REVIEW ARTICLE

Pediatric Obstructive Sleep Apnea

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Indian J Sleep Med 2006; 1.3, 131-140

Introduction

The global spectrum of sleep related breathing disorders encompasses more than a dozen disorders ranging from central and obstructive sleep apnea syndromes to primary snoring (1). Pediatric obstructive sleep apnea (OSAS), a highly prevalent condition affecting at least 2-3% of children, is the leading cause for referral to our pediatric sleep medicine center. However, awareness among pediatricians in many areas of the developed and developing world regarding OSAS and its consequences is low (2, 3). Recently published statements and health supervision guidelines by the American Academy of Pediatrics (4-6) endorse and underscore the clinical and public health importance of this condition.

Obstructive sleep apnea syndrome (OSAS) was initially described by McKenzie in 1880 (7). However, nearly a century elapsed before the importance of this disorder in children was recognized (8). Although pediatric OSAS is similar to its adult counterpart in many ways, it also exhibits unique peculiarities encompassing not only its epidemiology, but also its pathophysiology, clinical manifestations, diagnostic criteria, and approaches to management. While a comprehensive discussion of OSAS in children is clearly beyond the scope of this chapter, the reader is directed to excellent resources in the suggested readings section.

The Pediatric OSAS spectrum

The second edition of the International Classification of Sleep Disorders (ICSD) distinguishes adult and pediatric varieties of sleep apnea. Pediatric OSAS is characterized by prolonged partial upper airway obstruction, intermittent complete obstruction or partial obstruction (obstructive apnea or hypopnea), or both prolonged and intermittent obstruction that disrupts normal ventilation during sleep, normal sleep patterns, or both (1).

The currently accepted gold standard in the diagnosis of OSA remains the overnight polysomnogram in the sleep laboratory (4). Physiologically, children have relatively lower functional residual lung capacity and higher respiratory rates than adults. Not surprisingly, the criteria used for scoring apneas and hypopneas are different from those used in adults. As such, *obstructive apnea* is defined as the cessation of oro-nasal airflow for two respiratory cycle lengths (instead of the 10 sec adult criterion) in the presence of ongoing respiratory efforts. *Hypopnea* is identified when a distinct fall (usually >30-50%) in the oro-nasal thermistor airflow signal occurs with continued breathing efforts, and is associated with either a 3 sec EEG defined arousal or an oxyhemoglobin desaturation (> 3-4%) on pulse oximetry (Fig 1). *Central apnea* occurs when there is no airflow and absent respiratory effort, with duration being usually >15 sec or associated with hypoxemia. *Mixed apnea* shows features of both obstructive and central apnea. *Obstructive hypoventilation* is characterized by periods of prolonged partial airway obstruction associated with hypercarbia, arterial oxygen desaturation, or both (Fig 2). The pattern here is distinct from the cyclical obstructions and desaturations seen with the “classical” OSA in adults. *Upper airway resistance syndrome* (UARS) is defined by a pattern of repetitive increases in inspiratory effort with ensuing EEG arousals and sleep fragmentation, but without obvious changes in the airflow signal (1). Some of the methods used to assess these events are described elsewhere in this volume.

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Based upon these polysomnographic features the clinical spectrum of OSAS has been suggested to range from *primary snoring* (no associated polysomnographic or neurobehavioral abnormalities), to UARS, obstructive hypopnea/hypoventilation, and finally, frank OSA (9).

Epidemiology

OSAS occurs in children of all ages, including young infants. However, the age spectrum of 2-8 years is most commonly affected, likely related to disproportionate growth of adenotonsillar tissues in the upper airway of vulnerable children. The stimuli and determinants of such lymphadenoid tissue proliferation and hyperplasia are currently unknown, but likely to include viral and allergic etiologies. OSAS affects about 2-3% of children, with 8%–12% snoring on most nights (habitual snoring) and close to 30% having snoring on some nights (10-12). Children of the African-American race are at increased risk but, unlike adults, there seem to be no gender differences (13).

Predisposing conditions and pathophysiology:

The pathophysiology of OSAS in children has been reviewed recently by Marcus (14, 15) and involves a complex interplay between anatomical, endocrine, and neural factors that are further modulated by genetic influences. Of the anatomical factors, adenotonsillar hypertrophy is by far the commonest. However, it is important to remember that the clinically or radiographically assessed adenotonsillar size does not correlate with disease severity. Indeed, removal of enlarged tonsils and adenoids does not always lead to resolution of OSAS (16-18). Other factors such as abnormal craniofacial anatomical components (e.g. retrognathia, mid-facial hypoplasia, macroglossia), and obesity play a role as well. The latter will not only physically compromise upper airway dimensions, but will also impose restrictive effects on lung mechanics (hence accelerating hypoxemia onset), and may blunt central respiratory drive (i.e. Pickwick syndrome).

However, clear anatomic factors cannot always be identified suggesting that alterations in upper airway neuromotor tone and compensatory reflexes involving the intricate musculature of the upper airway also play an important role in the etiology of OSAS (19). Thus, disorders involving the brainstem (i.e., meningomyelocoele, Chiari malformations), or hypotonia will contribute to the increased prevalence of OSAS, and this is most evident in disorders such as cerebral palsy, neuromuscular diseases, and Prader-Willi and Down syndromes. While hormonal factors are known to impact on the pathogenesis of OSAS in adults (20), where the disease predominates in males and increases in women post-menopausally, no gender differences are apparent in childhood.

Upper airway collapsibility is increased in children with OSAS as measured by subatmospheric loading of the upper airway in sleep (21), and in the topically anesthetized oropharynx, as measured by acoustic pharyngometry during wakefulness (22). Further, a high prevalence of allergic sensitization was shown to increase risk for OSAS (23), and asthma and OSAS may mutually contribute to increase the prevalence of the other (24).

In summary, there are a wide range of mechanisms that may play a role in the development of OSAS in any given patient. This is perhaps best illustrated in children with Down syndrome, whereby adenotonsillar hypertrophy may occur in the setting of midfacial hypoplasia, macroglossia, obesity, generalized hypotonia, and hypothyroidism, all of which may contribute to the development of OSAS (25).

Clinical evaluation of OSAS

A sleep history that also screens for snoring should be part of routine health care visits. Since OSAS spans all age groups, the physician should maintain a high index of suspicion even in infants and toddlers. In children, OSAS is very unlikely in the absence of habitual snoring (4). History regarding unusual sleep postures, labored breathing during sleep and witnessed apnea needs to be obtained. The use of multiple pillows at night is not uncommon, and many patients may present with a history of sleeping with their head and neck hanging off the edge of the bed or, in one case, sleeping head down on an armchair recliner to aid airflow in sleep. Some parents will even admit to co-sleeping with children to monitor their breathing at night and physically stimulate them to encourage respirations. Other symptoms may include restless sleep, paradoxical respirations, frequent nighttime awakenings, diaphoresis, dry mouth, morning headaches, nightmares, night terrors, bruxism, and enuresis. Upper airway pathology may be suggested by presence of oral breathing, chronic nasal symptoms, upper airway allergies

or recurrent middle ear infections. While excessive daytime sleepiness (EDS) as a consequence of OSAS is not frequent (7-13% of children), the current approaches used to assess for the presence of EDS may not be sensitive enough (26). There is now substantial evidence for the presence of learning problems or aggressive behavior in children with OSAS and these children may frequently be misdiagnosed with attention-deficit/ hyperactivity disorder (27, 28).

Surprisingly, findings on physical examination during wakefulness are often noncontributory. Nonspecific findings related to adenotonsillar hypertrophy, such as mouth breathing, heavy audible nasal breathing, adenoidal facies, allergic shiners, and nasolalia, might be present. Other physical findings consistent with systemic and/or pulmonary hypertension and poor growth should be sought (4). A growing proportion of the children referred for evaluations are overweight and/ or obese (>50% of our referral population in 2004), and such pattern tracks the general societal trend towards increasing obesity. Digital clubbing and dependent edema is rare. The clinician should also routinely screen for clinically evident nasal pathology including restricted nasal airflow and turbinate hypertrophy, dental misalignment, macroglossia, and assessment for evident cranio-facial syndromes or neuromuscular disorders.

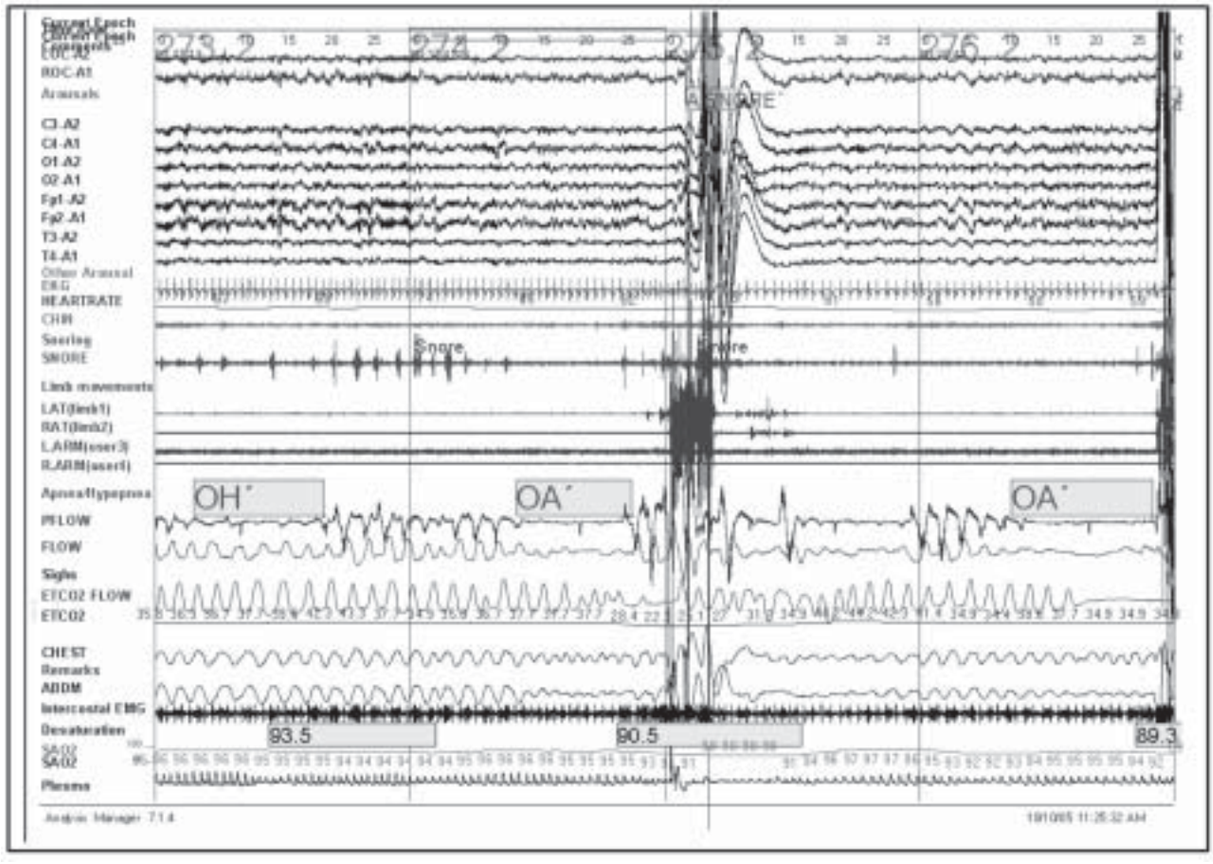

Fig 1: This 120 sec segment in stage 2 of sleep from an overnight polysomnogram of a patient with Down syndrome shows an obstructive hypopnea (OH) and two obstructive apneas (OA) as well as associated cyclical desaturations (SAO2) and two arousals (open arrows) captured on EEG and four-limb EMG (Limb1,2; Arm). Pressure transducer (PFLOW) and oronasal thermistor (FLOW) channels show attenuations in the face of continuing respiratory efforts in the chest, abdominal (ABDM) and intercostal EMG tracings. The plethysmographic channel (plesmo) helps to ascertain where saturation readings may be erroneous secondary to movement (closed arrow). Snoring is clearly seen in the snore channel. EKG shows normal sinus rhythm and no significant heart rate fluctuations. Right and left ocular (ROC, LOC) and eight channels of EEG are part of this standard montage in our laboratory. The reader will note that another possible obstructive apnea (not marked) is present 5 seconds after the first arousal.

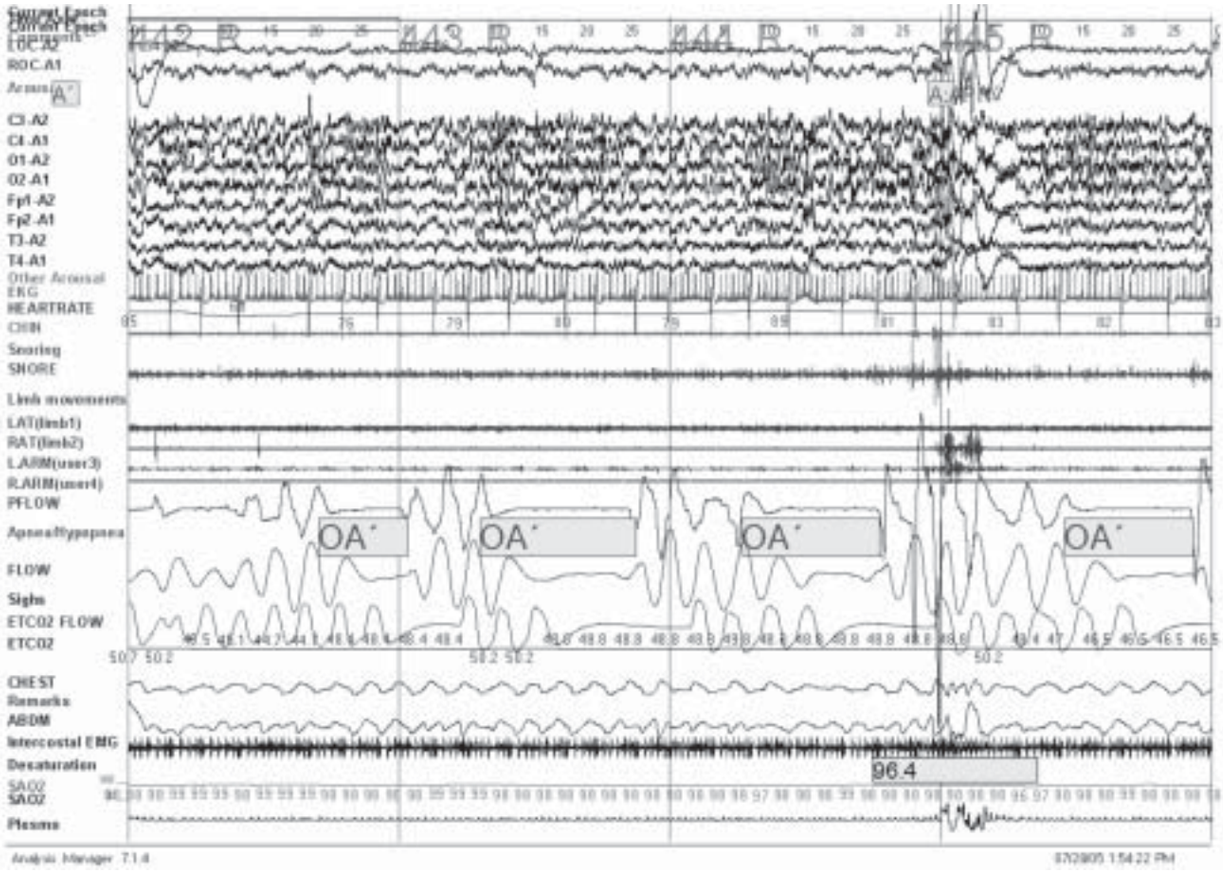

Fig 2: This is a 120-second segment from another child showing repetitive obstructive apneas but without any desaturations on pulse-oximetry channel in stage REM. Notably, the capnographic trace (ETCO2) shows evidence of hypoventilation. The montage is similar to the one in the previous figure. Hypoventilation may be the only sign of OSA and may not be associated with clear attenuations of airflow. Non-obstructive hypoventilation may occur in obesity and other neuromuscular disorders underscoring the importance of end-tidal and/or transcutaneous CO2 monitoring.

Investigations

The gold standard for the diagnosis of OSAS is the overnight polysomnogram, which provides detailed cardio-respiratory and gas exchange information in addition to alterations in sleep macrostructure, cyclicity, and arousal patterns. However, this test is lengthy and labor intensive. Moreover, there are only a limited number of pediatric sleep centers available, leading to unduly prolonged waiting times. Not surprisingly therefore, over the years a number of alternative methods for diagnosing OSAS have been evaluated. These are reviewed in the guidelines published by the American Academy of Pediatrics in 2002 (4) and more recently by Katz and Marcus (29). Such investigations may include video and audio recordings of the sleeping child, overnight pulse oximetry, and abbreviated (nap) polysomnographies. Unfortunately, most of these have poor negative predictive values, such that negative findings cannot be used to confidently exclude OSAS. An important factor in oximetry interpretation for example is that longer averaging times will compensate for movement artifact, but will lose sensitivity for brief desaturations. Moreover, oximetry fails to identify events associated only with arousals without accompanying desaturations. Similarly, OSAS related respiratory events are primarily clustered during REM sleep, and therefore OSAS typically worsens progressively with the later REM periods through the night (Fig 3), such that nap studies will underdiagnose OSAS.

The upper airway anatomy can further be evaluated by lateral X-rays of the neck or by fiberoptic rhinoscopy

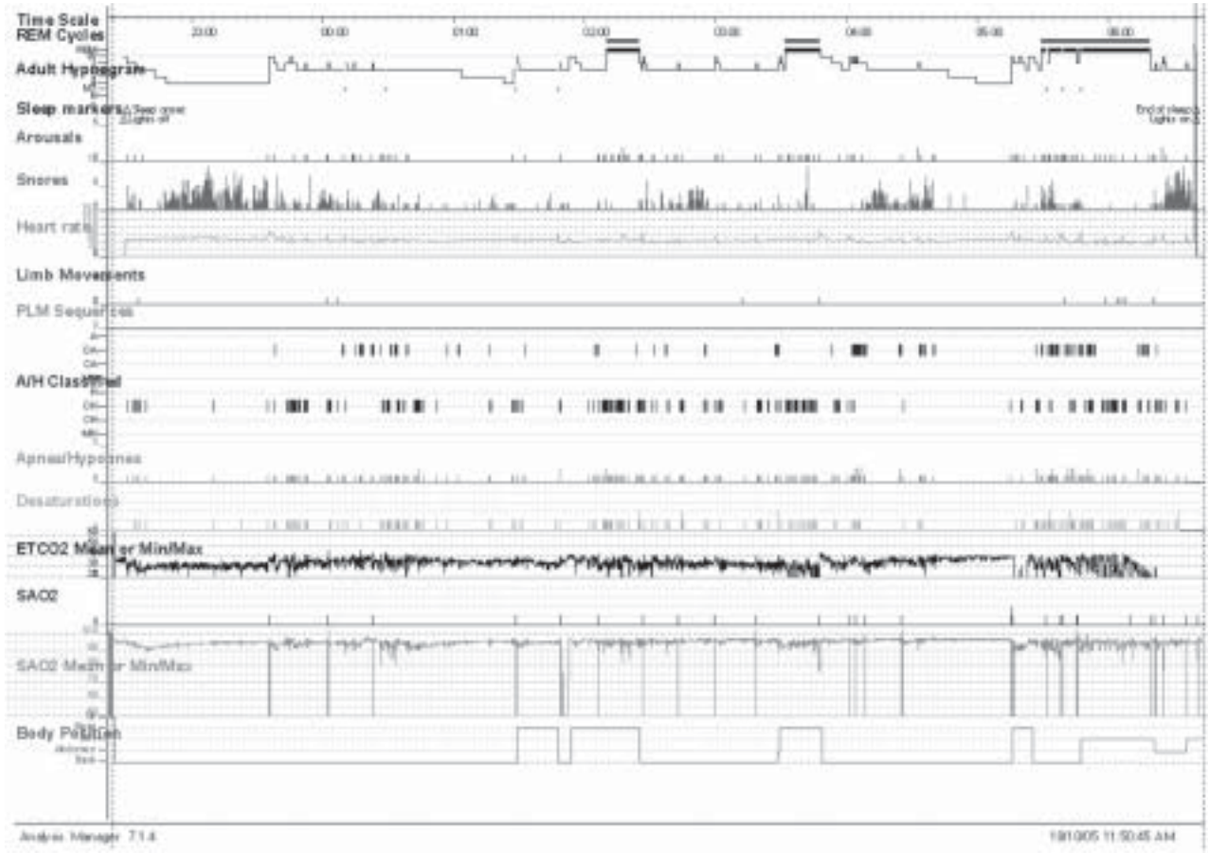

Fig 3: This is a summary (hypnogram) of an overnight polysomnogram on a patient with Down syndrome with severe OSAS. Similar patterns are seen in many patients with OSAS. "Adult" scoring criteria dividing the sleep stages into wake, 1, 2 , 3, 4 and REM are used after the first 6-12 months of age. Apneas and hypopneas are classified into several categories (e.g. OA= obstructive apneas, OH= obstructive hypopneas). Each short vertical blue bar represents an individual event and solid blue areas represent many events occurring close together. The clock time is shown at the very top and overnight pulse-oximetry summary as well body position summary is recorded at the bottom. Note the see-saw pattern of desaturations (short arrows) in stage REM (long arrows). The summary gives an overview of the distribution and severity of the disorder and is helpful to rapidly visualize trends. This particular example shows OSA events occur in both non-REM and REM sleep, but more prominently clustered in REM sleep. Nap studies may easily miss OSA if the patient has no or little REM.

for assessing size of adenoids and other structural abnormalities. Adjunctive techniques may include indirect biological markers for chronic hypoxia/ hypoventilation (hematocrit, serum bicarbonate), daytime sleepiness measures (MSLT), and consequences affecting the cardiovascular system (echocardiogram, EKG). More sophisticated upper airway imaging such as cephalometrics, CT scan, or MRI are not currently used routinely. However, these imaging techniques may facilitate management decisions in particular patients, in whom complex surgical interventions are contemplated (e.g. craniofacial syndromes).

In summary, the combination of history or physical examination is markedly ineffective in reliably distinguishing OSA from primary snoring, such that overnight polysomnograhpy remains the diagnostic instrument of choice (30, 31). Moreover, a single night polysomnogram is considered reliable for this purpose (32), and recent normative data has become available for the pediatric age range (33).

Consequences of OSAS:

The impetus to treat any disease is a function of its potential impact on patient well being and quality of life. The increasing importance of OSAS in the pediatric

and adult literature stems from the burgeoning data delineating morbidity and mortality associated with this condition. Mechanistically, the morbidity can be due to a combination of increased work of breathing, intermittent hypoxia, alveolar hypoventilation and sleep fragmentation. These factors have been shown to have wide-ranging systemic effects and have been reviewed recently (34, 35). Failure to thrive (FTT) may result from increased caloric needs, decreased food intake or perturbations in the growth hormone axis and may be reversed by adenotonsillectomy (36, 37). OSA related hypoxemia can cause systemic and pulmonary hypertension, as well as severity-dependent changes in left ventricular geometry and contractility (38-41). In contrast to adults, excessive daytime sleepiness is not a prominent symptom in children even when measured objectively using the multiple sleep latency test (26). Nevertheless, a host of learning and behavioral problems, including attention deficit hyperactivity disorder (ADHD)-like presentation, have been recognized as being frequently present, and in many instances may lead to the misdiagnosis of ADHD and inappropriate use of psychostimulants, rather than the early detection of sleep disordered breathing (28). Learning and memory may be affected but may improve, at least partially, after treatment (27, 42, 43). Further, children who snore in early childhood may be at higher risk for lower academic achievements in their teenage years (44). Sleep enuresis is common and may be reversible with treatment (45). Serum markers of inflammation and increased cardiovascular morbidity risk such as CRP and P-selectin have been found to correlate with sleep measures of OSAS severity (46, 47). From a broader public health perspective, children with OSAS are heavier consumers of health care services, particularly related to increased symptoms of respiratory tract infections, and treatment of OSAS significantly reduces future health care costs (48, 49).

Differential diagnosis (1):

- *Central sleep apnea*: apneas are associated with lack of any respiratory effort.
- *Non-obstructive alveolar hypoventilation*: due to altered lung and chest wall mechanics. Snoring is not common but this may co-exist with OSAS especially in very obese children.
- *Fixed upper airway obstruction*: children obstruct in wake and sleep. The presence of stridor or wheezing may serve as a clinical clue.
- *Disorders of excessive daytime sleepiness:* these include insufficient sleep syndrome, narcolepsy and periodic limb movement disorder.

Treatment

In children, OSAS is generally defined as the presence of an apnea index of more than 1 or an apnea-hypopnea index of greater than 5. In addition, end-tidal CO_2 levels >50 torr for > 10% of sleep duration or peaking above 53 torr are also considered abnormal (29). UARS is defined by either normoxia and normocarbia in the face of more than 2 respiratory efforts (snore)-related arousals per hour or an AHI>1 but < 5/hrTST (50). Normative data for an extensive healthy population of 540 children has recently become available (33).

Adenotonsillectomy is considered the treatment of choice in children once OSAS is diagnosed. Outcomes studies for this procedure and its attendant complication rates have been recently reviewed by Lipton and Gozal (18). A cumulative rate of about 80% as far as normalization of sleep breathing patterns and morbidity rates of 18-34% were found in a metanalysis of published literature (18). Patients are considered to be high risk for post adenotonsillectomy complications if they are less than 4 years old, have severe OSAS on polysomnography, cardiac complications of OSAS, FTT, morbid obesity, prematurity, recent respiratory infection, asthma, craniofacial anomalies or neuromuscular disorders (4, 51).

Continuous positive airway pressure (CPAP) therapy is usually reserved for those who do not respond to surgery or for those in whom surgery may be contraindicated. The approach is not trivial and requires a committed family and medical team. Unlike adults, the vast majority will do poorly with split-night studies where CPAP titration is started after a few hours of diagnostic polysomnography. In our center, the routine approach consists of giving the child the choice of the mask, allowing a selection of decorative stickers to personalize the mask, and prescribing an initial empirically derived low pressure (e.g. 5 cm water) therapy for 1-3 weeks for habituation in the home setting before undertaking a titration polysomnogram. Once adherence with this intentional "under-treatment" is determined as favorable, CPAP pressures are then increased gradually through

the night until the minimum adequate pressure that eliminates OSA is reached, the latter being determined in the sleep laboratory. CPAP has been successfully used in children of all ages. However, caution needs to be exercised by periodic re-evaluation of prescribed pressures in the growing child (52, 53). Tolerance to therapy may be increased by use of in-line heated humidification of the airflow. Periodic reviews for complications and adherence to therapy are mandatory. Bi-level positive pressure devices may be indicated in selected patients.

Pharmacological intervention has been tried for treatment of OSAS in adults and children. While pediatric sleep experts will generally advocate adenotonsillectomy as first line of management if the AHI is greater than 5/hrTST and agree that habitual snoring (AHI <1/hrTST) does not require intervention, there is debate about the best treatment strategy for those symptomatic children who have AHI in between. In such cases, a role for anti-inflammatory therapy aimed at the upper airway has been proposed. Intranasal steroids appear to be beneficial (54). In addition, increased expression of leukotriene (LT) and glucocorticoid subunit receptors in adenotonsillar tissue, as well as increased concentrations of leukotrienes in exhaled condensates from the upper airway and in adenotonsillar tissues (55-57) suggest a favorable therapeutic profile for topical steroid therapy in snoring children with adenotonsillar hypertrophy. We have recently shown that administration of a leukotriene modifier may be effective in treatment of mild OSAS (58), and have further shown that a combination of intranasal steroids and leukotriene receptor antagonist leads to complete resolution of residual OSAS after adenotonsillectomy (59). Thus, a trial of LT modifiers and intranasal steroids is a viable alternative for the treatment of mild OSAS provided a close medical follow-up is assured.

Other interventions (see suggested readings for details) include *cranio-facial surgery* in patients with severe congenital anomalies or isolated micrognathia. These may include uvulopalatopharyngoplasty, tongue reduction, mandibular osteotomy and distraction, hyoid suspension, epiglottoplasty and nasal septoplasty. *Orthodontic treatments* including rapid maxillary expansion and mandibular positioning devices have been used in selected cases but data is scanty (60, 61). *Weight management* is useful as adjunctive therapy for all overweight children; bariatric surgery has been tried in extremely obese children in a few centers. *Supplemental oxygen* has been used as a temporizing measure in selected situations with the caution that hypoventilation secondary to this therapy needs to be ruled out. It is rarely used as a first line intervention because it will not abolish the sleep fragmentation associated with OSAS. *Environmental control* for allergens and irritants (cigarette smoke) may reduce nasal resistance. Finally, the "last resort" definitive treatment of severe OSAS is *tracheotomy*. However, with the increasing use of non-invasive positive pressure therapy and sophisticated corrective surgical techniques, this option is now rarely, if ever, used.

The future

Despite the tremendous strides made in the diagnosis and treatment of OSAS in childhood, there are many unanswered questions about the natural history of OSAS, the best screening tools, the correlation between OSAS and clinical outcomes and best treatment choices for those with mild disease. The role of orthodontic treatment and cranio-facial surgery and the long term outlook for treated and untreated OSAS at various levels of disease severity awaits well coordinated long-term multicenter research cooperations.

Practice points

- OSAS is seen in 2-3% of the pediatric population and is a major source of significant morbidity.
- The presence of snoring in children is the clinical hallmark of pediatric OSAS.
- All children should be screened periodically during health checks for sleep related problems including OSAS.
- Clinical history and examination is inadequate to diagnose OSAS and the polysomnogram remains the test of choice.
- Adenotonsillectomy is the first-line treatment.
- Medical management is becoming increasingly attractive as an option for milder forms of the disease.
- High-risk patients deserve special attention and close intensive perioperative monitoring.
- A non-negligible proportion of children with OSAS will not sustain complete resolution of their disorder with surgery. Alternative therapies include CPAP.

- Long term prognosis and recurrence risks await further research.

Suggested readings

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