Obstructive sleep apnea in children: a critical update

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Abstract: Obstructive sleep apnea (OSA) in children is a highly prevalent disorder caused by a conglomeration of complex pathophysiological processes, leading to recurrent upper airway dysfunction during sleep. The clinical relevance of OSA resides in its association with significant morbidities that affect the cardiovascular, neurocognitive, and metabolic systems. The American Academy of Pediatrics recently reiterated its recommendations that children with symptoms and signs suggestive of OSA should be investigated with polysomnography (PSG), and treated accordingly. However, treatment decisions should not only be guided by PSG results, but should also integrate the magnitude of symptoms and the presence or absence of risk factors and signs of OSA morbidity. The first-line therapy in children with adenotonsillar hypertrophy is adenotonsillectomy, although there is increasing evidence that medical therapy, in the form of intranasal steroids or montelukast, may be considered in mild OSA. In this review, we delineate the major concepts regarding the pathophysiology of OSA, its morbidity, diagnosis, and treatment.

Keywords: adenotonsillar hypertrophy, polysomnography, pathophysiology, morbidity, treatment, pediatric sleep disordered breathing

Introduction

Children with obstructive sleep apnea (OSA) experience partial or complete obstruction of the upper airway during sleep, with resultant oxygen desaturation and hypercapnia, leading to increasing respiratory effort and attendant changes in intrathoracic pressures, ultimately culminating in subcortical or cortical arousals. Following such arousals, the child will typically drift back to sleep, and the cycle then repeats itself, with similar episodes occurring throughout the night and resulting in sleep fragmentation and nonrestorative sleep.1 It is now recognized that pediatric OSA is not only a common health problem, but also one that can result in significant morbidity. Estimates of prevalence vary, depending on the populations studied and on the stringency of the diagnostic criteria but are traditionally reported to range between 1%–5%, with the peak prevalence occurring at 2–8 years of age.1–5

The distinctive symptoms of OSA in children are remarkably scarce and usually require a high level of suspicion or alternatively, require systematic implementation of explorative screening questions to enable their detection. Common nighttime symptoms include snoring, excessive sweating, restless sleep, mouth breathing, apneas, gasping, labored or paradoxical breathing, and hyperextension of the neck during sleep. Daytime symptoms most commonly include difficulty concentrating, behavioral and mood problems, morning headaches, excessive daytime sleepiness (EDS), and failure to thrive.1
In this review, we will selectively identify issues of contention in pediatric OSA that address aspects of the pathophysiology, morbidity, diagnosis, and treatment of the disease. As such, this work is not meant to serve as a comprehensive and exhaustive overview, but rather, to illustrate and invigorate the debate on issues for which either conclusive evidence is lacking or a substantial level of conflictive evidence is present.

Pathophysiology of OSA

Although interactively related, the pathophysiological factors involved in OSA can be broadly and arbitrarily divided into anatomical factors that effectively reduce airway caliber and those that promote increased upper airway collapsibility (Figure 1). Examples of the former include craniofacial factors, eg, a small or retruded mandible, a large or retropositioned tongue, increased pharyngeal fat pads, and hypertrophic upper airway lymphoid tissues (particularly of the adenoids and tonsils). Among the factors underlying collapsibility, the presence of upper airway inflammation and altered neurological reflexes involving respiratory control of upper airway muscles emerge as the most prominent. These elements readily explain why children at higher risk of OSA include those with craniofacial syndromes (eg, Treacher Collins syndrome, Crouzon syndrome, Apert syndrome, and Pierre Robin sequence), achondroplasia, cerebral palsy, neuromuscular disorders, myelomeningocele, sickle cell disease, trisomy 21, allergic rhinitis, asthma, micrognathia, mucopolysaccharidoses, macroglossia, Afro Caribbean race, and those who are obese. Notwithstanding, the fundamental understanding of the individual mechanistic factors explaining why children with similar degrees of adenotonsillar hypertrophy may either suffer from OSA or not even snore during sleep remains somewhat elusive.

To resolve some of these issues, Arens et al used magnetic resonance imaging (MRI) techniques to delineate in detail the upper airway and surrounding tissues as well as the lower facial skeletal structure, in children with OSA. The volumetric measurements obtained indicated that the adenoids and tonsils were significantly increased in children with OSA compared with matched controls, concomitant with smaller upper airway volumes. Furthermore, in this case-control study, when the percent difference of the combined tonsil and adenoidal volume between each subject and his/her corresponding age-, height-, weight-, gender-, and ethnicity-matched control was plotted against the apnea hypopnea index, a positive correlation was seen. The volume of the soft palate was also noted to be on average 30% larger in subjects with OSA, adding additional restriction to the airway lumen size. However, no study has addressed the major question as to what factors differ between children with OSA and no OSA, when matched for the degree of adenotonsillar tissues, or alternatively, why in otherwise similar children with OSA, adenotonsilllectomy (AT) may yield different surgical outcomes as far as the degree of resolution of OSA. Furthermore, the interactions between obesity and adenotonsillar hypertrophy are only now being elucidated.

In addition to enlarged adenoids and tonsils, children with OSA have recently been shown to also have hypertrophy/hyperplasia of the lymphoid tissues in other regions of the airway as well, such as in the deep cervical lymph nodes (ie, those outside Waldeyer’s ring). Upper respiratory tract perturbations, such as prominence of the inferior nasal turbinates, deviation of the nasal septum, middle ear effusions, and opacification of the sinuses have also been described. These observations raise the question as to whether there is in fact, a broader disorder affecting the airway as a whole, mediated by inflammatory processes, chronic or recurrent infectious processes, or a combination thereof. In other words, are there unique mechanisms that underlie the lymphoid tissue proliferation that leads to OSA as compared with mechanisms that lead to such proliferation but that do not elicit OSA?

The exact mechanisms underlying follicular lymphoid proliferation and hyperplasia of the tonsils and adenoids remain poorly understood. When tonsillar tissues from children with OSA were placed in an in vitro culture system, the proliferative rates of the associated cluster of differentiation (CD)3, CD4, and CD8 cells were higher compared with tonsillar tissues from children with recurrent tonsillitis. Furthermore, the proinflammatory cytokines tumor necrosis factor (TNF)-α, interleukin (IL)-6, and IL-1α were more highly expressed in the OSA-derived tonsils. It is postulated that respiratory viruses and possibly recurrent vibration of the upper airway wall may promote localized inflammation. Exhaled breath condensate levels of leukotriene B4 and cysteiny1 leukotrienes have been reported to be higher in children with OSA. Similarly, induced sputum from children with OSA has been shown to exhibit increased neutrophilia compared with controls.

As indicated above, anatomical factors are clearly not the whole story for OSA in children: we have all seen children with large kissing tonsils who do not have OSA. Furthermore, the apnea–hypopnea index (AHI) has not been shown to directly correlate with airway volume, and the coefficients
of correlation between AHI and adenotonsillar size have been found to be usually relatively weak, albeit statistically significant, suggesting that other factors feature in the pathophysiology of pediatric OSA. The concept of airway collapsibility has thus been proposed to provide a more comprehensive and unified approach to this issue.

One of the earliest studies of airway collapsibility in children with OSA was by Marcus et al. In the Starling resistor model of the upper airway, under conditions of flow limitation, the maximum inspiratory airflow is determined by the pressure changes upstream (nasal) to a collapsible locus of the upper airway and is independent of the downstream (tracheal) pressure generated by the diaphragm. The pressure at which the upper airway collapses has been termed the critical closing pressure (Pcrit). Pcrit is thus, an objective measure of airway collapsibility and was found to be higher (ie, less negative) in children with OSA than in those with primary snoring and correlated with the AHI. In other words, children with OSA had demonstrably more collapsible upper airways during sleep. However, during wakefulness, active neural processes preserve upper airway patency and make it difficult to recognize such increased collapsibility. Interestingly, the surgical treatment of OSA was associated with a decline in Pcrit, ie, the upper airways became less collapsible post-AT.

Gozal and Burnside therefore postulated that measurement of upper airway dynamics using acoustic pharyngometry in the awake child, before and after application of local anesthetic to the pharyngeal introitus, may provide a useful clinical adjunct to the diagnosis of OSA. Upper airway collapsibility was determined from the percentage change in cross-sectional area before and after topical anesthesia, and an upper airway collapsibility less than or equal to −30% proved to be highly sensitive and specific in the identification of children with an AHI > 5/hour of total sleep time (TST). In agreement with these findings, another group also showed that children with OSA have a more collapsible upper airway than do normal children, even when awake, using the negative expiratory pressure (NEP) technique. However, although this technique could distinguish between children with OSA and normal controls, it could not distinguish between children with OSA and primary snorers. Similar approaches using the Müller maneuver have also been proposed as potentially predictive of OSA severity.

Thus, it is probably safe to conclude that a multiplicity of causative factors appear to coexist in every child with OSA. As a corollary to such assumptions, children with sickle cell disease have, for example, not only reduced upper airway size due to overgrowth of the surrounding lymphoid tissues, but they are also likely to be of African American ethnicity, which is also a risk factor for OSA. However, not all children with sickle cell disease have OSA, and those who do may have less prominent upper airway reflexes than those who do not.

**Obesity**

With the obesity epidemic that is sweeping through many of the developed countries, the demographics of childhood OSA appear to be changing. Compared with the classical presentation of a child with adenotonsillar hypertrophy and failure to thrive, as described in the not so distant past, nowadays, there are increasing numbers of children being diagnosed with OSA who are obese. Although all of the pathophysiological mechanisms described above for nonobese children would still remain applicable in the context of obesity, it is likely that other contributors may be operational in obese children as well. Indeed, not all obese children with OSA have adenotonsillar hypertrophy, often present at a slightly later age, and their clinical presentation is more likely to resemble the adult OSA phenotype.

Obesity has become one of the most significant risk factors for OSA in children. Each 1 kg/m² increment in body mass index above the 50th percentile (adjusted for gender and age) is associated with an increased risk of OSA by 12%. However, we should also point out that 45% of obese children with OSA also have evidence of adenotonsillar hypertrophy. When the upper airways of obese children with OSA were critically examined using MRI volumetric approaches, an increased size of upper airway lymphoid tissues, parapharyngeal fat pads, and abdominal visceral fat became apparent. When obese and nonobese children with OSA were matched for age, gender, ethnicity, and obstructive AHI, the size of the adenotonsillar tissues in obese children was smaller, while their Mallampati scores were higher, indicating that the presence of obesity increases the risk for OSA, not only via increased lymphadenoid tissue proliferation, but also, by restricting the overall pharyngeal space.

Furthermore, the percentage of obese children who have residual OSA post-AT is significantly higher than in nonobese children. It has thus been suggested that alterations in the functional mechanisms regulating upper airway patency may be present in obese children and promote increased airway collapsibility. The presence of a linear association between obesity and Pcrit values would then explain, at least in part, the increased propensity of these subjects to develop OSA. Fatty infiltrates within the compartments of the upper airway...
structures and the neck are likely to result in upper airway narrowing and increased pharyngeal collapsibility. Central obesity also reduces the functional residual capacity of the lungs, due to abdominal visceral fat impinging on the chest cavity, limiting diaphragmatic descent, particularly when lying in the supine position; in addition, thoracic fat weighing on the chest wall can effectively decrease lung compliance, leading to hypoventilation, atelectasis, and ventilation–perfusion mismatch. The reduced lung volumes may decrease airway stiffness by reducing the tracheal tethering effect, further increasing the risk of upper airway collapse during sleep. In a recent study, in which MRI scans were performed both pre- and post-AT in obese children with OSA, there was not only increased residual adenoidal tissue, but also the volume of the tongue and soft palate were greater after AT. Taken together, all of these factors could be operational contributors to the low success rate of AT reported in obese children with OSA.

A reciprocal interaction between obesity and OSA has also been suggested, whereby in addition to the contributions of obesity to OSA discussed above, OSA may also be contributing to the pathogenesis of obesity. Leptin is a key hormonal regulator of appetite and metabolism, mainly secreted by adipocytes, that promotes satiety and reduces food intake. In contrast, ghrelin is an orexigenic hormone secreted in the gut. OSA can induce leptin resistance and increase ghrelin levels, both of which can potentiate obesogenic behaviors, in particular, the intake of high-calorie comfort foods. OSA can also cause EDS and fatigue, both of which are likely to reduce the commitment to and engagement in physical activity. The low-grade inflammatory responses induced by OSA could further interact and potentiate the underlying inflammatory responses, due to obesity, and exacerbate the morbid phenotypes associated with either obesity or OSA.

OSA and inflammation

It is now recognized that OSA can promote the activation and propagation of systemic inflammatory responses. Elevation of proinflammatory cytokines such as IL-6, interferon (IFN)-γ and TNF-α have all been reported, albeit inconsistently, in children with OSA, while levels of the anti-inflammatory cytokine IL-10 were reduced. Microarray analyses of ribonucleic acid (RNA) from peripheral leukocytes has revealed the coordinated recruitment of functionally relevant gene clusters involved in the regulation and propagation of inflammatory pathways and the inflammasome. One of the potential mechanisms responsible for the initiation of inflammation may reside in molecular events in specific genes. For example, the promoter region of the FOXP3 gene, which controls the transcriptional fate and differentiation of lymphocytes into regulatory T lymphocytes (Tregs), exhibits severity-dependent increases in methylation in pediatric OSA. Such epigenetic alterations were subsequently linked to the presence of reduced counts of Tregs in the peripheral blood of children with OSA, a significant finding considering the major role that Tregs play in the suppression of inflammation. It is therefore possible that differentially orchestrated responses of various tissues to the presence of OSA-induced perturbations may further interact with environmental factors and intrinsic genetic variance to elicit a wide spectrum of inflammatory phenotypes that is linked to end-organ morbidities.

Morbidity of OSA

The foremost relevance of OSA relates to the fact that it imposes a vast array of morbidities. It has been proposed that such morbidities result from the combination of the activation of inflammatory cascades alluded to above and the induction of oxidative stress mechanisms, collectively leading to cellular injury and dysfunction, senescence, and various forms of cell death. Although these mechanisms are probably universal across the various targeted organs, we will describe each of the morbid consequences in greater detail below. They are also summarized in Figure 2.

Cardiovascular system

Arguably, one of the most serious complications of severe OSA is pulmonary hypertension, and the resultant cor pulmonale and right-sided heart failure if left untreated. Fortunately, with increased awareness and earlier diagnosis, the frequency of such cases is now much less commonly seen. However, it is unclear whether pulmonary hypertension will develop only in the severest cases, such that increased recognition and awareness of sleep disordered breathing in children would lead to a reduced likelihood of long-standing disease and concurrent pulmonary hypertension, or whether the current techniques for noninvasive assessment of the pulmonary circulation in children are insufficiently sensitive to detect much milder involvement of the pulmonary vasculature. Furthermore, it is also unclear whether chronic mild intermittent hypoxia may result in lesser recruitment of the pulmonary vascular network than following exposures to sustained hypoxia of similar duration. This issue merits further research, particularly considering that the occurrence of intermittent hypoxia and mobilization of the lung capillary
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Anatomical factors
- Craniofacial:
  - Retrognathia
  - Hyperglossia/retropositioned tongue
- Ethnicity
- Adenotonsillar hypertrophy

Obesity
- Fatty infiltrates in upper airway structures/neck
- Decreased FRC
- Decreased lung compliance
- Alterations in functional mechanisms regulating upper airway patency

Increased upper airway collapsibility
- Altered neurological upper airway reflexes
- Hypotonia
- Upper airway inflammation

Obstructive sleep apnea
- Intermittent hypoxia
- Hypercapnia
- Intrathoracic pressure changes
- Sleep fragmentation

Environmental factors
- Genetic predisposition

Cardiovascular morbidity
- Endothelial dysfunction
- BP dysregulation
- Left ventricular strain

Nocturnal enuresis
- With concurrent obesity \(ightarrow\) insulin resistance

Metabolic morbidity
- Dyslipidemia

Increased health care utilization
- Excessive daytime sleepiness

Obstructive sleep apnea
- Induction of inflammatory cascades
- Oxidative stress

Neurocognitive and behavioral functioning
- Hyperactivity attention deficits
- Impulsivity
- Concentration difficulties

Figure 1 Pathophysiological factors involved in pediatric OSA.
Abbreviations: FRC, functional residual capacity; OSA, obstructive sleep apnea.

Figure 2 Morbidity of pediatric OSA.
Abbreviations: BP, blood pressure; OSA, obstructive sleep apnea.
endothelial network may promote long-term susceptibility to pulmonary hypertension even during adulthood.\textsuperscript{49}

Notwithstanding, there is increasing evidence that OSA can impose even “subclinical” effects on the autonomic and cardiovascular systems and promote cardiovascular disturbances in blood pressure (BP) regulation, ventricular remodeling, and endothelial dysfunction, all of which can lead to far-reaching detrimental consequences if left unattended.\textsuperscript{51–66}

One of the earliest studies exploring the relationship between BP and OSA in children found that children with OSA tend to have higher diastolic BP during sleep compared with children with primary snoring.\textsuperscript{50} The degree of increase in BP during rapid eye movement (REM) sleep has also been shown to correlate with the severity of OSA,\textsuperscript{51} which is perhaps unsurprising considering that OSA, in the majority of children, tends to occur during REM sleep and that surges in arterial BP have been shown to occur after respiratory event termination.\textsuperscript{52} Amin et al studied slightly older children, and found that children with OSA had evidence of BP deregulation: they had significantly greater mean BP variability during wakefulness and sleep, a higher night-to-day systolic BP, and marked reductions in nocturnal dipping of the mean BP.\textsuperscript{53} In fact, children with OSA had night-to-day systolic BP ratios that surpassed the established cutoff ratios of 0.899 for females and 0.9009 for males, both of which are known to increase the risk for cardiovascular morbidity in adults.\textsuperscript{54} A few years later, the same group of investigators reported that children with OSA exhibit increases in morning BP surges, BP load, and 24-hour ambulatory BPs compared with healthy controls.\textsuperscript{55} Furthermore, these differences were associated with left ventricular remodeling, and the effects were apparent even in children with mild OSA. Interestingly, even habitually snoring children without evidence of OSA, ie, “primary snorers,” were also found to be at higher risk for elevations in systemic BP.\textsuperscript{56–58}

The evidence of left ventricular strain and reduced contractility reported by Amin et al\textsuperscript{55} led to exploration of potential mechanisms that may account for the left ventricular involvement in OSA. Among the various putative factors, assessment of changes in brain natriuretic peptide (BNP) seemed logical, considering that this 32 amino acid peptide is released by cardiac myocytes in response to cardiac wall distension. Indeed, overnight changes in BNP levels were found to be greater in children with moderate/severe OSA compared with mild OSA and controls,\textsuperscript{59} most likely related to the increased and more frequent negative intrathoracic pressure swings seen in more severe OSA, further supporting the presence of nocturnal cardiac strain in children who have moderate to severe OSA. It remains unknown whether the left ventricular changes associated with pediatric OSA are completely reversible or indicate a group of susceptible individuals at risk for more adverse cardiovascular disease during adulthood.

Endothelial dysfunction is thought to be an early precursor to atherosclerosis. Assessment of postocclusive hyperemic responses in children, using various methodologies, such as flow-mediated dilation, pulse arterial tonometry, and laser Doppler reperfusion kinetics,\textsuperscript{60–63} has revealed significant impairment in endothelial function among children with OSA compared with controls. Furthermore, although the majority of these children demonstrated resolution of the endothelial dysfunction following treatment with AT,\textsuperscript{64} a subgroup who also had a strong family history of cardiovascular disease did not show the anticipated improvements in endothelial function, suggesting that the effects of OSA in a genetically susceptible subset of children may persist for unknown periods of time, potentially into adulthood. As anticipated, in children with concurrent obesity and OSA, the magnitude of endothelial dysfunction was greater than when either condition was present in isolation, suggesting the convergence of the deleterious consequences of obesity and OSA.\textsuperscript{65–66}

The evidence for severity-dependent alterations in endothelial function was confirmed in children with OSA, using pulse arterial tonometry to derive the reactive hyperemia index, whereby significant differences in evening-to-morning changes of endothelial function emerged in children with OSA, and such overnight changes in endothelial function were closely associated with the severity of the disease.\textsuperscript{67} It should be stressed, however, that not every child with OSA manifests endothelial dysfunction.\textsuperscript{64} One potential explanation for the variance in endothelial phenotype of pediatric OSA may well reside in the intrinsic ability to recruit endothelial progenitors to the circulation via the release of stromal derived factor 1 (SDF-1).\textsuperscript{61}

C-reactive protein (CRP), an acute-phase reaction protein produced in the liver, has emerged as a robust and independent predictor of cardiovascular morbidity and is extensively used to stratify the risk for ischemic heart disease.\textsuperscript{68} It has been postulated that CRP may even participate directly in atheromatous lesion formation, through reduction of nitric oxide synthesis and induction of the expression of adhesion molecules in endothelial cells.\textsuperscript{67–68} Increased CRP levels have been demonstrated in children with OSA, correlate with severity of the disease, and decrease following effective treatment.\textsuperscript{69–72} It should be stressed that not all children with OSA have elevated CRP levels, as the interplay of genetic
variants in IL-6 and CRP genes as well as environmental factors plays an important role (Gozal et al\textsuperscript{27}). However, we would surmise that the children in whom CRP levels are elevated constitute a higher-risk group for the development of long-term cardiovascular complications. Indeed, markers of vascular injury and endothelial activation, such as adhesion molecules, myeloid-related protein 8/14, fatty acid–binding protein, and circulating microparticles have all been shown to be elevated in children with OSA and are associated with the presence of endothelial dysfunction.\textsuperscript{73–76} Efforts are now ongoing to develop a panel of biomarkers that may identify those children at risk for cardiovascular morbidity as a result of OSA.

**Metabolic system**

Although in adult cohorts OSA has been identified as an important risk factor for insulin resistance and diabetes,\textsuperscript{77–83} the presence of this association in children is not as clear cut and may well depend on factors such age, ethnicity, pubertal status, the degree of inflammatory response, and the concurrent presence of obesity.

In a community-based study of predominantly postpubertal adolescents, strong associations were demonstrated between OSA and the metabolic syndrome, as well as with individual metabolic parameters, such as fasting insulin and homeostatic model assessment (HOMA).\textsuperscript{79,84,85} Sleep fragmentation and intermittent hypoxia were also found to be associated with decreased insulin sensitivity in obese adolescent boys.\textsuperscript{86} In younger children, OSA was associated with reduced insulin sensitivity only when obesity was concurrently present,\textsuperscript{87,88} and effective treatment of OSA ameliorated HOMA in these children.\textsuperscript{89} However, when highly sensitive bioinformatics approaches and pathway analyses were employed, in conjunction with transcriptome microarray analyses, in children with primary snoring, alterations in insulin homeostatic mechanisms emerged and were further confirmed with HOMA in such children, suggesting that even mild perturbations in sleep may impose subclinical changes in peripheral tissue insulin receptor sensitivity.\textsuperscript{90}

OSA has also been implicated in rises in low-density lipoprotein (LDL) cholesterol with concomitant decreases in high-density lipoprotein (HDL) cholesterol, in both obese and nonobese children.\textsuperscript{89,91} Significant improvements in lipid profile were observed in all children after treatment of their OSA.

Even in childhood, evidence of end-organ morbidity, in the form of fatty liver disease, has been demonstrated in obese children with OSA.\textsuperscript{92–94} Of note, the treatment of OSA, usually with AT followed by continuous positive airway pressure (CPAP), in a large subset of these obese children resulted in improved liver serum aminotransferases in the majority of the patients.\textsuperscript{92}

**Neurocognitive and behavioral functioning**

The first seminal paper to highlight the potential causative links between OSA and its detrimental consequences on academic performance was published by Gozal in 1998.\textsuperscript{95} In a prospective study looking at 297 first-grade children whose school performance was in the lowest tenth percentile of their class, screening for OSA revealed a marked elevation in the prevalence of OSA. Furthermore, the children who were treated for OSA showed significant academic improvements in their school grades the subsequent year, while children who had OSA but who were not treated failed to improve academically. Since then, there have been numerous studies reporting the association between OSA and neurocognitive and behavioral morbidity, and several, albeit not all, studies have shown improvements in some of these functions after treatment.\textsuperscript{106–107} Impairments in executive functioning have also been reported: the Tucson Children’s Assessment of Sleep Apnea (TuCASA) study identified a negative correlation between AHI and immediate recall, Full Scale IQ, Performance IQ, and math achievement, while nocturnal hypoxemia adversely affected nonverbal skills.\textsuperscript{108} Children with OSA have also been shown to take longer and need more learning opportunities to learn a pictorial-based, short-term and long-term declarative memory test.\textsuperscript{109} From the behavioral standpoint, OSA and habitual snoring have been associated with hyperactivity, attention deficits, concentration difficulties, and impulsivity. Therefore, it should come as no surprise that such children are frequently misdiagnosed as having attention deficit hyperactivity disorder.\textsuperscript{110–112} Recent 5-year follow up results from the TuCASA study revealed that youth with untreated OSA exhibited hyperactivity, had attention problems and aggressive behaviors, lower social competencies, poorer communication, and/or diminished adaptive skills.\textsuperscript{113}

Notwithstanding such considerations, it is important to emphasize that not all children with OSA exhibit cognitive or behavioral deficits. It is therefore plausible that susceptibility modifiers, both genetic and environmental, may play a role in phenotypic expression.\textsuperscript{45} Accordingly, several genetic factors have been thus far been identified to account for discrepancies in the cognitive functional performance of children with OSA. For example, differences in systemic inflammatory
responses, as reported by plasma CRP levels, will differentiate children with OSA of similar severity who exhibit or do not exhibit cognitive deficits.\textsuperscript{114} Similarly, genetic variants in a gene critically involved in the formation of free radicals have been shown to account for discrepancies in cognitive outcomes in pediatric OSA.\textsuperscript{115} Additional factors, such as IGF-1 and apolipoprotein E allelic variants, have also been identified as either protective or detrimental to neurocognitive function.\textsuperscript{116,117}

Khadra et al further hypothesized that OSA causes changes in regional cerebral blood flow during sleep, thus favoring the occurrence of neurocognitive impairments.\textsuperscript{118} However, these investigators found that the situation was more complex than expected, with both arousal indices and mean arterial pressure being strongly associated with OSA severity. On the one hand, increasing arousal indices were associated with decreasing regional cerebral oxygenation and on the other hand, increasing mean arterial BP was associated with increasing regional brain oxygenation. In other words, OSA can both augment and decrease regional cerebral blood flow. A model based on the interplay between factors such as age, mean arterial pressure, oxygen saturation, REM sleep, gender, arousal index and NREM sleep has been proposed to predict the effect of sleep disordered breathing on regional cerebral oxygenation. The findings linking vascular function and cognitive outcomes were further confirmed in several additional studies, such that the presence of endothelial dysfunction in OSA may serve as a surrogate reporter of altered cognitive functioning.\textsuperscript{119,120}

As mentioned above, improvements in learning and behavior occur following treatment of OSA.\textsuperscript{107} However, some neurocognitive consequences may only be partially reversible if left too late,\textsuperscript{121} highlighting the importance of early diagnosis and prompt effective treatment.

**Excessive daytime sleepiness**

In contrast to adults, EDS does not tend to be as prominent a symptom in pediatric OSA. Nonetheless, children with OSA have been shown to have higher Epworth Sleepiness Scale (ESS) scores compared with controls (8.1 ± 4.9 versus 5.3 ± 3.9) (P < 0.001).\textsuperscript{122} Objective measurements of EDS using the Multiple Sleep Latency Test have shown that children with OSA have severity-dependent shortening of their sleep latencies but that EDS is relatively infrequent and tends to manifest among more severe and/or obese patients. Interestingly, the magnitude of sleep latency reduction has been shown to be associated with measures of systemic inflammation, such as plasma TNF-α level, the latter being modulated by polymorphisms in the TNF-α gene.\textsuperscript{37,123}

**Healthcare utilization**

Interestingly, children with OSA have been reported to have increased health care utilization compared with their peers, predominantly for respiratory infections.\textsuperscript{124,125} From their first year of life to the time of diagnosis, children with OSA had 40% more hospital visits, 20% more repeated visits, and higher prescriptions of medication.\textsuperscript{124} Although one might argue that children who have recurrent upper respiratory tract infections may be at higher risk of OSA or that children who have more contact with healthcare professionals are more likely to be screened for OSA, another prospective study by the same group showed that after treatment of OSA by AT, health care utilization was significantly reduced to the extent that total annual health care costs were reduced by a third.\textsuperscript{126} These findings have since been further confirmed in another population-based cohort.\textsuperscript{127}

**Nocturnal enuresis**

A higher prevalence of nocturnal enuresis has been reported in children with OSA.\textsuperscript{128–130}

It has been postulated that increased enuresis may be due to the dampening effects of OSA on arousal responses, to changes in bladder pressure, or potentially associated with secretion of the hormones involved in fluid regulation. A recent systematic review of the literature identified 14 studies investigating OSA and enuresis, in which a third of the total 3,550 children with OSA had a diagnosis of enuresis.\textsuperscript{129} In the seven studies with follow up data, post-AT improvements in enuresis occurred. However, the data were derived from studies with weak design and skewed cohorts, and randomized controlled trials are still needed to establish a more definitive cause–effect relationship between OSA and enuresis in children.

In children with sickle cell disease, a prospective, multicenter cohort study of 221 children demonstrated that enuresis was significantly associated with an AHI of >2/hr TST, after adjusting for age and gender.\textsuperscript{131} The authors recommended that children with sickle cell anemia who present with enuresis should be evaluated by a pulmonologist for sleep disordered breathing.

As mentioned previously in the context of nocturnal cardiac strain, changes in BNP have been demonstrated in children with OSA. As BNP increases sodium and water excretion and also influences hormones in the renin–angiotensin pathway and vasopressin, a population-based cohort study aimed...
to examine the relationship between BNP levels and enuresis in habitually snoring children. The presence of habitual snoring was associated with an increased prevalence of enuresis, and morning BNP levels were found to be elevated in children with OSA. Furthermore, children with nocturnal enuresis have been shown to have higher BNP levels compared with those without, at any degree of sleep disordered breathing severity, providing support to the hypothesis that sleep fragmentation and increased release of BNP secondary to OSA may contribute to the higher prevalence of enuresis in habitually snoring children.\textsuperscript{132}

**Diagnosis**

One of the major difficulties with the diagnostic process of pediatric OSA is the fact that history and clinical examination perform poorly. In a recent reassessment of this issue by the American Academy of Pediatrics (AAP), a positive predictive value of 65% for history and 46% for clinical examination were quoted,\textsuperscript{4} essentially representing a success rate equivalent to that of tossing a coin! Unsurprisingly, the AAP recommendations are that children with symptoms of OSA should be referred for further investigation.\textsuperscript{4}

In this context, the current gold standard for the diagnosis of OSA, as recommended by the AAP, is a nocturnal, in-lab polysomnography (PSG) study. A typical montage would include several electroencephalography (EEG) channels, chin and anterior tibial electromyography (EMG), bilateral electrooculography, pulse oximeter and pulse waveform, nasal pressure transducer, oronasal airflow thermistor, end-tidal capnography, chest and abdominal respiratory inductance plethysmography, body position sensor, microphone, and real-time synchronized video monitoring. Rechtschaffen and Kales devised the initial sleep staging system in 1968,\textsuperscript{133} which was in use for almost 40 years. The American Academy of Sleep Medicine (AASM) modified and updated the staging criteria in 2007 and further revised it in 2012, with sleep laboratories now scoring according to these newer AASM guidelines.\textsuperscript{134} This approach provides an objective, quantitative evaluation of disturbances in respiratory parameters and sleep patterns, thus allowing patients to be stratified into disease severities and thereby enabling clinicians to tailor clinical management accordingly. However, stratification into severity categories has thus far been performed empirically, without any critical evidence to support one classification approach versus another. There is as of yet, no international consensus regarding the AHI cutoff values for therapy initiation. The current accepted practice has consisted of the use of an arbitrary cutoff for AHI corresponding to $>3$ standard deviations beyond the mean of the normative AHI in healthy children. Most clinicians would agree that a child with an AHI $>5$/hour TST requires treatment and that a child with an AHI $<1$/hour TST does not have significant OSA. However, the interpretation of the AHI values in between these two cutoffs are fraught with great discord. Some algorithms have recently been proposed and recognize the importance of treating the patient and not just the values obtained from the sleep study.\textsuperscript{135,136} In addition to polysomnographically derived measures, these algorithms take into account factors such as the severity of symptoms, risk factors, and the presence of any OSA-related morbidity and may therefore provide a more coherent, clinically applicable approach to the diagnosis and prioritization of treatment, when OSA is diagnosed in children.

**Treatment**

AT is the primary treatment for pediatric OSA for children with adenotonsillar hypertrophy.\textsuperscript{117} The recently published Childhood Adenotonsillectomy Trial (CHAT), which constitutes the first-ever randomized controlled trial (RCT) for OSA, showed that compared with watchful waiting, the surgical treatment of OSA improved symptoms, behavior, and quality of life, even though improvements in the trial's primary endpoint, ie, neuropsychological measures of attention and executive function, did not occur.\textsuperscript{32} However, it is important to note that this study did not include children aged $<5$ years or children with moderate/severe OSA, as it would have been difficult to ethically justify withholding standard treatment from children with significant oxygen desaturation. Furthermore, similar to the findings reported in previous studies,\textsuperscript{28} (discussed below), the presence of particular risk categories, such as African American ethnicity and obesity, was associated with a reduced probability for normalization of the sleep study result after surgery.\textsuperscript{117}

Indeed, a large multicenter, retrospective study showed that although the majority of children had marked AHI improvements following AT, residual OSA was still frequent and clinically significant in a relatively large subset.\textsuperscript{28} Residual OSA was particularly prevalent in obese children, children who had severe OSA before surgery (AHI $>20$/hour TST), older children (those aged $>7$ years), and children with asthma.\textsuperscript{28} Similar findings have been reported in other studies involving vastly smaller cohorts. In addition, several other risk factors for residual OSA have been identified and include high Mallampati score, African-American ethnicity, craniofacial anomalies, chromosomal defects, and neuromuscular disease (including trisomy 21, achondroplasia,
Clinicians should be aware that (1) specific protocols may be needed to direct clinicians to automatically pursue postsurgical sleep studies in a subset of children at high risk for residual OSA; (2) the recurrence of OSA symptoms post-AT warrants reevaluation, particularly in children with the aforementioned risk factors. The role of other surgical procedures, such as tonsillotomy (in lieu of tonsillectomy) alone or in combination with adenoidectomy has not been established, even though advocates for these approaches claim similar outcomes with reduced postoperative pain.\textsuperscript{139,140}

In children who manifest residual OSA after AT or in those who present minimally enlarged upper airway or lymphadenoid tissues or who opt not to undergo surgery, positive airway pressure, in the form of CPAP or BiPAP (bilevel positive airway pressure), has been recommended.\textsuperscript{137} Although positive airway pressure can undoubtedly be a highly effective treatment,\textsuperscript{141,142} adherence can be particularly challenging in children, particularly those with behavioral problems or developmental delays. Behavioral modification techniques can improve adherence, but are time and labor intensive, often require admission to the inpatient service and therefore add substantial costs to their implementation, and are impossible to implement without a priori engagement with the child and family.\textsuperscript{143} Indeed, family and demographic factors have been shown to play a large role in CPAP adherence.\textsuperscript{144}

A possible and recently proposed alternative to mask-based positive airway pressure is high flow nasal cannula (HFNC) oxygen therapy. Although there has been only one study so far looking at 12 patients on HFNC,\textsuperscript{145} the reduction in AHI was comparable with that of CPAP, leading the authors to postulate that HFNC may be a viable and possibly more child-friendly alternative.

Since less invasive therapies are more desirable, there has been considerable interest in anti-inflammatory agents, particularly leukotriene-receptor antagonists (such as montelukast) and intranasal steroids.\textsuperscript{146} Tonsils from children with OSA have been shown to express increased levels of leukotriene receptors 1 and 2 compared with tonsils from children with recurrent tonsillitis.\textsuperscript{147} Furthermore, the application of leukotriene antagonists in an in vitro cell culture system of tonsillar tissues from children with OSA elicited dose-dependent reductions in cell proliferation and reductions in the secretion of the cytokines TNF-\(\alpha\), IL-6, and IL-12.\textsuperscript{148} In an open-label intervention study where children with mild OSA received 16 weeks of montelukast, significant reductions in adenoidal size and respiratory-related sleep disturbances occurred.\textsuperscript{149} These findings have since been reproduced in a recent double-blind, randomized, placebo-controlled trial.\textsuperscript{150}

Similarly, the use of in vitro steroids resulted in decreased proliferative rates of mixed tonsillar tissues, and in increased apoptosis and reduction in the secretion of the proinflammatory cytokines IL-6, IL-8, and TNF-\(\alpha\).\textsuperscript{151} A randomized crossover trial of 6 weeks treatment with intranasal budesonide for mild OSA showed reductions in the severity of OSA as well as in the size of adenoidal tissues. Importantly, discontinuation of therapy for 8 weeks did not promote the occurrence of rebound symptoms.\textsuperscript{152} Intranasal fluticasone has also shown similar results.\textsuperscript{153} Use of both montelukast and nasal budesonide for 12 weeks in children who had residual mild OSA after AT\textsuperscript{154} led to significant improvements in the AHI, nadir oxygen saturation, and in the respiratory arousal index, whereas no significant changes occurred over this time period in the control subjects. Anti-inflammatory therapy appears to be gaining wider acceptance in the treatment of mild OSA, such that studies examining the desirable optimal duration of treatment, longer term outcomes, combinatorial approaches, criteria for patient selection for optimal outcomes, etc, are critically needed.

In selected patient populations, some orthodontic procedures, such as rapid maxillary expansion, have been proposed as efficacious.\textsuperscript{155–157} Procedures such as tongue-base suspension and uvulopalatopharyngoplasty have also been studied in children with cerebral palsy and OSA.\textsuperscript{158} Recently, the use of more comprehensive assessments and interventions, including myofascial reeducation has been advocated in a series of uncontrolled studies.\textsuperscript{159–162}

In complex or persistent cases of OSA, sleep endoscopy is a technique that enables the exact level of obstruction in the child to be identified, thus facilitating site-specific surgical therapy.\textsuperscript{163,164} Further work to delineate the children who would benefit most from these procedures is needed, but some recent work in obese children and in children with trisomy 21 showed that lingual tonsils may contribute to residual disease and that lingual tonsillectomy may be effective in those cases.\textsuperscript{165–171}

**Future developments**

Although sleep studies provide an objective measure of sleep disturbance, it is now evident that measures derived from sleep studies are not predictive of OSA-associated morbidities, and therefore, their cost–efficiency in the management of habitually snoring children is less than perfect, particularly considering the high cost, intensity of labor, and family burden that such studies impose. It is possible that
home-based studies or more restricted multichannel studies may provide a more economical and accessible option in the future, once the appropriate validation studies are conducted. Alternatively, the identification and implementation of diagnostic biomarker approaches may be possible and merits further exploration.172

Another important issue in the context of the evaluation of habitually snoring children is the wide spectrum of phenotypic variance that exists in OSA. As with many other diseases, factors such as individual genetic susceptibility and environmental exposures/lifestyle play major contributing roles to the variance in phenotype. In other words, the optimal threshold for diagnosis and treatment is likely different in different children. Simply stated, not every child fulfilling current polysomnographic criteria for OSA manifests end-organ morbidity,173 and conversely, some children with primary snoring display neurocognitive or cardiovascular sequelae and/or signs of systemic inflammation, despite a normal sleep study.90,110

In the future, algorithms that incorporate measures derived from the sleep study, from blood or urine tests, and from clinical elements obtained during the history and physical examination may provide improved approaches to determining which children require treatment, which children may benefit most from a specific treatment, or which children are at risk for residual disease and require incremental therapies. There has been exciting research into urinary biomarkers as a potential measure. Preliminary data has shown an association between pediatric OSA and significant nocturnal alterations in urinary neurotransmitters.174 It is likely that the episodic hypoxemia and arousals that characterize sleep in OSA patients enhances sympathetic activity, therefore leading to increased levels of urinary epinephrine and norepinephrine. Overnight changes in the levels of three other neurotransmitters, notably increases in gamma-aminobutyric acid (GABA), decreases in taurine, and decreases in β-phenylethylamine (PEA) have appeared to differentiate children with OSA with neurocognitive deficits from those without.174

Conclusion
In summary, the recent decades since the initial description of pediatric OSA in 197645 have witnessed extensive and meaningful progress in research on the pathophysiology, morbidity, and treatment of pediatric OSA. However, there are still many fundamental questions to be answered. If the age of personalized medicine is to become a reality, a greater understanding of the mechanisms underlying the pathogenesis of the disease will be required to help develop novel biomarkers and individualized therapies.

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