

Pediatric Sleep Apnea Syndrome: An Update



Zhenhong Li, MD, PhD^a, Jocelyn Celestin, MD^a, and Richard F. Lockey, MD^b Albany, NY; and Tampa, Fla

Obstructive sleep apnea syndrome (OSAS) may be central neurologic (<5%) or obstructive (>95%) in origin and is a relatively prevalent condition in children. It affects 1%-5% of children aged 2-8 years and is caused by a variety of different pathophysiologic abnormalities. Cardiovascular, metabolic, and neurocognitive comorbidities can occur in both children and adults when left untreated. It also can cause severe behavioral problems in children. The American Academy of Pediatrics recommends that all children be screened with an appropriate history and physical examination for symptoms and signs suggestive of OSAS. The diagnosis is primarily made clinically and confirmed by polysomnographic findings. Treatment depends on the child's age, underlying medical problems, polysomnography findings, and whether or not there is upper airway obstruction usually secondary to enlarged adenoids and/or tonsils, allergic and nonallergic rhinitis, acute and chronic sinusitis, and other upper airway pathology. If enlarged adenoid or tonsils or both conditions exist, an adenoidectomy, tonsillectomy, or adenotonsillectomy remains the treatment of choice. Pharmacotherapy of OSAS has shown some effect in children with mild symptoms. This paper reviews the prevalence, pathophysiology, clinical presentation, diagnosis, and treatment of OSAS. © 2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2016;4:852-61)

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Obstructive sleep apnea syndrome (OSAS) is a sleep disorder that usually results from upper airway obstruction in both children and adults and causes episodes of complete or partial airway obstruction during sleep. It leads to increased respiratory effort, sleep

fragmentation, and alterations of gas exchange and is associated with numerous sequelae, primarily involving the cardiovascular, metabolic, and neurocognitive systems. Both central and peripheral factors can be related to OSAS. The former includes central nervous system impairment involving the respiratory control center. Examples of peripheral problems include structural abnormalities of the upper airway; obesity; adenoid and/or tonsil hypertrophy; inflammation of the upper airways; dental abnormalities, in particular, micrognathia; and neuromuscular diseases. Clinical signs and symptoms of OSAS can be both diurnal and nocturnal. Diurnal symptoms include mouth breathing, hyponasal speech, difficulty in awakening, morning headache, excessive daytime sleepiness, and napping. Depression, attention deficit, hyperactivity, aggressive behavior, and impulsivity also occur in children with OSAS often leading to poor school performance. Nocturnal symptoms include snoring, increased effort to breathe, witnessed apnea episodes, restless sleep, diaphoresis, unusual positioning during sleep, frequent awakenings, enuresis, and parasomnias. Polysomnography is the gold standard to diagnose the disease. Early recognition and treatment are very important with adenoidectomy and/or tonsillectomy (AT) remaining a first line of treatment for OSAS in most children. Medications including intranasal corticosteroid and oral montelukast may be helpful, in particular, for those subjects with OSAS associated with allergic rhinitis.

CASE

A 5-year-old boy complains of sneezing, itchy nose, nose rubbing, clear rhinorrhea, postnasal drip, nasal stuffiness, and intermittent sore throat for 3 to 4 years. Perennial nasal symptoms are worse in Florida during late January through April. His grandmother, the historian, states that he has been diagnosed with attention deficit hyperactivity disorder. He has insomnia, night sweats, props himself up on several pillows to sleep, and is a chronic mouth breather. He snores so loudly that it can be heard outside his bedroom. The grandmother thinks that he stops breathing periodically during sleep. His nasal symptoms are exacerbated by exposure to cats, dogs, dust, and mowing of the grass. He has no food, drug, or insect allergy. There are no animals, unusual hobbies or occupations practiced, or smoking in the home.

He has no history of nasal polyps, nasal or sinus surgeries, and trauma to the nose or face, and the teeth are in good condition. There is no history of recurrent ear infections, but he has had yellow and green nasal discharge for "months." There is no history of asthma.

The patient has a history of mild atopic eczema with associated pruritus since age 1, primarily in the antecubital and popliteal areas, which induces scratching. He does not scratch much at night.

^aDivision of Allergy and Immunology, Department of Internal Medicine, Albany Medical College, Albany, NY

^bDivision of Allergy and Immunology, Department of Internal Medicine, Morsani College of Medicine, University of South Florida, Tampa, Fla

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Corresponding author: Jocelyn Celestin, MD, Division of Allergy and Immunology, Department of Internal Medicine, Albany Medical College, 176 Washington Avenue Extension, Albany, NY 12203. E-mail: celestj@mail.amc.edu.

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Abbreviations used

AASM- American Academy of Sleep Medicine's
AHI- Apnea-hypopnea index
AT- Adenoidectomy and/or tonsillectomy
CAI- Central apnea index
IGF- Insulin-like growth factor
MCP-1- Monocyte chemoattractant protein-1
OSAS- Obstructive sleep apnea syndrome
PAP- Positive airway pressure
Pcrit- Pharyngeal critical pressure
PSG- Polysomnography

Past medical, social, and family histories are remarkable for a family history of atopy and "sinus trouble." He has had no other illnesses, surgery, or injuries, and the review of systems is otherwise unremarkable and noncontributory.

Physical examination revealed a well-developed, well-nourished cooperative male oriented as to time and place who seemed hyperactive. Vital signs were within normal limits. He was a mouth breather. A white-yellow discharge was noted in both nares with edematous turbinates and nasal obstruction. Tonsils were moderately enlarged. The rest of the examination was unremarkable. A diagnosis of allergic rhinoconjunctivitis, mild atopic eczema, sleep apnea, and chronic sinusitis was made.

He underwent prick/puncture skin tests to the major aeroallergens of the Tampa Bay Area, which were markedly positive to tree pollens, consistent with the exacerbation of allergic rhinoconjunctivitis during the spring, and to the major weeds, grasses, cat, and dog.

Sleep apnea symptoms were reconfirmed in a 3-week follow-up. He subsequently underwent a tonsillectomy and adenoidectomy. He returned to the clinic 3 weeks after the surgery essentially asymptomatic. His insomnia, night sweats, and snoring had resolved and his hyperactive behavior improved dramatically. He continued on intranasal fluticasone 50 µg one puff each nostril twice daily. He was asked to remain on a daily basis of the lowest dose of fluticasone that controls his nasal symptoms and return to the clinic in late December or early January, before the oak season in Florida, at which time adjustments would be made in his medications in preparation for the spring season.

EPIDEMIOLOGY

Up to 50% of children may experience a sleep problem.^{1,2} However, from that group only 1%-5% will end up been formally diagnosed with OSAS.³⁻⁵ OSAS has a peak incidence around 2-8 years of age, most likely due to the relative size of the adenoids and/or tonsils versus the diameter of the upper airway.⁶ Since the first case report of pediatric OSAS in 1976,⁷ much has been learned about this disease. First, the prevalence of OSAS in children varies from 1% to 5%³ and is more common in males than females.⁸ Second, Americans of African descent and obese children are both at increased risk for OSAS.⁸⁻¹⁰

PATHOPHYSIOLOGY

The pathophysiology of OSAS is not fully understood; however, factors that effectively decrease airway caliber or increase upper airway collapsibility can predispose to airway collapse that include anatomic, genetic, and neuromuscular factors as well as consciousness alterations during sleep stages and anesthesia (Table I). Systemic or upper airway inflammation, associated with allergic

TABLE I. Pathogenesis of pediatric OSAS

Anatomic obstruction	Adenotonsillar hypertrophy Craniofacial anomalies Hypertrophy and/or hyperplasia of cervical lymphoid tissue Nasal obstruction
Neuromechanical dysfunction	Peripheral: Congenital or acquired muscle hypertonia and/or hypotonia Central: Decreased central ventilator drive
Obesity	Upper airway fatty infiltrate Increased abdominal visceral fat Decreased functional lung capacity
Genetic and/or environmental factors	Ethnicity Genetic polymorphism Sedative drugs Airway irritants: Cigarette smoking, respiratory virus Family history
Inflammation	Rhinosinusitis Asthma Nasal polyps Increased systemic inflammatory markers

and nonallergic rhinitis and acute and chronic sinusitis, is also a risk factor for airway occlusion. The proper interaction of the neurologic, muscular, and bony structures is very important to maintain airway patency, which follows the Starling resistor model with rigid upstream (nasal passages) and downstream (trachea) segments and a collapsible region between. The pharyngeal region, mostly surrounded by soft tissue, collapses with the high surrounding pressure. Pharyngeal critical pressure (Pcrit) is the term used for the pressure at which point the airway collapses. In children, with adenoid and/or tonsil hypertrophy, associated with OSAS, both the pressure from the nose (upstream) and trachea (downstream) are lower than the Pcrit, which causes partial or complete occlusion of the airway. The pharyngeal patency is maintained by a group of pharyngeal dilators that are modulated by the respiratory control center. During sleep, the central respiratory drive that contributes to the factors that cause dilatation decreases, causing a reduction in pharyngeal size and a concomitant increase in upper airway resistance.¹¹⁻¹³ The pharyngeal dilator activity decreases more during rapid eye movement (REM) sleep in children¹⁴ compared with adults, which correlates with the fact that OSA occurs predominantly during REM sleep in children. This repetitive cycle of upper airway collapse during sleep results in OSA with hypoxia and sleep fragmentation.

ETIOLOGY AND RISK FACTORS

Upper airway edema and narrowing

The most common anatomic cause of upper airway narrowing in children is adenoid and/or tonsil hypertrophy. The retropalatal area has the smallest cross-sectional area making it the most common site of obstruction. The adenotonsillar tissue is largest between ages 3 and 6, correlating with the peak incidence of OSAS.^{15,16} However, the exact correlation between adenotonsillar size and OSAS severity is unclear.¹⁷ Hypertrophy and/or hyperplasia of the lymphoid tissue in the upper airway, allergic or nonallergic rhinitis, and infectious rhinosinusitis are all associated with nasal mucosal edema and are risk factors for OSAS.¹⁸ Histamine, cysteinyl leukotrienes, IL-1β, and IL-4 are all

TABLE II. Clinical symptoms of OSAS

Clinical presentation of OSAS	References
Diurnal	54-59
Daytime sleepiness	
Difficulty awakening	
Headaches	
Hyponasal speech	
Nasal congestion	
Inattention	
Hyperactivity	
Impulsivity	
Depression	
Mood instability	
Irritability	
Aggression	
Nocturnal	54,60-63
Snoring	
Witnessed apnea	
Mouth breathing	
Snorting and/or gasping	
Restless sleep	
Paradoxical chest wall movement	
Diaphoresis	
Unusual sleep position	
Sleep terrors	
Sleep walking	
Frequent awakenings	
Nocturnal enuresis	

associated with allergic rhinitis. Children with craniofacial anomalies such as midfacial hypoplasia, retro/micrognathia, nasoseptal obstruction, and macroglossia are also at increased risk of developing OSAS and may have residual OSAS symptoms after adenoidectomy, tonsillectomy, or both.

Obesity

Obesity is a significant risk factor for OSAS in children, although less common than adenoid and/or tonsil enlargement. Shorter sleep times and greater oxygen desaturation were observed in obese children.¹⁹ Each kg per m² increment in body mass index above the 50th percentile, adjusted for gender and age, is associated with a 12% increased risk for OSAS. Forty-five percent of obese children with OSAS also have evidence of adenoid and/or tonsil hypertrophy⁶ and are more likely than nonobese children to have residual OSAS symptoms after their removal. Obesity causes upper airway narrowing due to multiple mechanisms. First, fatty infiltrate in the soft tissue along the airways results in upper airway narrowing and increased pharyngeal collapsibility. Secondly, increased visceral fat impinging on the chest wall leads to reduced lung functional residual capacity making these subjects more vulnerable to hypoxemia during sleep. In addition, lung volume reduction predisposes to airway collapse by reducing tracheal traction and airway stability.^{20,21}

Neuromuscular dysfunction

Neuromuscular and anatomic factors often cause OSAS, especially in children with craniofacial malformations such as

TABLE III. Physical findings associated with OSAS

Physical manifestation	References
Obesity	3,31,54,64-71
Poor growth	
Long face syndrome	
Midfacial hypoplasia	
Micrognathia and/or retrognathia	
Eye shiners	
Nasal atrophy	
Nasal mucosa swollen	
Deviated nasal septum	
Bulging nasal turbinate	
High arched palate	
Hypertrophied tonsils	
Cross bite/overbite	
Macroglossia	
Oropharynx crowding	
Systemic hypertension	
Loud P2	
Extremity edema and/or clubbing	

Down syndrome (trisomy 21) that has unique physical characteristics including midface anomalies, small upper airway, hypoplasia, macroglossia, and cranial base anomalies. In addition, any congenital or acquired conditions that affect the respiratory control center can lead to the development of OSAS. Examples include myelomeningocele, Arnold Chiari malformation, and brain injuries from trauma, tumors, surgery, or radiation. Arousal from sleep is a protective response to upper airway obstruction as well as hypoxemia and hypercapnia. OSAS children have slightly elevated arousal thresholds to hypercapnia and thus tend to wake up at a higher pCO₂.^{22,23} Insufficient gas exchange might be responsible for some of the clinical presentations of OSAS, such as sleep fragmentation, unrefreshed sleep, difficulty awakening, and morning headaches. Alternated muscle tone, such as hypertonia and hypotonia, associated with cerebral palsy, congenital muscular dystrophy, myotonic dystrophy, or cervical spinal cord injury are the most common peripheral neuromuscular factors that contribute to OSAS.

Inflammatory factors

Inflammation also might play a role in the development of OSAS. Evidence exists to demonstrate that systemic inflammatory markers such as C-reactive protein (CRP), TNF- α , IL-6, IL-8 IL-1 α , IL-1 β , and IFN- γ are elevated in subjects with OSAS, together with a concomitant reduction of anti-inflammatory factor IL-10, suggesting a tilted proinflammatory state in OSAS.²⁴⁻²⁷ A similar persistent inflammatory condition has been observed in insulin resistance and vascular dysfunction.²⁸ For instance, adipocytes, especially in obese subjects, secrete a variety of proinflammatory cytokines, such as TNF- α , IL-6, leptin, plasminogen activator inhibitor-1 (PAI-1), and adiponectin,²⁹ some of which have been shown to impair insulin signaling, which therefore leads to insulin insensitivity.³⁰ Levels of matrix metalloproteinase-9 (MMP-9), monocyte chemoattractant protein-1 (MCP-1), leptin, and PAI-1 are usually high in obese children with OSAS and decrease significantly after AT.^{25,31} MMP-9 is capable of degrading type IV collagen, and hence

causes basement membrane damage and leads to endothelial dysfunction.³² Continuous release of MCP-1 by activated endothelial cells attracts macrophage migration, resulting in inflammation perpetuation.³³ PAI-1 is an inhibitor of tissue plasminogen activator and suppresses plasma fibrinolysis. High leptin levels were found in patients with OSAS and strongly associated with apnea-hypopnea index (AHI).³⁴ Elevated PAI-1 is implicated in the endothelial dysfunction and atherothrombosis.²⁵ Other immunological changes, such as a Th17:Treg imbalance,³⁵ elevated nuclear factor kappa B³⁶ and endothelial dysfunction also were shown to be associated with the severity of OSAS.³⁷

Acute or chronic inflammatory conditions, as previously discussed, including various forms of rhinitis, with or without nasal polyps and paranasal sinusitis are also known risk factors for pediatric OSAS. Studies demonstrate that children with adenoid hypertrophy and chronic rhinosinusitis have improved outcomes when treated with a combination of adenoidectomy and antibiotics compared with children treated with adenoidectomy alone.³⁸⁻⁴¹

Genetics

Genetic association has been demonstrated in the pathogenesis of pediatric OSAS; however, the exact mechanisms are unclear. Some clinical syndromes have been associated with OSAS including Prader-Willi and Bechwith-Wiedemann.^{42,43} Specific gene polymorphisms, for example, the ApoE4 allele,^{44,24} TNF- α -308G gene polymorphism, nicotinamide adenine dinucleotide phosphate polymorphism,^{45,46} and mucopolysaccharidosis⁴⁷ are associated with pediatric sleep disordered breathing and OSAS.

Other potential risk factors

A study by Snow and Goldbart demonstrated that children who had respiratory syncytial virus bronchiolitis in infancy had significant higher obstructive apnea/hypopnea index compared with those who did not.^{40,41} Familial aggregation of OSAS has been demonstrated by Redline et al⁴⁸ and Sundquist et al.⁴⁹ Environmental factors including seasonal allergies and cigarette smoking exacerbate upper airway symptoms thus aggravate upper airway obstruction.⁵⁰ Currently, there is no evidence to suggest that sedatives have deleterious effects on the severity of pediatric OSAS. However, most studies were small and of short duration. Caution is still required when prescribing sedatives to subjects with OSAS.⁵¹

CLINICAL PRESENTATION

OSAS disrupts normal sleep patterns and normal ventilation and often results in gas exchange abnormalities and sleep fragmentation.⁵² Hill in *BMJ* described the symptoms of OSAS in the 19th century as follows: "The stupid-lazy child who frequently suffers from headaches at school, breathes through his mouth instead of his nose, snores and is restless at night, and wakes up with a dry mouth in the morning, is well-worthy of the solicitous attention of the school medical officer."⁵³ This description still applies to pediatric subjects with OSAS. The symptoms, signs, and physical findings are listed in Tables II and III.

MORBIDITIES ASSOCIATED WITH OSAS

Cardiovascular system

Sustained hypoxia in severe untreated OSAS increases pulmonary vascular vasoconstriction and endothelial dysfunction thus promoting long-term susceptibility to pulmonary hypertension, cor pulmonale, and right heart failure.⁷² Increased brain natriuretic peptide was found in children with moderate to severe OSAS supporting the presence of left ventricular strain in these children population.⁷³ Children with a high CRP level have an increased risk for cardiovascular complications^{74,75} and systemic hypertension may also occur.⁷⁶ Elevated levels of adhesion molecules, myeloid-related protein 8/14, fatty acid-binding protein, and circulating microparticles, markers of vascular injury and endothelial activation, all have been demonstrated in children with OSAS.⁷⁷⁻⁷⁹

Neurocognitive and behavioral functioning

Cognitive deficits associated with OSAS include poor school performance, impaired learning^{19,80} (information processing and memory), poor language and/or verbal skills, hyperactivity, low general intelligence, and diminished adaptive function.⁸¹ Alterations in regional cerebral blood flow during sleep, intermittent hypoxia, that leads to increased oxidative stress and inflammation response, lipid peroxidation, and subsequent cellular damage as well as genetic and environmental factors might account for neurocognitive impairment.^{24,82,83} Children show a significant academic improvement, although not uniformly, after receiving OSAS treatment.⁸⁴

Metabolic consequences

Metabolic syndrome is the clustering of obesity, insulin resistance, hypertension, and dyslipidemia. The association between OSAS and insulin resistance and diabetes in children is not as clear-cut as in adults. However, some studies did show that sleep fragmentation and intermittent hypoxia in obese children were associated with decreased insulin sensitivity.⁸⁵⁻⁸⁸ Fatty liver disease and dyslipidemia (elevated low-density lipoprotein and decreased high-density lipoprotein) have both been described in children with OSAS.^{85,89,90} Excessive work of breathing, reduction of insulin-like growth factor (IGF) and IGF binding protein 3 as well as elevated leptin levels have been associated with failure to thrive.⁹¹⁻⁹⁴

DIAGNOSIS

Early diagnosis and treatment of pediatric OSAS are very important, yet challenging. Guidelines published in 2012 recommend screening every child and adolescent for snoring and sleep apnea-related signs and symptoms.⁹⁵

Clinical history and physical examination

Using clinical symptoms alone or in combination with physical findings is inadequate to accurately diagnose OSAS.⁹⁶ Studies of certain parameters, such as excessive daytime sleepiness, snoring, and learning problems, were all found to have a weak association with the severity of OSAS.⁹⁷ One pediatric sleep questionnaire survey has a sensitivity of 85% and specificity of 87%⁹⁸; however, a follow-up of the same study only demonstrated a sensitivity of 78% and a specificity of 72%. These questions are only recommended to suspect sleep apnea.⁹⁹ If the answers to the questionnaire are positive, definitive diagnostic studies are warranted.

Polysomnography

The nocturnal in-lab polysomnography (PSG) study, recommended by American Academy of Pediatrics, remains the gold standard for diagnosing OSAS. It should be performed and interpreted in accordance with the recommendations of the American Academy of Sleep Medicine's (AASM) Manual for the Scoring of Sleep and Associated Events. PSG is indicated for preoperative evaluation for subjects with sleep apnea to assess the response to treatment. It is also indicated for other respiratory disorders when there is suspicion of accompanying sleep-related breathing disorders. Some of these include cystic fibrosis, pulmonary hypertension, bronchopulmonary dysplasia, and kyphoscoliosis.

Other tests

Nap PSG records sleep and breathing in a sleep laboratory during daytime. Its sensitivity ranges from 69% to 75% and specificity from 60% to 100%. It is insufficient to rule out OSAS because of the short recording time and the possibility of missing the REM sleep stage.¹⁰⁰ Home videotaping has a sensitivity of 89% and specificity of 77%,¹⁰¹ whereas audio taping has a sensitivity of 43%-86% and specificity of 67%-80%.¹⁰²

Nocturnal pulse oximetry to detect oxyhemoglobin desaturation is cost effective, widely available, and easy to apply, especially where pediatric PSG is not available. However, false positive results can occur because of movement artifact. A negative or inconclusive oximetry result requires a subsequent PSG to definitely rule out OSAS.¹⁰³

Ambulatory PSG, or home PSG, which is an unattended sleep study, is considered appropriate for adults. However, there is paucity of evidence for adequacy in children. Three studies have shown variable sensitivity and specificity for diagnosing pediatric OSAS. It might be technically feasible in school-aged children; however, further studies are needed.¹⁰⁴⁻¹⁰⁶ Electro and echocardiographs and a chest x-ray should be performed, when necessary, for children with suspected OSAS to rule out underlying cardiopulmonary diseases. A study by Gutierrez-Tobal et al¹⁰⁷ found that the spectrum information contained in airflow recordings is helpful in the diagnosis of pediatric OSAS.

Biomarkers

Biomarkers are noninvasive and easy to use in both compliant and noncompliant children. The combined measurement of Kallikrein-1, uromodulin, urocortin-3, and orosomucoid-1 may have enough accuracy to be used as OSAS diagnostic tests in children.^{108,109} Serum alpha amylase level,¹¹⁰ urinary 8-isoprostane,^{111,112} cysteinyl leukotrienes, and lipocalin-type prostaglandin D synthase may be used as specific inflammatory markers to predict the severity of OSAS.¹¹³ A study by Park et al¹¹⁴ showed that salivary cortisol level was negatively associated with OSAS severity and can be a useful biomarker for OSAS. Another study by Chou et al¹¹⁵ reported that central apnea index (CAI) is negatively correlated with age. Thus, younger children with OSAS have a significant higher CAI than older ones. However, all these tests demonstrated variable sensitivity and specificity. Clinicians should be familiar with these variables when choosing the test and consider full PSG if the test results are inconclusive.

Diagnosis criteria

Two criteria, as defined by the AASM,¹¹⁶ are needed to diagnose childhood OSAS.

1. Criteria 1: Presence of one or more of the following clinical symptoms: Snoring; labored, paradoxical, or obstructed breathing during sleep; excessive sleepiness; behavioral problems; hyperactivity or aggressive behavior; growth impairment or learning problems.
2. Criteria 2: One or both of the following PSG findings:
 - (a) One or more obstructive apneas, mixed apneas, or hypopneas per hour of sleep.¹¹⁷
 - (b) Twenty-five percent of total sleep time with hypercapnia ($\text{PaCO}_2 > 50$ mm Hg) in association with one or more of the following: snoring, flattening of the nasal pressure waveform, or paradoxical thoracoabdominal motion.

There is no clear-cut classification of severity for childhood OSAS. The diagnosis is usually made when there are relevant symptoms and an AHI greater than 1 per hour of sleep in a laboratory-based sleep study. The severity of OSAS is classified based on a combination of apnea index and other additional sleep study findings.

TREATMENT

There are various therapeutic options for childhood OSAS, and treatments are based on the child's age, underlying medical conditions, and PSG findings.

Surgery

Adenoidectomy and/or tonsillectomy are the treatment of choice for adenotonsillar hypertrophy. The Childhood Adenotonsillectomy Trial (CHAT study), a large randomized clinical trial conducted in 2013, demonstrated that early surgical treatment had better outcomes compared with watchful waiting.⁸⁴ However, the latter may be a reasonable option for several months in children with a low OSAS symptom burden, especially mild snoring and low AHIs without obesity.¹¹⁸

The complication rates of AT are minimal for most children including a temporary decreased oral intake due to localized pain. More severe complications are rare and include dehydration due to poor oral intake, bleeding, secondary infection, respiratory compromise, velopharyngeal insufficiency, and subglottic stenosis. Post-tonsillectomy death is rare (2 deaths in 36,221 tonsillectomies).¹¹⁹ Life-threatening complications from anesthesia, such as laryngospasm and/or bronchospasm, can occur but likewise are rare. Benedek et al¹²⁰ demonstrated in their study that no complications were found in mild OSAS cases; however, complications were noted in 12% of moderate and 51% of severe groups, respectively. Increased severity of OSAS and young age are all associated with increased rate of complications.¹²¹ Guidelines published by American Academy of Pediatrics in 2012 recommend postoperative admission for children under age 3, who are obese, or have serious comorbidities or severe OSAS ($\text{AHI} > 24/\text{hour}$, peripheral capillary oxygen saturation [SpO_2] nadir $< 80\%$ and/or end-tidal CO_2 peak > 60 mm Hg on PSG).^{122,123} A study by Thongyam et al¹²⁴ in 2014, found that age < 3 years, Americans of African heritage, and perioperative PSG findings (SpO_2 nadir $< 80\%$ and/or peak $\text{CO}_2 > 60$ mm Hg) were strong predictors for postoperative respiratory complications. High-risk children require careful perioperative management including corticosteroids use to minimize pharyngeal edema and Continuous Positive Airway Pressure (CPAP) or Bilevel Positive Airway Pressure for airway support. The majority

of children experience a significant improvement after surgery. OSAS symptoms persist in approximately 19% to 73% of children using $AHI \geq 1$ as the criteria. However, if using $AHI \geq 5$ as the criteria, the estimated persistence of OSAS ranges from 13% to 29%.³

Uvulopalatopharyngoplasty and tongue reduction surgery have been performed in children with OSAS with poor muscular tone and/or macroglossia and with cerebral palsy and Down and Beckwith-Wiedemann syndromes.¹²⁵⁻¹²⁷ Tracheotomy is reserved for severe refractory OSAS.

Medications

Less invasive therapies are always desirable. There have been numerous trials using corticosteroids and/or leukotriene receptor antagonists. Five days of systemic corticosteroids failed to show any therapeutic effect in an open-label pilot study by Brouillette et al in 1997.¹²⁸ Topical glucocorticosteroid administered via a nasal spray has demonstrated some efficacy in children with OSAS. Triple-blinded, randomized, controlled trials in 25 children with mild to moderate OSAS conducted by Brouillette et al¹²⁹ demonstrated a significant reduction in the obstructive AHI, and a decreased mixed/obstructive apnea/hypopnea index and decreased frequencies of hemoglobin desaturation, respiratory movement/arousals terminating apneas and hypopneas, after treatment with intranasal fluticasone for 6 weeks. An open study by Alexopoulos et al¹³⁰ in 2004 demonstrated that 4 weeks of nasal budesonide improved both polysomnography findings and clinical symptoms in children with mild sleep-disordered breathing. The clinical effect was maintained for 9 months after treatment. A double-blind, randomized, crossover trial by Kheirandish-Goza and Goza¹³¹ showed that 6 weeks of treatment with intranasal budesonide effectively reduced the severity of mild OSAS and the magnitude of adenoidal hypertrophy in 62 children; this effect persisted for at least 8 weeks after cessation of therapy. A randomized, double-blinded, placebo-controlled trial by Chan et al¹³² in 2015 indicated that 4 months of treatment with intranasal mometasone furoate effectively reduced the severity of mild OSAS and appeared to be more effective in the subgroup with allergic rhinitis. A study by Mansfield et al¹³³ in 2004 demonstrated that intranasal budesonide improved the nasal symptoms and daytime quality of life in children with OSAS with allergic rhinitis. Therefore, topical glucocorticoids may be considered as a treatment modality for mild to moderate OSAS.

Studies investigating the role of leukotriene therapy for childhood OSAS are relatively scarce. There are 3 studies (1 double-blind, placebo-controlled study and 2 open-labeled studies) investigating the effects of leukotriene receptor antagonists on OSAS in children. Of the 3 studies, 2 yielded positive results. Leukotriene receptor antagonists improve OSAS symptoms possibly because of the reduction of inflammatory mediators and nasal congestion.¹³⁴ In a prospective, double-blind, randomized trial, 46 children with nonsevere OSAS were treated with montelukast 4 or 5 mg (<6 or >6 years of age, respectively) for 12 weeks. There was a significant improvement in nocturnal respiratory disturbance, clinical symptoms, and adenoid size.¹³⁵ An open-labeled, nonrandomized 16-week study of montelukast in children with mild OSAS found a significant improvement in the AHI (AHI decreased from $3.0 \pm 0.2/\text{hour}$ to $2.0 \pm 0.3/\text{hour}$; $P = .017$) and a significant reduction in adenoid size and respiratory-related sleep disturbances.¹³⁶

Another small open-labeled, nonrandomized, 12-week study of combined montelukast and intranasal budesonide use in 22 children with residual OSAS symptoms after AT found a significant improvement in the AHI (from $3.9 \pm 1.2/\text{hour}$ to $0.3 \pm 0.3/\text{hour}$; $P < .001$) as well as in the nadir arterial oxygen saturation (from $87.3\% \pm 1.2\%$ to $92.5\% \pm 3.0\%$; $P < .01$).¹³⁷ More studies in larger populations with longer follow-up are needed.

There is no consensus as to the role of antibiotics in the management of adenotonsillar hypertrophy and OSAS. A prospective, randomized, double-blinded, placebo-controlled trial by Sclafani et al¹³⁸ in 1998 demonstrated that a 30-day treatment with amoxicillin and clavulanate reduced the need for surgery in the short term (1 month follow-up). In their study, tonsils from 25 randomly selected children (of 167) were cultured and were all positive for bacteria. Another double-blinded, prospective clinical trial in 2005 suggested that a course of a broad-spectrum antibiotic may be effective in temporarily improving OSA due to adenotonsillar hypertrophy accompanied by a bacterial infection, however, the improvement is not large enough to obviate the need for surgery.¹³⁹

Positive airway pressure

Positive airway pressure (PAP) is not recommended as a first line therapy for OSAS when surgery is an option. However, in a child who has failed or has a contraindication for surgical treatment, PAP remains the most common nonsurgical therapy. Indications for PAP therapy include persistent OSAS symptoms despite AT, a child who has minimal adenotonsillar tissue, or when surgery is contraindicated.⁹⁵ Complications of PAP include conjunctivitis and skin ulceration and/or discoloration around the face that can be avoided by making sure that the mask fits appropriately on the face. Nasal congestion and rhinorrhea are common complaints that improve with humidification, where appropriate, and nasal corticosteroids. Adherence can be a major barrier to effective PAP use.¹⁴⁰ Behavior modification techniques,¹⁴¹ heated humidity/tubing, extended ramp time, and longer (8- or 10-foot) tubing improve adherence. Long-term multidisciplinary follow-up to assess facial development and mask adjustment is essential for all children who are on PAP therapy because of the possible complications from the treatment and airway pressure changes as children grow.¹⁴²

Studies have shown improvement of OSAS symptoms and the AHI after rapid maxillary expansion.¹⁴³⁻¹⁴⁵ Nasal breathing training and exercise have shown some efficacy in a few small studies. However, the nasal expiratory resistor device has demonstrated variable response.

Other behavioral therapies include weight loss, positional therapy, proper sleep hygiene, and avoidance of indoor and outdoor pollutants and allergens. Currently, there are no significant data to support the use of oxygen supplement via nasal cannula.

FUTURE RESEARCH

Nocturnal PSG remains the gold standard for diagnosis of OSAS. However, it is costly, time consuming and not always available. Other tests for OSAS diagnosis have variable sensitivity and specificity. Well-designed, large prospective studies are needed to determine the validity of these screening tools in the diagnosis of OSAS. In terms of noninvasive tests, systemic

inflammation has shown association with OSAS. Further studies are required to determine whether biomarkers are potentially useful tools for diagnosing OSAS and monitoring the response to treatment. AT continues to be the first-line treatment for children with OSAS with adenotonsillar hypertrophy. However, a number of questions remain unanswered: How strongly does the clinical improvement of OSAS correlate with the resolution of its complications? What are the PSG parameters that predict post-operative complications? Although CPAP is efficacious in the treatment of OSAS, compliance is a major issue. More educational work needs to be done to improve CPAP compliance. Nasal corticosteroid and montelukast have demonstrated efficacy in ameliorating mild OSAS. More studies in larger populations with longer follow-up are needed to determine the optimal duration, therapeutic benefit and adverse effects of medical management compared with surgery.

CONCLUSION

OSAS is a very common and serious cause of cardiovascular, metabolic, neurocognitive, and behavioral functioning morbidity in children. The prevalence of OSAS in the pediatric population is increasing. This represents a major, yet poorly addressed public health burden, with many years of potential consequences for affected individuals, their families, and society. There has been extensive and meaningful research progress on the pathophysiology, morbidity, and treatment of pediatric OSAS since it was first described in 1976. Despite this, OSAS may be under-diagnosed and unrecognized. Clinicians need to have a high index of suspicion when assessing children with breathing problems during sleep. Early diagnosis and prompt medical intervention is crucial to prevent severe complications.

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