Pediatric Obstructive Sleep Apnea
Complications, Management, and Long-term Outcomes

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Obstructive sleep apnea (OSA) in children has emerged not only as a relatively prevalent condition but also as a disease that imposes a large array of morbidities, some of which may have long-term implications, well into adulthood. The major consequences of pediatric OSA involve neurobehavioral, cardiovascular, and endocrine and metabolic systems. The underlying pathophysiological mechanisms of OSA-induced end-organ injury are now being unraveled, and clearly involve oxidative and inflammatory pathways. However, the roles of individual susceptibility (as dictated by single-nucleotide polymorphisms), and of environmental and lifestyle conditions (such as diet, physical, and intellectual activity), may account for a substantial component of the variance in phenotype. Moreover, the clinical prototypic pediatric patient of the early 1990s has been insidiously replaced by a different phenotypic presentation that strikingly resembles that of adults afflicted by the disease. As such, analogous to diabetes, the terms type I and type II pediatric OSA have been proposed. The different manifestations of these two entities and their clinical course and approaches to management are reviewed.

Keywords: obstructive sleep apnea; adenotonsillar hypertrophy; treatment; inflammation, upper airway; snoring

Habitual snoring during sleep, the hallmark indicator of increased upper airway resistance, is an extremely frequent occurrence during childhood, with a median incidence of about 10% among preschool and school-aged children (1–9), with subsequent declines in frequency after 9 years of age (10). The exact polysomnographic criteria that differentiate between innocent snoring (i.e., habitual snoring that does not lead to gas exchange abnormalities, sleep disruption, and/or to any morbid consequences), and snoring that is associated with adverse consequences, have yet to be defined. Nevertheless, a consensus statement has been generated (11), and defines a set of empiric criteria, on the basis of which we currently estimate that of the many children with habitual snoring, approximately 2–3% will have clinically relevant disease (12). Therefore, the ratio between symptomatic habitual snoring and obstructive sleep apnea (OSA) is usually between 3:1 and 5:1.

Worthy of mention as well is the rather accelerated increase over the last two decades in the prevalence of pediatric obesity, which has led to substantial changes in the cross-sectional demographic and anthropometric characteristics of the children being referred for evaluation of habitual snoring. Indeed, whereas less than 15% of all symptomatic habitually snoring children were obese (i.e., body mass index z score > 1.57) in the early 1990s, more than 50% fulfilled such criteria among all clinical referrals for suspected OSA in the last 2–3 years at our sleep center (University Sleep Center, University of Louisville, Louisville, KY) (13). Considering that obesity can clearly play a role in the pathophysiology of upper airway obstruction during sleep, it is likely that the ratio between habitual snorers and those with clinically relevant OSA among obese children will differ from that in nonobese children (14). On the basis of the relative contributions to the pathophysiology of OSA by adenotonsillar hypertrophy and increased fat deposits in the upper airway structures, we have proposed that two distinct types of OSA exist in children, namely one associated with marked lymphadenoid hypertrophy in the absence of obesity (type I), and the other associated primarily with obesity and with milder upper airway lymphadenoid hyperplasia (type II) (15) (Table 1). In this context, it would also be tempting to include an additional pediatric category in the nomenclature of OSA (i.e., type III), which would address some of the unique presentation and outcome features of children with a variety of craniofacial and neuromuscular disorders (e.g., Crouzon and Apert syndromes, Pierre Robin sequence, Down syndrome, Goldenhar syndrome, achondroplasia, myelomeningocele, and cerebral palsy). However, the evidence to justify the addition of such categorical subtype is not as well developed, and therefore careful meta-analysis of all these conditions will be required to delineate the unique clinical features and differential consequences that would justify this additional subtype. We further suggest that these proposed changes in the classification of pediatric OSA into two subtypes (possibly even three in the near future) may also have implications regarding the frequency and severity of several of the morbid consequences that can develop in children affected with this condition. Therefore, as we review the topics of interest in the remainder of this article, we point out potential disparities in the morbidities and treatment outcomes associated with type I and type II pediatric OSA.

CONSEQUENCES OF PEDIATRIC OSA

We have begun to understand that sleep disorders in general, and more particularly, sleep-disordered breathing, can lead to substantial morbidities affecting the central nervous system (CNS), the cardiovascular and metabolic systems, and somatic growth, ultimately leading to reduced quality of life. On the basis of a series of elegant studies using rodent models of OSA (16–33), it is highly plausible that many if not all of these end-organ consequences impart common pathogenic mechanisms triggered by the interactions of intermittent hypoxia and hypercapnia, repeated intrathoracic pressure swings, and episodic arousal.

CONSEQUENCES OF SLEEP DISRUPTION IN CHILDREN

Although experimental sleep fragmentation and its impact on daytime functioning have not been adequately studied in children, significant relationships have been identified between the degree of sleep disturbance or reduction and the magnitude of behavioral changes (3, 34–37). Daytime hyperactivity and inat-

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TABLE 1. COMMON FEATURES AND DIFFERENCES IN THE CLINICAL PRESENTATION OF PEDIATRIC OBSTRUCTIVE SLEEP APNEA TYPES I AND II

Symptoms and Findings Similarly Frequent in OSA Types I and II
Habitual snoring (at least 3 nights/wk)
Agitated sleep with frequent awakenings
Diaphoresis
Night terrors and nightmares
Bedwetting
Breathing pauses reported by parents
Nasal speech pattern and stuffy nose
Mouth breathing and limited nasal airflow
Frequent visits to primary care physician for respiratory-related symptoms
Retrognathia

Symptoms and Findings Relatively Specific to OSA Types I and II		
Symptom/Finding	OSA Type I*	OSA Type II*
Excessive daytime sleepiness	+	++++
Weight gain	–	++
Hyperactive behavior	++++	– or +
Attention problems	++++	+++
Truncal/visceral obesity	– or +	+++
Enlarged neck circumference	– or +	+++
Enlarged tonsils/adenoids	++++	++
Recurrent otitis media/tympanostomy tube placement	+++	+
Depression and low self-esteem	+	+++
Shyness and social withdrawal	+	+++
Left ventricular hypertrophy	++	++++
Systemic hypertension/altered blood pressure regulation	+	++++
Insulin resistance	–	++++
Serum lipid abnormalities	+	++++
Elevated C-reactive protein	++	++++
Elevated liver enzymes	–	++

* –: absent; + to ++++: infrequent to very frequent.

tention are associated with restless sleep, and conversely improved sleep patterns lead to better behavior (38, 39). Acute sleep restriction for one night promoted inattentive behavior (40), and more extended sleep restriction for seven nights led to oppositional and inattentive behaviors in children (41).

However, although total sleep duration may certainly alter behavioral patterns, it has become increasingly apparent that disruption of the sleep process, rather than total amount of sleep, may be one of the key factors underlying the behavioral alterations that accompany pediatric sleep disorders. In other words, sleep fragmentation, such as found in pediatric OSA and in other sleep disorders such as periodic leg movement disorder of sleep, may indeed promote the occurrence of impaired daytime functioning (42, 43; and *see below*).

NEUROBEHAVIORAL CONSEQUENCES

Behavioral and neurocognitive dysfunction as well as reduced scholastic achievements are now well-characterized morbidities of OSA in children (34, 44–48), and associations between OSA and hyperactivity and inattentive behaviors as well as cognitive deficits have been identified (37, 49–53). In addition, parentally reported daytime sleepiness, hyperactivity, and aggressive behaviors can also develop, albeit to a lesser extent in children who habitually snore but in the absence of OSA (54–60). The major intriguing component of the association between OSA and cognitive functioning lies in the observation that not all children with OSA actually manifest cognitive morbidities, suggesting that other factors may be playing a role in this process.

One of our initial observations suggested that increased body mass index (BMI) would translate into increased cognitive vulnerability to OSA (60). Our group is now conducting a more extensive population-based assessment of this assumption, and attempting to identify the potential role of inflammation in the *a priori* enhanced cognitive susceptibility of obese children to OSA. Although obesity could be a marker rather than a cause of low academic performance (61–64), it is important to emphasize that both obesity and OSA are systemic inflammatory diseases (65–67). Under such a conceptual framework (67, 68), we have shown in a community-based study of snoring and nonsnoring school-aged children that OSA in children increases C-reactive protein levels and if such increases occur the probability for decreased cognitive performance is markedly elevated compared with control children (69). Thus, when the magnitude of the systemic inflammatory response to OSA in children is assessed as the circulating morning levels of C-reactive protein, the latter emerges as a potential risk marker for OSA-induced cognitive deficits in children. As further evidence of genetically determined vulnerability, we reported on the potential role of an allelic variant of the gene encoding apolipoprotein E (70). Indeed, the presence of apolipoprotein ε4 has been associated with increased risk for Alzheimer's disease and atherosclerosis, and increased incidence of cardiovascular disease, as well as with obstructive sleep apnea in adults (71, 72). We found that apolipoprotein ε4 is more likely to be present not only among children with OSA, but also among those with OSA who displayed reductions in cognitive performance during administration of standardized neuropsychological test batteries (70). The association of apolipoprotein E polymorphisms with pediatric OSA has since been confirmed by another group of investigators (73). In addition, it will be important to incorporate pertinent information regarding environmental elements such as nutrition (e.g., breastfeeding [74], saturated fat and trans–fatty acid content of food intake [28]), recurrent exposure to respiratory viruses, passive or active exposure to cigarette smoking, level of physical activity, and intensity of intellectual activity, because all these can affect both the pathophysiological risk for OSA as well as modify the susceptibility to the consequences of OSA (67, 74). Unfortunately, most of this important information is not routinely collected during clinical assessment of pediatric patients referred for evaluation of habitual snoring. The potential interactions between disease severity and potential genetic and environmental determinants of susceptibility are shown in Figure 1.

Notwithstanding these considerations, improved learning and behavior occur after effective treatment of children with type I OSA (45, 75–80), and such findings are therefore supportive of the putative partial to complete reversibility of the neurocognitive and behavioral deficits, provided treatment is administered in a timely fashion (81). However, no studies are available on the reversibility of such deficits on treatment in type II OSA, and we would propose that, based on the poorer outcomes pertaining to treatment (*see below*), the cognitive outcomes may similarly not be as favorable. Because children with type II OSA are much more likely to present a phenotype resembling that usually seen in adults, the presence of obesity is highly likely, and as such, such overweight children will be more likely to display *a priori* significantly lower math and reading scores compared with nonoverweight children, and to be held back in grade (61–63), and therefore be increasingly susceptible to OSA.

In summary, both obesity and OSA may adversely affect cognitive functioning in children. Coincidence of these two conditions in the same patient, as would be anticipated in type II pediatric OSA, would be expected to promote and exacerbate the severity of the systemic inflammatory response separately elicited by each of these diseases, and further supports the legitimacy of the novel proposed taxonomy of pediatric OSA (15, 60).

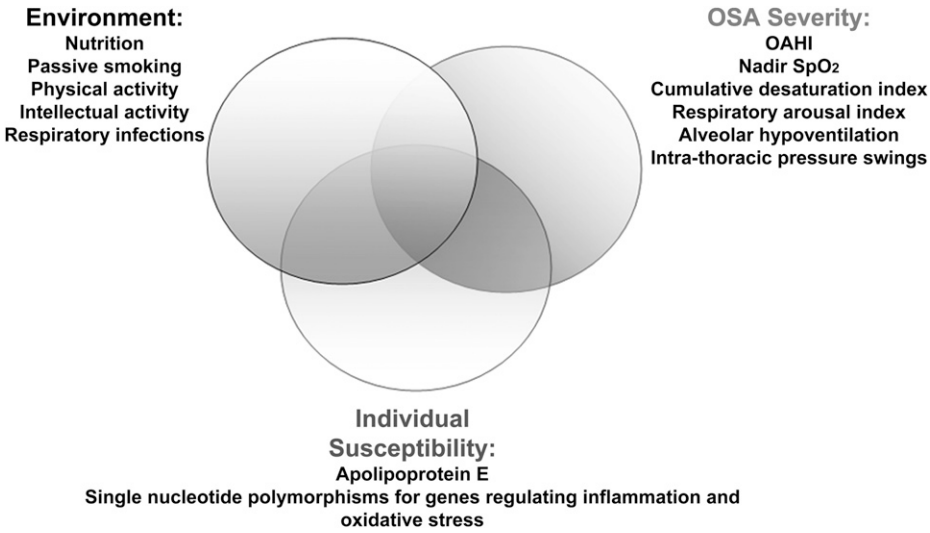

Figure 1. Potential interactions between pediatric obstructive sleep apnea (OSA), genetic factors, and environmental/lifestyle conditions in the pathophysiology of end-organ morbidity associated with the disease. OAHI = obstructive apnea–hypopnea index; Sp_{O_2} = arterial oxygen saturation measured by pulse oximetry.

It should be emphasized that we are unaware of any studies that have examined whether the duration of OSA before treatment modifies the overall reversibility of the outcome after effective treatment. It would be tempting to speculate that the longer the duration of symptoms, the less likely that complete reversibility will occur. Similarly, the effect of age at which OSA develops could also modify the frequency and severity of the morbid consequences, as well as influence the degree of reversibility after treatment. Thus, it is imperative that studies incorporating such important considerations be designed to provide us with critical definitions of elements that are operative within specific windows of vulnerability to OSA during childhood.

The exact mechanisms by which OSA elicits such neural deficits remain relatively unresolved. Most likely, both the sleep fragmentation and episodic hypoxia that characterize OSA lead to alterations within the neurochemical substrate of the prefrontal cortex with resultant executive dysfunction (82–84), and may also elicit neuronal cell losses (17, 85).

EXCESSIVE DAYTIME SLEEPINESS

The prevalence of excessive daytime sleepiness (EDS) in children with OSA is somewhat unclear, and probably depends on the perceptions of caretakers because children are unlikely to verbalize such symptoms. Parental reports concerning children being evaluated for suspected OSA initially indicated that only a small minority of these children (7%) presented with symptoms compatible with EDS (86). However, in more recent years, questionnaires that include more specific questions on behaviors associated with EDS indicate that the frequency of EDS may be much higher, and revolve around the 40–50% range (87). When sleepiness is measured objectively, using the Multiple Sleep Latency Test, approximately 13–20% of children fulfilling the criteria for OSA displayed EDS (59, 88). Furthermore, the presence of obesity appeared to increase the likelihood of EDS (88). We would also propose that, allowing for a substantial degree of overlap, the manifestations of EDS may somewhat diverge in children with type I OSA when compared with children with type II OSA. In the prototypic type I OSA, both inattention and hyperactivity would constitute the primary behavioral correlates of EDS (i.e., low modified Epworth scores) (59), whereas in type II OSA, increased Epworth scores along with reports of tiredness and falling asleep in school, car travel, or while watching television would be frequently found. One of the major questions emanating from the aforementioned studies is whether polysomnographic measures can provide insights and identify increased risk for EDS in children with OSA. To this effect, we examined the magnitude of sleep fragmentation induced by OSA in both children and adults and differentiated between spontaneous arousals and respiratory-related arousals in a large cohort of more than 600 children and more than 300 adults, and found that the relative proportion of spontaneous arousals was increasingly reduced as a function of the OSA severity–related increase in respiratory arousals (89, 90). These findings suggested that both children and adults will attempt to preserve sleep homeostasis by reducing the number of respiratory arousals and that when a certain obstructive apnea–hypopnea index is reached, sleep pressure will start accumulating, albeit at different apnea–hypopnea indexes (AHIs) for children and adults (89). Of note, the sleep pressure numerical score derived from the arousal indices correlated with both cognitive and behavioral disturbances occurring in snoring children (91). Using similar assumptions, Chervin and colleagues showed the presence of respiratory cycle-related electroencephalographic spectral changes in patients with OSA that correlate with EDS (92).

CARDIOVASCULAR CONSEQUENCES

Similar to adult OSA, pediatric OSA has been now associated with a higher risk for cardiovascular morbidities, albeit with reduced severity of these manifestations, most likely the corollary of the increased compensatory vascular capacitance in children. For example, increased prevalence of altered blood pressure regulation (93), systemic hypertension (94–96), and changes in left ventricular geometry (97, 98) have all now been reported in children with OSA, and appear to be dose dependent (99). The mechanisms mediating cardiac and blood pressure changes are most likely associated with the increases in sympathetic activity and reactivity that progressively develop in the context of OSA (100, 101). In addition, evidence supports the assumption of potential endothelial dysfunction in children with OSA, as evidenced by increases in circulating levels of several adhesion molecules (102). Parenthetically, the endothelial dysfunction associated with OSA is most likely the result of initiation and propagation of inflammatory responses within the microvasculature (103). C-reactive protein, which has been traditionally linked to increased risk for cardiovascular disease even if such assumptions have been challenged (104, 105), provides a good systemic marker for the presence of inflammation.

In a series of studies, plasma concentrations of C-reactive protein were elevated in a severity-dependent fashion among children and adolescents with OSA, even after correction for body mass index (106–108). Only one study by Kaditis and colleagues failed to identify these relationships in a study of Greek children (109).

The intermittent hypoxia during sleep that occurs in children with OSA may induce elevations of pulmonary artery pressures, at least during sleep, and such events may lead to some degree of right ventricular dysfunction. However, the prevalence of pulmonary hypertension in pediatric OSA has not been systematically examined (110, 111), and as such, we still have not defined the main sleep-related determinants of such potential occurrence.

QUALITY OF LIFE AND DEPRESSION

The cumulative evidence indicates that both OSA and obesity lead to significant decreases in quality of life in a large proportion of children, particularly when both obesity and OSA coincide (15, 112–117). Furthermore, quality of life is improved after treatment of OSA (112). It is also likely that the sleep disturbance associated with OSA will increase fatigue and lead to increased irritability, depressed mood, impaired concentration, and decreased interest in daily activities, and that these impairments in daily functioning may in turn interfere with other aspects of the child's life, including relationships with family, school, and peers (117).

INSULIN RESISTANCE, TYPE 2 DIABETES, AND METABOLIC SYNDROME

The term "metabolic syndrome" has been used to describe the clustering of insulin resistance, dyslipidemia, hypertension, and obesity. Consensus criteria for the metabolic syndrome have yet to be defined in the pediatric age range (118). However, the risk of metabolic syndrome was nearly 50% in severely obese young children, and this risk increased with every 0.5-unit increment in BMI, when expressed as *z* score (119). In addition, it has become apparent that elevated fasting insulin levels and increased BMI during childhood are the strongest predictors of metabolic syndrome in adulthood (120, 121).

Similar to obesity, OSA has been identified as an important risk factor for the metabolic syndrome in adult patients (122–124). In young children, both insulin resistance (measured on the basis of the insulin:glucose ratio and homeostatic model assessment) and altered lipidemia (evidence of increased plasma triglycerides and decreased plasma high density lipoprotein concentrations) appear to be determined by the degree of obesity, and the contribution of OSA does not seem to be a major one (125, 126). However, similar to adults, when obesity and OSA coincide in children the risk for metabolic disturbances is further increased (127, 128). In a study of adolescents, the presence of OSA had a sixfold increase in the odds of metabolic syndrome compared with those without OSA (129). On a similar plane, obese children with OSA are at increased risk for development of nonalcoholic liver steatosis (130), a finding that is also present in rodents and adults with OSA (131–135).

One of the emerging issues associated with OSA in adults involves recruitment of visceral adipose tissue and alterations in the release of several active compounds from this tissue, collectively referred to as adipokines. Among the several adipokines, leptin has emerged as being modified by OSA and also as playing an important role in the regulation of appetite, sleep, metabolic homeostasis, and respiratory control (136). Several studies indicate that leptin levels are altered in adult patients with OSA (137–139). We have reported on elevations of circulating leptin levels, independent of the degree of obesity, in pediatric patients with OSA (140). Although the implications of such findings remain to be established, we should also emphasize that adiponectin levels were reduced in obese children but were not affected by OSA, and that resistin concentrations were not affected by either OSA or obesity (140).

SOMATIC GROWTH IMPAIRMENT

Although the initial descriptions of pediatric OSA included a disproportionate number of children with failure to thrive, this is not the case nowadays, with only 5% or less of pediatric OSA manifesting this problem (141–143). Interestingly, even obese children with OSA will demonstrate accelerations in weight gain after treatment of OSA (144, 145). Among the proposed mechanisms for somatic growth alterations in OSA, decreased levels of insulin-like growth factor-I, insulin-like growth factor–binding proteins, and possibly growth hormone release are most likely involved (146, 147).

MANAGEMENT OF SLEEP APNEA IN CHILDREN

The pathophysiology of OSA has been previously reviewed (148, 149), and in more updated detail in this symposium (150), and it is clear from this review and other sources that OSA in children is most commonly associated with adenotonsillar hypertrophy (151), even if obesity is now a markedly frequent occurrence, and requires a lesser degree of lymphadenoid size (152). The recommended initial treatment, even in obese children, consists of surgical removal of the adenoids and tonsils (75, 153). However, not all children who undergo adenotonsillectomy (T&A) for OSA are cured (154–156). In a meta-analysis of the published literature, the success rate for T&A in the context of OSA was approximately 85% (157). This figure may actually be lower, particularly among obese children with OSA (158–162), or among children with severe OSA (158, 161). These findings have prompted the recommendation for repeated overnight sleep studies after adenotonsillar surgery for OSA (158). Although long-term outcomes are lacking after T&A in children with OSA, emerging evidence would suggest that recurrence of OSA will occur in a subset of these patients (163), particularly in those with craniofacial issues or family history of OSA (163–167). Additional issues for which no conclusive data are available involve the surgical technique used for extirpation of the lymphoid tissue (e.g., cold surgery, coblation, harmonic laser); and the need for tonsillectomy and adenoidectomy, either one of these two surgical procedures alone, or tonsillotomy alone (168–170). These issues will need to be addressed in future.

For children in whom T&A does not lead to complete resolution of OSA and in whom the residual severity of sleep-disordered breathing is considered moderate to severe (i.e., obstructive AHI $>$ 5/h), the only additional interventional option consists of the administration of nasal continuous positive airway pressure (CPAP) (171–176). Despite a relative paucity of size-appropriate masks, the overall adherence rates appear to be satisfactory (177), and such rates may be further improved by administration of behavioral interventions (178) and logistic support of the family.

The major gray zone regarding OSA therapy involves those children presenting with an AHI exceeding 1, but less than 5, events per hour of sleep. Indeed, whereas these patients are at significant risk for associated morbidity, the risk:benefit ratio of surgical adenotonsillectomy has not been conclusively defined, and CPAP is less likely to be beneficial and effective when applied to an airway that is partially blocked by enlarged

lymphadenoid tissues. Such considerations have led to the search for therapeutic alternatives. One approach has consisted of the topical intranasal application of high-potency corticosteroids. In a series of studies, significant improvements in AHI and oxygenation have been demonstrated in a cohort of children with OSA and AHI greater than 5 or in children with enlarged adenoids (179–182). Those findings are not surprising considering the expression patterns of glucocorticoid receptors α and β in the upper airway, which suggest favorable therapeutic responses to topical corticosteroid treatment in children with OSA (183). In addition, the concentration of inflammatory mediators such as leukotrienes and the expression of their receptors were found to be increased in children with OSA (184, 185), and a leukotriene receptor antagonist was effective in mild pediatric OSA (184). Of note, antiinflammatory therapy was also effective in ameliorating residual OSA after adenotonsillectomy (186).

Oral appliances or functional orthopedic appliances have also been tried in the treatment of OSA in children, with some degree of success (187–189). It remains unclear, however, which selection criteria to use for identification of the candidates likely to benefit from this therapeutic option, and what the long-term results of this approach might be.

As can be rapidly deduced from the current compilation of the literature regarding the management of pediatric OSA, there is a paucity of information regarding short-term and long-term outcomes. Future studies particularly addressing these issues in the context of type I, II, and III pediatric OSA categories will be essential for optimization of the care provided to our patients and the sustained improvement in their long-term health and quality of life.

CONCLUSIONS

The spectrum of disease that encompasses habitual snoring and OSA in children is associated with increased prevalence of a variety of morbidities spanning the CNS and the cardiovascular and endocrine systems. The coexistence of obesity and OSA appears to yield not only increased morbidity rates and poorer responses to therapy, but is altogether associated with a distinct and overall recognizable clinical phenotype. Therapeutic options have somewhat expanded since the initial treatment approaches were conducted, to include not only surgical extraction of hypertrophic adenoids and tonsils, but also nonsurgical alternatives such as CPAP, antiinflammatory agents, and oral appliances. However, the efficacy and optimal application of each of these options await firmer recommendations derived from suitably designed, randomized trials.

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