late-onset wheezers) will also be diagnosed with asthma in school age.^{29,30} Family history of asthma and personal history of atopy, environmental triggers such as exposure to tobacco smoke, viral infections of the lower respiratory tract and socioeconomic variables contribute to the wheezing phenotype in each individual.^{2,29,31–33}

EFFECTS OF RECURRENT WHEEZING/ASTHMA ON SLEEP QUALITY

Accumulating evidence reveals a negative impact of childhood asthma on sleep quality, which deteriorates with increasing disease severity³⁴ and poorer asthma control.⁵ Data from the Childhood Asthma Management Program indicate that several children with mild-to-moderate asthma experience nocturnal awakenings.³⁵ Those are mostly atopic children with severe asthma.³⁵ Although sleep macro-structure does not seem to be affected as it has been demonstrated by polysomnography, asthmatic children have decreased sleep efficiency relative to controls probably as a result of the frequent awakenings.³⁶ Interruptions of the sleep continuity correlate positively with presence of asthma symptoms and reduced lower airway function.³⁷ Frequency of awakenings is closely related to the number of missed school

days, presence of daytime sleepiness or tiredness, and memory and concentration deficits.^{36,38,39} Control of asthma results in improved sleep quality.^{36,40}

The relationship between asthma and poor sleep quality persists even if coexisting obstructive SDB is taken under consideration.⁴¹ Thus, the effects of asthma on sleep are independent of concomitant intermittent upper airway obstruction. In a cross-sectional pediatric study, subjects with parental report of wheezing in the last 12 months had twofold higher risk for difficulty falling asleep, fourfold higher risk for restless sleep and fivefold higher risk for daytime sleepiness as compared to children without wheezing after statistical adjustment for the presence of snoring.⁴¹

INTERACTIONS BETWEEN OBSTRUCTIVE SDB AND RECURRENT WHEEZING/ASTHMA

An association between obstructive SDB and recurrent wheezing/asthma is supported by several epidemiologic studies from all over the world including more than 25,000 subjects (Table 1). An increased prevalence of snoring or elevated apnea-hypopnea index have been found in children with history of wheezing or physician-diagnosed asthma.^{41–52} Most reports have been based on symptom questionnaires for the recognition of SDB and recurrent wheezing/asthma and only one has included objective evaluation of OSA by polysomnography (Table 1). The effect of asthma on the risk for SDB is “dose-dependent” i.e., children with persistent wheezing or frequent episodes of wheezing have higher risk for increased apnea-hypopnea index or snoring relative to those with less severe symptoms.^{44,51}

The relationship between recurrent wheezing/asthma and sleep apnea may be bidirectional since subjects with increased apnea-hypopnea index have increased likelihood for wheezing.⁵³ This has been demonstrated in a community-based cohort, using home polysomnography (Table 1).⁵³

PATHOGENETIC LINKS BETWEEN OBSTRUCTIVE SDB AND RECURRENT WHEEZING/ASTHMA

It has been proposed that the epidemiologic association of recurrent wheezing/asthma with obstructive SDB is the result of both conditions sharing common pathogenetic pathways.⁴⁴ Such pathways have been discussed in a recent review on the association of OSA with asthma in adults.⁵⁴ In children, airway inflammation related to leukotrienes and airway oxidative stress are possibly implicated in the pathogenesis of both disorders.

Elevated concentrations of leukotriene B₄, cysteinyl leukotrienes, and 8-isoprostane, an oxidative stress marker, have been detected in the exhaled breath

condensate collected from asthmatic children^{55–58} and from subjects with obstructive SDB.^{59,60} A variety of cells in the human airway can synthesize leukotrienes (e.g., bronchial epithelial cells, alveolar macrophages, neutrophils, eosinophils, basophils)^{61–63} or can release reactive oxygen species (e.g., neutrophils, alveolar macrophages, eosinophils).^{64–66}

Increased numbers of neutrophils which can be recruited by locally synthesized leukotriene B₄, have been detected in induced sputum from children with OSA.⁶⁷ Nocturnal intermittent alveolar hypoxia during apneas or hypopneas could promote release of toxic oxygen metabolites from neutrophils and other cells,⁶⁴ leading to up-regulation of 5-lipoxygenase activity, which is the key enzyme of leukotriene biosynthesis.^{68,69} It is possible that oxygen free radicals, isoprostanes, and cysteinyl leukotrienes synthesized in the airway act synergistically to increase bronchial hyper-responsiveness and reduce bronchial caliber in asthmatic individuals.^{70–72} Thus, intermittent upper airway obstruction and associated intermittent alveolar hypoxia during sleep may worsen recurrent wheezing/asthma (Table 2).

Asthma could also promote obstructive SDB. We speculate that pharyngeal lymphoid tissue is exposed to exhaled reactive oxygen metabolites released from the asthmatic airway that up-regulate activity of 5-lipoxygenase.⁵⁷ Hydrogen peroxide, specifically, can penetrate biomembranes. This speculation is consistent with the enhanced activity and content of cysteinyl leukotrienes found in adenoid and tonsils.^{73,74} Cysteinyl leukotrienes induce a proliferative response in tonsillar cell cultures and hence they contribute to adenotonsillar tissue hypertrophy.⁷⁵

Furthermore, respiratory syncytial virus (RSV) is one of the triggers of viral induced-wheezing in early life.⁷⁶ RSV exerts neuroimmunomodulatory effects in the lower respiratory tract that are mediated by the substance P/neurokinin 1 receptor and the nerve growth factor/tyrosine kinase receptor A pathways (neurotrophins),^{77,78} and it also increases synthesis of leukotrienes maintaining airway inflammation.⁷⁹ Since pharyngeal lymphoid tissue is the primary site of proliferation of respiratory viruses,⁸⁰ increased expression of neurotrophins and cysteinyl leukotrienes in adenotonsillar tissue of sleep apneic subjects^{74,81} may explain the increased prevalence of tonsillar hypertrophy and sleep apnea in children with wheezing.⁵²

In addition, there is some evidence that the high frequency of allergic rhinitis and the associated nasal mucosa edema among asthmatics increase nasal resistance and the risk for obstructive SDB.^{82–84} Finally, obesity is a risk factor for both obstructive SDB and asthma and mechanisms related to overweight may exacerbate both conditions.^{44,85} Pathogenetic mechanisms that may

TABLE 1—Epidemiologic Studies Supporting the Association Between Obstructive Sleep-Disordered Breathing and Recurrent Wheezing/Asthma in Childhood

First author location	Age	No. of subjects	Risk factors	Outcome measure	OR (95% CI)	Ref. no.
Corbo; Italy	6–13 y.o.	1,615	Cough and phlegm without cold	Snoring often	1.8 (1.1–3.0)	42
Teulescu; France	5–6.4 y.o.	190	Exercise-induced bronchospasm	Snoring often	8.7 (2.8–26.4) [relative risk]	43
Redline; USA	2–18 y.o.	399	Physician-diagnosed asthma	Apnea–hypopnea index > 10 episodes/hr	3.8 (1.4–10.6)	44
			Occasional wheezing		3.3 (1.2–8.9)	
			Persistent wheezing		7.5 (2.0–27.4)	
Lu; Australia	2–5 y.o.	974	Physician-diagnosed asthma	Snoring ≥ 4 nights/week in the absence of a cold	2.0 (1.3–3.1)	45
Ersu; Turkey	5–13 y.o.	2,147	History of asthma	Snoring always or frequently	2.0 (1.1–3.6)	46
Valery; Australia	0–17 y.o.	1,650	Ever had wheezing	Snoring > 1 night/week over the last 6 months	2.2 (1.4–3.2)	47
			Wheezing in the last 12 months		5.4 (3.6–8.1)	
			Ever had asthma		3.2 (2.2–4.7)	
			Wheezing during or after exercise in the last 12 months		4.7 (2.8–7.8)	
Chng; Singapore	4–7 y.o.	10,279	Physician-diagnosed asthma	Snoring	1.3 (1.1–1.6)	48
Sulit; USA	8–11 y.o.	835	Obstructive apnea–hypopnea index ≥ 5 episodes/hr or obstructive apnea index ≥ 1 episode/hr	Wheezing apart from colds in the last year or treatment with asthma medications in the last 3 months	1.9 (1.3–2.9)	53
Desager; Belgium	7–14 y.o.	943	Wheezing in the last 12 months	Snoring in the last 6 months	1.9 (1.0–3.9)	41
Marshall; Australia	5 y.o.	516	Wheezing in the last 12 months and either an asthma diagnosis between 18 months to 5 years or >12% increase in FEV1 after a bronchodilator	Snoring	2.7 (1.2–5.9)	49
			Wheezing in the last 12 months	Snoring ≥ 3 nights/week	3.4 (1.6–7.2)	
Verhulst; Sri Lanka	6–12 y.o.	652	1–10 attacks of wheeze	Snoring	2.8 (1.6–4.7)	50
Kuehni; UK	1–5 y.o.	6,811	>10 attacks of wheeze	Snoring almost always over the last 12 months	1.4 (1.1–1.7)	51
Kaditis; Greece	Children ≥ 2 y.o.	442	Physician-diagnosed wheezing requiring treatment in the past 12 months	Snoring ≥ 1 night/week over the last 6 months	2.6 (1.5–4.7)	52
					1.7 (1.1–2.7)	

TABLE 2—Some Speculative Pathogenetic Mechanisms That may Explain the Association Between Obstructive Sleep-Disordered Breathing and Recurrent Wheezing/Asthma

Obstructive sleep-disordered breathing may enhance recurrent wheezing/asthma

1. Intermittent upper airway obstruction during sleep is related to episodic alveolar hypoxia, release of oxygen free radicals and airway oxidative stress
2. Oxidative stress up-regulates activity of 5-lipoxygenase in neutrophils-found at increased numbers in the airway of sleep apneic children and in epithelial and other cells located in the airway wall
3. Leukotriene B₄ synthesized in the airway recruits additional neutrophils in the airway which further release leukotrienes and oxygen free radicals
4. Cysteinyl leukotrienes and oxygen free radicals released in the lower airway promote bronchial hyperresponsiveness, bronchoconstriction, and airway inflammation

Recurrent wheezing/asthma may enhance obstructive sleep-disordered breathing

1. Oxygen free radicals released from the asthmatic airway up-regulate 5-lipoxygenase activity in pharyngeal lymphoid tissues, promoting synthesis of cysteinyl leukotrienes and thus adenotonsillar hypertrophy
2. RSV infection manifested as wheezing enhances synthesis of cysteinyl leukotrienes and neurotrophins not only in the lower airway, but possibly in the pharyngeal lymphoid tissue, increasing the risk for adenotonsillar enlargement
3. High prevalence of allergic rhinitis in asthmatic children increases upper airway resistance and their risk for obstructive sleep-disordered breathing
4. Increased prevalence of obesity in asthmatics poses them at risk for intermittent upper airway obstruction during sleep

explain the association between OSA and recurrent wheezing/asthma are summarized in Table 2.

DOES TREATMENT OF OBSTRUCTIVE SDB IMPROVES RECURRENT WHEEZING/ASTHMA AND VICE VERSA?

Although compelling evidence suggests a significant relationship between obstructive SDB and recurrent wheezing/asthma, few studies have evaluated the hypothesis that treatment of one of the two disorders results in improvement of the other. Investigations including small numbers of adult participants reveal that treatment of OSA by nasal continuous positive airway pressure (CPAP) is accompanied by reductions in nighttime asthma symptoms and improvement in the quality of life, but not always by a change in respiratory function or bronchial hyperresponsiveness.^{86–89} Improved asthma control with the use of nasal CPAP in sleep apneic adults has been attributed primarily to relief of upper airway obstruction, since nasal CPAP administered to adult asthmatics without sleep apnea does not affect asthma symptoms.⁹⁰

Whether adenotonsillectomy as a treatment intervention for OSA in children, improves concomitant asthma symptoms has been a matter of investigation in only three studies.^{91–93} Busino et al.⁹¹ reported reductions in the number of hospital visits, and use of systemic steroids and asthma medications in a cohort of 93 asthmatic children, 1 year after adenotonsillectomy. Similar results were reported by Saito et al.⁹² in a smaller cohort of asthmatic children who underwent surgical excision of tonsils and adenoids.

In a recent study conducted by Kheirandish-Gozal et al.⁹³, a high prevalence of OSA (63%) was diagnosed by polysomnography in a cohort of 92 children with

poorly-controlled asthma. Adenotonsillectomy was performed in a subgroup of the asthmatic children with OSA and follow-up evaluation for asthma symptoms was conducted at 1 year post-operatively. Children with poorly-controlled asthma from the same cohort who did not have OSA, were studied as controls. Annual number of asthma exacerbations, weekly rescue use of bronchodilators and asthma symptom score decreased significantly, whereas FEV₁ increased significantly in the subgroup of subjects with asthma and OSA but not in asthmatic children without OSA.

No investigations have assessed the effects of improved asthma control on the severity of coexisting obstructive SDB. Nevertheless, in a multicenter, retrospective review of children who underwent polysomnography before and after adenotonsillectomy, it was concluded that presence of asthma was a significant predictor of residual SDB in non-obese subjects.⁹⁴ Thus, asthmatic, non-obese children may still have obstructive events during sleep despite excision of the enlarged pharyngeal lymphoid tissues. This finding may imply that lower airway obstruction contributes to intermittent upper airway obstruction during sleep.

CONCLUSIONS

- Obstructive SDB and recurrent wheezing/asthma frequently coexist in children. Therefore, when one of the two disorders is diagnosed, the possibility of the other disorder being present should be entertained.
- Both disorders have a negative impact on sleep quality.
- Many of the reported symptoms of sleep disturbance in children with allergic rhinitis may be mediated by obstructive SDB due to nasal obstruction and

increased upper airway resistance. More evidence is required to support this concept.

- Increased expression of cysteinyl leukotrienes and their receptors within the pharyngeal lymphoid tissues contributes to adenotonsillar hypertrophy and severity of SDB.
- Airway oxidative stress and airway inflammation related to leukotrienes in children with obstructive SDB or recurrent wheezing/asthma could be the pathogenetic links explaining the epidemiologic association between the two disorders.
- Preliminary evidence indicates that adenotonsillectomy for the treatment of sleep apnea improves control of coexistent asthma.

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